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Early Detection of Delirium in Older Medical Inpatients: Prodrome, Predictors and Motor Subtyping

A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the School of Medicine







December 2015

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LIST OF ABBREVIATIONS

4-AT	The 4 'A's Test
20-1	Twenty to one attention test
3MS	Modified Mini-Mental State Examination
6-CIT	Six- item Cognitive Impairment Test
AIC	Akaike Information Criterion
AMT-4	Abbreviated Mental Test - 4
ANOVA	Analysis of Variance
APACHE II	Acute Physiology and Chronic Health Evaluation II
AUC	Area under the Receiver Operating Characteristic curve
BI	Modified Barthel Index
BC(s)	Behavioural Change(s)
BMT	Bone Marrow Transplant
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CCI	Charlson Comorbidity Index
CCU	Coronary Care Unit
CI	Confidence Interval
CDT	Clock-Drawing Test
CREC	Cork Research Ethics Committee
CUH	Cork University Hospital
DEC	Delirium Etiology Checklist
DMC	Delirium Motor Checklist
DMSS	Delirium Motor Subtype Scale
DMSS-4	Four Item Delirium Motor Subtype Scale
DRS	Delirium Rating Scale
DRS-R98	Revised Delirium Rating Scale

DSI	Delirium Symptom Interview
DSM	Diagnostic and Statistical Manual for Mental Disorders
EEG	Electroencephalogram
EVSQ	Environmental Visuospatial Questions Test
FSD	Full-Syndromal Delirium
GDS	Geriatric Depression Scale
GEE	Generalised Estimating Equation
HDS	Hierarchic Dementia Scale
HR	Hazard ratio
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IPT	Interlocking Pentagons Test
IQCODE-SF	Informant Questionnaire for Cognitive Decline in the Elderly- Short Form
IQR	Interquartile range
K-DRS-R98	Korean version of the Revised Delirium Rating Scale
LTM	Long-term memory
M-CIRS	Modified Cumulative Illness Rating Scale
MDAS	Memorial Delirium Assessment Scale
MMSE	Mini-Mental State Examination
MMSE-K	Korean version of the Mini-Mental State Examination
MNA-SF	Mini Nutritional Assessment – Short Form
MOTYB	Months of the Year Backwards Test
MUH	Mercy University Hospital
NEECHAM	NEECHAM Confusion Scale

NICE	National Institute for Health and Clinical Excellence
Nu-DESC	The Nursing Delirium Screening Scale
NPV	Negative Predictive Value
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PI	Principal Investigator
POMS	Profile of Mood States
PPV	Positive Predictive Value
PRN	Pro re nata (in relation to 'as required' medications)
QIC	Quasi-AIC
RADAR	'Recognizing Acute Delirium As part of your Routine' Screening Instrument
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SFH	St. Finbarr's Hospital
STM	Short-term memory
SMMSE	Standardised Mini-Mental State Examination
SPSS	Statistical Package for the Social Sciences
SSD	Subsyndromal Delirium
SSF	Spatial Span Forwards
TMT A and B	Trail Making Tests A and B
UCC	University College Cork
UK	United Kingdom
WAIS	The Wechsler Abbreviated Intelligence Scale

DECLARATION

"This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism."

Signed _____

Date _____

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THESIS ABSTRACT

Background

Delirium occurs in 20% of inpatients, and at higher rates in older patients. It independently leads to adverse outcomes, but remains poorly recognised clinically, particularly hypoactive forms. This is partially due to poor consensus about delirium screening tools, as well as under-appreciation of the importance of hypoactivity. Although early identification and intervention may improve prognosis, delirium prevention programmes have had the most impact on outcomes to date. The delirium prodrome concept has been considered in the literature for decades, but remains poorly characterised. Greater understanding of this prodromal phase would facilitate identification of delirium-prone patients prior to delirium onset, potentially leading to improved strategies for delirium prevention and management.

Methods

Medical inpatients of ≥70 years in two hospitals in Cork city were initially screened for prevalent delirium using the Revised Delirium Rating Scale (DRS-R98) and also assessed using a series of cognitive tests which were then tested for diagnostic accuracy in delirium detection. Participants without prevalent delirium on initial screening were assessed on a daily basis for delirium development, prodromal features and motor subtype. Baseline predictors of incident delirium were identified using multivariable logistic regression. Survival analysis models identified which prodromal features predicted the emergence of incident delirium in the cohort in the first week of admission. The Delirium Motor Subtype Scale-4 (DMSS-4) was used

ascertain motor subtype in those with full syndromal (FSD) and sub-syndromal delirium (SSD), and the longitudinal course and stability of subtypes were examined. A small cross-sectional study was also conducted to assess the clinical utility of the NICE guidelines (2010) screening recommendations. A questionnaire based on the guidance was developed and administered to nursing staff by trained researchers blinded to the delirium assessments, and diagnostic accuracy was then calculated.

Results

Of 555 patients approached, 470 had full delirium assessments performed and 184 (33.2%) had prevalent delirium. Of six cognitive screening tests, the 6-CIT was most robust in detecting delirium (AUC 0.88), 95% CI 0.84-0.91). The most efficient cut-off for use as a screening tool was found to be 8 / 9 with a sensitivity of 89.9% (95% CI 83.8-93.9) and specificity 62.7% (95% CI 56.6-68.5). A total of 191 patients were included in the prospective study of incident delirium. The median age was 80 (IQR 10), 101 (52.9%) were male and 32 (16.9%) had premorbid dementia. Sixty-one patients developed incident delirium within the first week of admission. Independent baseline predictors of delirium development were premorbid dementia; functional impairment; and higher comorbidity. Controlling for these factors, several prodromal features predicted the emergence of delirium in the cohort. Using a novel Prodromal Checklist based on the existing literature, seven predictive behavioural features were identified: increasing confusion or 'fogginess' (HR 2.28, 95% CI 1.4-3.72); being easily distractible or going 'off-track' (HR 1.89, 95% CI 1.11-3.21); needing prompting for usual tasks (HR 1.86, 95% CI 1.1-3.14); seeming tired in the morning (HR 1.77, 95% CI 1.12-2.81); drowsiness during the day (HR 1.74,

95%CI 1.12-2.71); being 'fidgety', restless or wandering (HR 1.72, 95%CI 1.08-2.75); and irritability (HR 1.72, 95% CI 1.06-2.78). Using serial cognitive tests, prodromal impairments in orientation, attention, short-term memory and visuospatial function were also found, independent of premorbid dementia and other confounders. Additionally, using the DRS-R98 daily, multiple core delirium features were detected in the prodrome, including disturbances in sleep-wake cycle, perception, attention, and short-term memory, as well as lability of affect and symptom fluctuation. Examining longitudinal motor subtypes in those with delirium, subtypes were found to be predominantly stable over time, the most prevalent being hypoactive subtype (62.3%). Furthermore, hypoactive subtype was almost twice as common in SSD and FSD events than in 'no delirium' ($p<0.001$), whereas 'no delirium' periods most commonly presented with no subtype. Finally, regarding the clinical utility of an operationalised version of the NICE guidelines screening recommendations, where *any* positive response was considered a positive screen, the sensitivity of the instrument was too low (at 64.3%-66.7%), to be a useful screening tool for delirium.

Discussion

This thesis explored multiple aspects of delirium in older medical inpatients, and includes an in-depth characterisation of the delirium prodrome; evaluation of the baseline predictors of incident delirium; detailed examination of the motor subtyping of FSD and SSD with respect to course, stability, and relationship to other factors; as well as investigation of the efficacy of several methods for delirium screening. The findings of this thesis should help to inform future delirium educational programmes, as well as future detection and prevention strategies.

1. INTRODUCTION

1.1. INTRODUCTION

Delirium is a serious neuropsychiatric syndrome which occurs in the setting of acute illness, injury, or toxicity. It is extremely common, occurring in approximately 20% of hospital inpatients (1), and at higher rates in older patients (2). Delirium is independently associated with adverse outcomes, such as mortality, and cognitive and functional decline (3), yet it remains under-detected with up to 72% of older medical inpatients being missed or misdiagnosed (4). Because delirium is challenging to diagnose without training and experience, it is now generally accepted that a two-phase approach should be employed such that a sensitive, simple test should first be used to screen for possible delirium cases, followed by formal diagnosis in those who screen positive (5). Unfortunately, although multiple screening methods have been proposed, there remains no consensus as to which approach is best. Moreover, the concept of subsyndromal delirium (SSD), in which a patient presents with certain delirium features without reaching full diagnostic thresholds, further obfuscates the issue.

Although early intervention may improve prognosis (6), studies over the past few decades have demonstrated that in order to meaningfully impact on the long-term burden of delirium, prevention is the key (7). However, and unsurprisingly given the multifactorial aetiology of delirium, successful delirium prevention strategies involve a systematic and widespread multifaceted approach, which requires that delirium is

considered a serious healthcare concern by clinical leaders, senior health management and practicing healthcare professionals alike (8). Unfortunately, with the ever-increasing workload on busy clinical staff, delirium prevention and intervention strategies are commonly neglected. To date, the development of strategies for the prevention and early intervention of delirium has been informed by numerous studies of delirium risk factors in various study populations. A vast array of risk factors have been identified, the most consistent being advancing age and premorbid cognitive impairment (9). Our ageing population means that the prevalence and associated adverse sequelae of delirium is set to rise significantly, hence our preventative efforts are likely to be spread even more thinly. It is thus important that we aim to direct these efforts towards the most delirium-prone.

One potential way to reduce the occurrence of full-syndromal delirium is to identify patients with impending delirium and focus intensive prevention efforts on this group. Although one of the key diagnostic features of delirium is its acute onset, over the last number of years the concept of a delirium prodrome has emerged, referring to a variety of symptoms which may occur in the days prior to delirium development. Although this concept has appeared in the literature for decades, it remains poorly characterised, the few studies conducted differing greatly in methodology, populations studied and assessments used (10). A further understanding of this prodromal period may facilitate early detection, intervention and possibly prevention of delirium in the particularly vulnerable.

1.2. AIM

The overall aim of this study is to characterise delirium and its prodrome in older medical inpatients, and to identify methods for the early detection of delirium in this cohort.

1.3. OBJECTIVES

The primary objective of this thesis was to characterise the delirium prodrome in older people admitted medically to the acute hospital. This prodrome was studied in detail by evaluating patients for the emergence of (i) behavioural features (somatic; emotional; and non-specific); (ii) cognitive features; and (iii) delirium phenomenological features in a prospective fashion, while simultaneously assessing for incident delirium development.

Secondary objectives were:

- To determine the prevalence of delirium in older medical inpatients on admission and identify which screening tools are most efficacious in detecting prevalent delirium in this cohort - objective (iv).
- To determine the incidence of delirium in older medical inpatients and identify predictors of incident delirium in this group - objective (v).

- To examine the clinical utility of the NICE guidelines' screening recommendations (using a novel operationalised tool) in detecting incident delirium - objective (vi).

- To assess the prevalence and stability of different motor subtypes of incident delirium in older medical inpatients - objective (vii).

- To characterise the phenomenology and motor profile of subsyndromal delirium in older medical inpatients - objective (viii).

1.4. Research Setting

This project studied older people admitted to acute hospitals who were at high risk of developing delirium. The cohort were followed closely on a longitudinal basis to detect incident delirium during the hospitalisation. Patients were assessed for the presence of a range of delirium risk factors, in order to ascertain which factors predicted the development of incident delirium in this cohort. The delirium was carefully characterised, in relation to phenomenology and motor activity profile, and evidence of potential prodromal symptoms was also sought on a daily basis, by interviewing both the patient and the relevant nursing staff. A novel prodromal checklist was devised to detect behavioural features and patients were assessed for cognitive decline and for other prodromal delirium features daily. Patients were also evaluated daily for motor subtype expression using the DMSS-4 and longitudinal subtypes were applied to patients with both full-syndromal delirium (FSD) and subsyndromal delirium (SSD) using criteria from earlier similar studies (11).

This thesis also tested the validity of the 'indicators of delirium' that have been proposed by the National Institute for Health and Clinical Excellence (NICE) guidelines for the detection, prevention and management of delirium (5). An operationalised version of these recommendations was developed and tested for diagnostic accuracy. Additionally, a series of other potential delirium screening tests were also assessed for utility in detecting delirium in older medical inpatients on admission.

1.5. Thesis Outline

This thesis is comprised of eight papers (as yet unsubmitted) which explore the phenomenology of the delirium prodrome; the motor profile of both FSD and SSD; predictors of incident delirium; and the diagnostic accuracy of multiple screening methods. The thesis aims, objectives and associated papers are outlined in figure 1. Chapter 2 provides an introduction to delirium with particular emphasis on early detection and the existing evidence on the delirium prodrome. This thesis also includes a detailed methodology chapter (Chapter 3).

In the results chapters (Chapters 4 to 11), for ease of reading, I will report the findings in order of the chronology of data collection and analysis, rather than the order of the objectives (figure 1 shows the link between each chapter and objective).

Prevalent delirium: Older medical inpatients were assessed within 36 hours of admission for prevalent delirium. They were also assessed using a series of cognitive tests, which have potential as delirium screening tests, including the 6-CIT (Six-item

Cognitive Impairment Test). Chapter 4 examines the diagnostic accuracy of these cognitive tests in screening for prevalent delirium on admission.

Predictors of Incident Delirium: Those who did not have prevalent delirium nor any other exclusion criterion were then included in a prospective study of incident delirium and underwent daily assessment. Data pertaining to a variety of baseline risk factors was collected, for example demographics, functional impairment, pre-morbid dementia and comorbidity burden. Chapter 5 outlines the baseline features which independently predicted delirium development in this cohort.

NICE Delirium Indicators: The NICE (National Institute for Health and Clinical Excellence) Guidelines on Delirium: Diagnosis, Prevention and Management were published in 2010, (5) shortly before this PhD was commenced. In these guidelines, it is recommended that patients at risk of delirium are screened daily for 'indicators of delirium' (see Chapters 3 and 6 for detail), however this method of screening has not been validated in the clinical setting. Chapter 6 investigates the clinical utility of these screening recommendations.

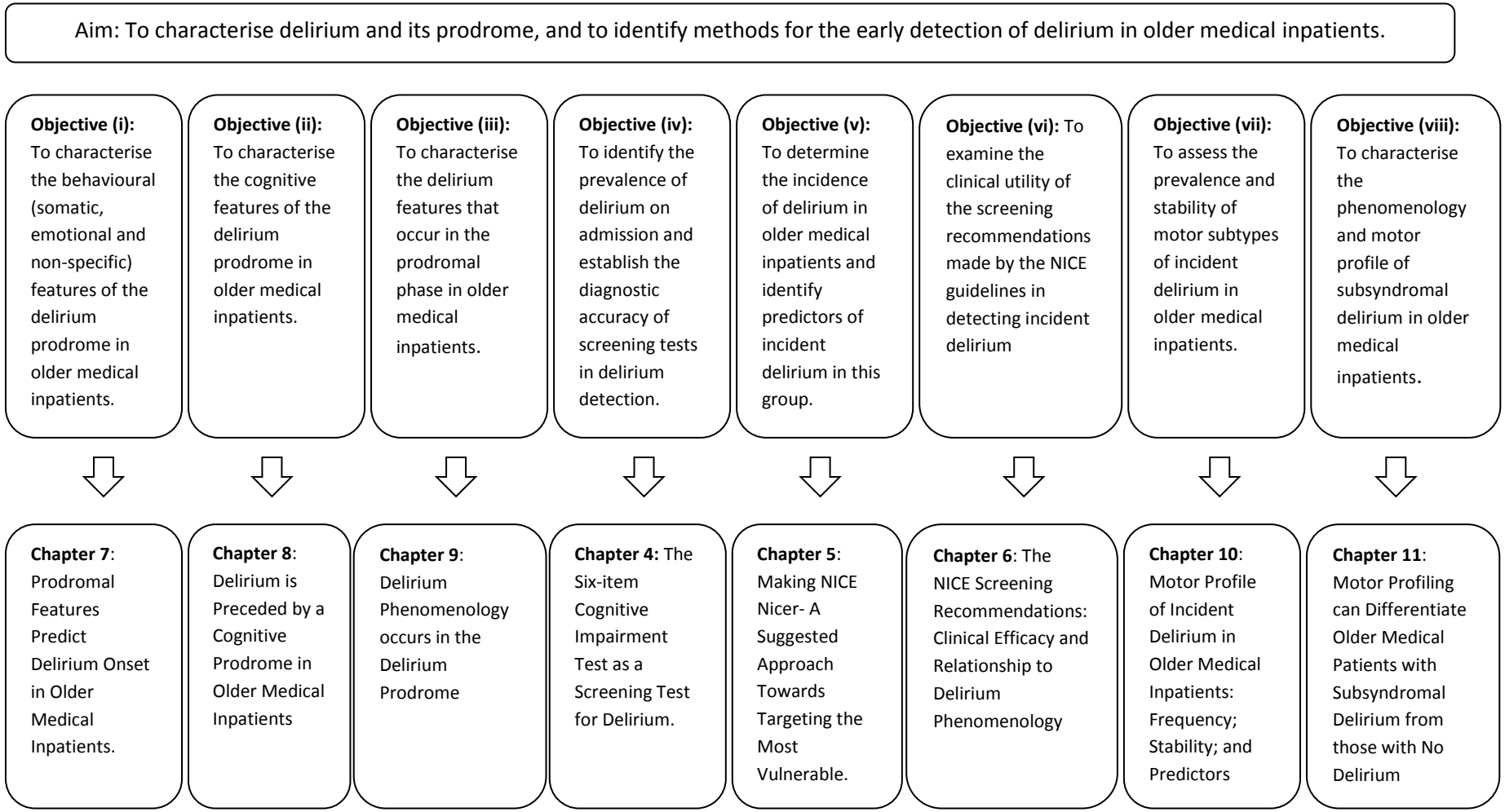
Delirium Prodrome: The characteristics of the delirium prodrome are explored in Chapters 7 to 9. Chapter 7 outlines evidence for the presence of behavioural features in the prodromal period. Chapter 8 investigates if cognitive decline occurs in the delirium prodrome and which cognitive domains are affected during this period. Chapter 9 examines which delirium phenomenological features occur in the prodromal period before full delirium development.

Motor Subtypes: Chapter 10 describes the prevalence, course and stability of motor subtypes in older medical inpatients with delirium and explores factors related to subtype stability, such as demographics, functional ability, presence of pre-morbid dementia and comorbidity. Chapter 10 also investigates if motor subtype relate to cognitive performance in this population.

Subsyndromal delirium: Chapter 11 examines the motor profile and phenomenology of SSD, and investigates the phenomenological differences between SSD and full-syndromal delirium (FSD), and particularly between SSD and normal controls.

An overall discussion of the main study findings, strengths and limitations, clinical implications, and suggested directions for future research is provided in Chapter 12.

Figure 1: Overview of thesis results chapters, illustrating how aims and objectives were met



1.6. AUTHOR'S CONTRIBUTION

I am the lead author for all the research papers in Chapters 4 through 11. This involved the formulation of the research question (with the assistance of my supervisors), data collection, literature review for each paper, and drafting of each manuscript. I had some assistance in data collection and data entry from James Fitzgerald (a graduate-entry medical student in University of Limerick), whose delirium research study was nested within mine, however I conducted all delirium, cognitive and prodromal assessments. James collected some data pertaining to mood and nutritional status, whereas I collected the remaining baseline data. Data pertaining to the NICE clinical indicators (to which I was blinded) was collected by a group of post-graduate medical trainees (Dr. Maeve Davis; Dr. Mary Buckley; Dr. Theva Jayaraman; and Dr. Annmarie Hannon). Katrina Maughan, a masters student in the School of Applied Psychology, also assisted with data entry. I conducted the statistical analysis with the assistance of Dr. Dimitrios Adamis, an expert in this field, currently of Sligo Mental Health Services, Sligo.

2. BACKGROUND

This chapter provides a brief overview of delirium and its prodrome, with particular focus on the importance of early detection and current and potential diagnostic approaches. The clinical features of full-syndromal and subsyndromal delirium are outlined, and motor subtypes are described. The concept of the delirium prodrome is introduced and the existing literature on this area is summarised.

2.1. DELIRIUM: EPIDEMIOLOGY AND SIGNIFICANCE

Delirium is a complex neuropsychiatric syndrome characterised by acutely declined cognitive function and can be precipitated by a variety of factors including acute illness or injury, substance toxicity or withdrawal. It is one of few conditions to permeate across all treatment settings, occurring in one-fifth of all hospital inpatients (1) , in up to half of the hospitalised elderly (2) and at higher rates in the critically ill and other vulnerable groups (12, 13). Although delirium is a serious condition which independently leads to increased mortality (14); increased length of hospital stay (15) and readmission rates (16); and increased cognitive (17) and functional decline (16), it is often viewed as simply a marker of underlying pathology and is commonly overlooked. Studies have highlighted that the adverse outcomes linked to delirium can be modified by prompt detection and early intervention (6, 7), but are further intensified by late or misdiagnosis (18, 19). Despite this, delirium remains missed or mistaken for other conditions, particularly in older patients (2), those with pre-existing dementia (20) and those with hypoactive features (21, 22). Studies in the emergency department (ED) have found that delirium is missed by ED

physicians in 65% to 75% of cases (23, 24). Collins and colleagues reported detection rates to be as low as 28% in older medical inpatients (4) and Kishi and co-workers found in a study of general hospital referrals to liaison psychiatry, that 46% of delirium diagnoses were missed by the referring team (25).

2.2. Delirium Pathophysiology and The Role of Biological Markers

Although multiple hypotheses have been suggested as to the underlying pathophysiology of delirium, the exact process is not yet fully understood. Theories include disturbances in the neurotransmitter system; altered central responses to peripheral inflammation; hypothalamic pituitary adrenal axis dysregulation; and direct cerebral insults such as hypoxia and trauma (26). Given the wide differential of aetiological contributors to delirium, it is probable that each of these hypotheses play a role in delirium development and that the initial insult and resultant triggering mechanism ultimately leads to a final common pathway of reduced cholinergic and GABAergic activity and increased dopamine, glutamate and noradrenaline release (27). Irrespective of the theories underpinning delirium pathogenesis, it is important to recognise that delirium occurs particularly frequently in those with a vulnerable brain (e.g. dementia, learning disability, stroke), where an exaggerated central physiological reaction occurs as a consequence of an aberrant stress response in the setting of apparently mild peripheral illness or injury (28).

Hypotheses concerning delirium pathogenesis have prompted multiple studies of biomarkers and genetic polymorphisms which indicate relationships with delirium incidence, course and severity (26, 29). Studies of peripheral inflammatory mediators, for example IL-8 (interleukin-8), cortisol and CRP (C-reactive protein), have shown some promise in relation to signalling imminent delirium, however results are somewhat conflicting (30-34), particularly in relation to CRP. Low levels of the cytoprotectant peptide insulin-like growth factor 1 (IGF-1) are associated with a greater delirium risk (35, 36), but are not predictive of delirium emergence (37). Further studies of the neurobiological processes underlying delirium and the role of biological markers in delirium detection are required, before we can assess whether biomarkers can be utilised as a diagnostic approach for delirium.

2.3. Clinical Presentation and Motor Subtypes

Delirium has been recognised as a clinical syndrome since ancient times, however it was not until the publication of DSM III (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition) in 1980 that its definition became standardised. Prior to this, acute and subacute cognitive disturbances were labelled by a wide variety of terms based on differences in aetiology and clinical settings, which hampered meaningful progress in delirium research and clinical care. However, considering delirium as a unitary syndrome has helped to foster a greater awareness of its significance and its ubiquitous nature, and has facilitated research across treatment settings over the past few decades (38).

Delirium presents in a myriad of ways, its constellation of symptoms representing widespread cortical dysfunction. The features vary greatly not only from patient to patient but also within the same patient as they fluctuate in severity and nature over the course of the day, partly explaining why achieving consensus as to its definition was a slow process. Certain delirium features are central to diagnosis, for example inattention and acuity of onset, and hence form the basis for gold-standard diagnostic systems such as DSM, which is now in its fifth edition (Diagnostic and Statistical Manual of Mental Disorders - 5th edition (39)). Some delirium features occur frequently but not universally (such as psychomotor disturbance), and others present more sporadically (for instance, affective lability, perceptual abnormalities and delusions) (40), the result being a protean condition which is difficult to diagnose unless trained and experienced. Factor analysis has been used to examine the inter-relationship of these features (41), and has identified a three-factor structure to delirium, comprising (i) attention / other cognitive; (ii) circadian (psychomotor and sleep-wake cycle disturbances); and (iii) higher level thinking (disorders of language, thought process and executive function) (42, 43). This construct facilitates improved understanding of the inter-play between delirium features and future work should focus on efforts to illuminate the relationship between these factors and delirium neuro-pathogenesis, amongst other areas (41).

Identification of clinical sub-categories of delirium may facilitate delirium detection and promote more targeted approaches in research and in the clinical setting. Attempts to categorise delirium have included classifications based on severity,

aetiology, comorbidity status, evidence of psychosis, actigraphic profile and motor activity profile (38). To date, the most successful approaches have defined subtypes based on psychomotor change. Because motor disturbance occurs with such frequency in delirium, it is considered a core element of delirium phenomenology. Although some motor features, particularly hypoactive aspects, are subtle to the untrained eye, motor activity disturbance is readily observable when it is actively sought out. Describing delirium based on motor profile is not a modern concept, with references dating back as far as the ancient Greeks who used the terms 'lethargicus' and 'phrenitus' to label reduced and increased activity profiles respectively (38). More recently, Lipowski (44) suggested the words 'hyperactive' and 'hypoactive' to categorise these individual subtypes, before adding a third 'mixed' subtype to include patients who present with elements of both hypo- and hyperactivity within short time periods.

Early endeavours to define these motor subtypes resulted in multiple methods, including an array of both motor and non-motor features. The wide disparity between these tools was highlighted when concordance between the four most commonly used tools was found to be only 34% (45). Hence, in order to improve consistency, thirty of the elements from antecedent methods were combined to form the Delirium Motor Checklist (DMC), which was then employed to ascertain the frequency of different motor features in delirious patients and non-delirious controls (45, 46). Using principal components analysis and replication analysis, thirteen of the original thirty DMC items significantly distinguished between motor subtypes and

also correlated with independent measures of motor activity on the Delirium Rating Scale-Revised ’98 (DRS-R98), and a new 13-item scale called the Delirium Motor Subtype Scale (DMSS) (46, 47) was the result. Unlike earlier approaches, the DMSS has undergone meticulous validation and correlates highly with objective measures of motion using accelerometry (48). Furthermore, the DMSS is relatively delirium-specific, and has predictive validity with respect to outcomes (47). Recently it has been further reduced to the four-item DMSS-4, by latent class analysis, allowing for quicker assessment without compromising on subtyping accuracy (49). A recent study in older medical inpatients found that the DMSS-4 has high concordance with the DMSS and good inter-rater reliability (50).

The epidemiology and prognosis of the individual delirium subtypes have varied widely across studies, due to inconsistent methodologies and referral bias within study samples (38). Additionally, most studies have been cross-sectional in methodology, which gives misleading results, given the dynamic and fluctuating nature of delirium. Longitudinal work in the palliative care setting has found that subtypes are most commonly stable across time, with the most prevalent subtype being hypoactive (11, 51). Conversely, in a longitudinal study of hip fracture patients, approximately 87% of patients had a variable motor profile throughout the delirium episode (52). It is possible that hip fracture patients follow a different course to other patient cohorts. For example, it is now generally accepted that in most settings hypoactive delirium carries the worst prognosis, whereas Marcantonio and colleagues found that amongst hip fracture patients with delirium, it was those with

hypoactive motor profile (albeit using categories based on the Memorial Delirium Assessment Scale, MDAS) who achieved the best outcomes, independent of delirium severity and other confounders (53).

Longitudinal studies in palliative care patients have found that motor subtype is more closely related to delirium phenomenology than to medication exposure or aetiology (54). The subtypes can differ with respect to the non-cognitive features of delirium, but they do not differ in relation to the spectrum and severity of cognitive impairment (38, 54), except that in patients without a motor subtype, cognitive impairment is less pronounced than in those presenting with a subtype. This former group have also been shown to experience a less phenomenologically intense delirium than the other subtypes and often have rating scores in the subsyndromal range on the DRS-R98 (54). Although there are few studies investigating how motor subtypes relate to various risk factors for delirium, some work suggests that increasing age and premorbid cognitive impairment may be more common in those with hypoactive presentation (55, 56).

To date, studies in older medical inpatients with delirium have all been cross-sectional in nature and results have been widely conflicting. In 1992, Liptzin and Levkoff found that 52% of 125 older medical inpatients with incident delirium had a mixed profile, whereas only 19% were hypoactive, and that motor subtype did not relate to sex, age, place of residence or presence of comorbid dementia (57).

O'Keeffe and Lavan found that mixed subtype predominated in 94 acute geriatric medicine patients with delirium, but that those with hypoactive profile had higher illness severity and longer length of stay (58). A more recent cross-sectional study of older medical inpatients primarily designed to identify MMSE (Mini-Mental State Examination) items on admission that predict the occurrence of incident delirium, used DRS-R98 motor items to apply motor profile and found that the most common subtype in patients with incident delirium was hypoactive (13 / 34, 38%) (59). Furthermore, a study investigating the occurrence of delirium in older patients in the emergency department found that 92% of cases were hypoactive, based on the Richmond Agitation Sedation Scale, and worryingly over three quarters of cases were missed by emergency physicians (23). Drawing meaningful conclusions from these discordant results is limited by the cross-sectional nature of these studies and also because each study differed in relation to the subtyping methods employed. Longitudinal data, using a validated instrument, is needed to accurately examine the motor profile expression in this patient group. Hence, in this thesis, I aim to investigate the course and stability of motor subtypes in older medical inpatients, and to examine the relationship between these subtypes and both baseline risk factors (such as demographics, functional ability, presence of pre-morbid dementia and comorbidity), as well as cognitive performance.

2.4. SUBSYNDROMAL DELIRIUM

In addition to full-syndromal delirium (FSD), in which patients meet criteria for delirium using diagnostic systems such as DSM, a clinical spectrum exists such that

subsyndromal delirium (SSD) describes the clinical presentation of certain delirium features without fully meeting FSD diagnostic thresholds. SSD definitions and prevalence rates have varied across research groups, with both categorical and dimensional methods being used and therefore lack of clarity still exists in relation to accurate SSD definition and diagnosis. Categorical methods for SSD definition are based on the presence or absence of key diagnostic features (60-66) whereas dimensional approaches incorporate symptom severity scores on a spectrum from absence of delirium to presence of the full-syndromal state (67-73). Our understanding of SSD is further complicated by the fact that that outside the delirium spectrum, some delirium symptoms can occur in isolation as components of illness behaviour (for example drowsiness, hypoactivity) or in clusters as part of other non-delirium diagnoses (for example hypomania, acute psychosis). Hence defining features which differentiates SSD from non-delirium presentations is important, particularly given the clinical relevance of SSD. Multiple studies have found that SSD has prognostic significance with SSD patients experiencing adverse outcomes intermediate between those with delirium and normal controls (53, 62, 65, 69, 74). The context in which SSD develops is not fully understood, but it has been suggested that SSD can exist either in isolation, without ever crossing full syndromal thresholds (75), or occur as a transitional state either preceding delirium as a prodrome, or following delirium in the post-dromal or recovery period. One study found that antipsychotic prophylaxis during SSD in post-cardiotomy patients reduced progression to FSD in the post-operative period (73), indicating that SSD may present an opportunity for delirium prevention strategies, however further work is needed in other populations.

Recently, analysis of pooled multicultural data has found that SSD is phenotypically closer to delirium than non-delirium and that core delirium features occur in SSD, albeit with milder intensity than in FSD (75), providing evidence for a dimensional spectrum of delirium presentation. Furthermore, results from our research group indicate that certain core diagnostic features (including deficits in higher order thinking and cognition, particularly attention) were the key features to differentiate between SSD and FSD, and SSD and no delirium (76). In this cross-sectional study, SSD patients with inattention had higher DRS-R98 severity and total scores than those without, and also scored higher on items related to cognition (including attention); higher order thinking; motor agitation; and on diagnostic items such as acuity of onset and severity of fluctuations. This more anchored definition of SSD recognises that although other delirium features can vary between patients with SSD (as they do in FSD), certain features are core and mandatory to SSD diagnosis, namely impaired attention span; and an acute or subacute onset of symptoms. These important features are crucial to the diagnosis and philosophy of full-syndromal delirium and so their significance in defining a milder delirium spectrum disorder is unsurprising (76).

Hence, SSD and FSD are conceptually similar, the former presenting with milder manifestations of core delirium features that do not reach FSD diagnostic criteria. Although studies as cited above have investigated the phenomenology of SSD, and notwithstanding the significance of abnormal motor behaviour in FSD, the relevance of motor subtypes in SSD has yet to be explored. Understanding the prevalence and

presentation of motor subtypes in SSD may improve approaches towards detecting SSD in the clinical setting, as motor presentations are the most clinically observable features of delirium phenomenology. Thus, one of the aims of this thesis was to measure the prevalence and stability of motor subtypes in SSD using validated motor subtyping methods in older medical inpatients.

2.5. Delirium Detection

2.5.1. Importance of Early Diagnosis

Research has highlighted the importance of early and more optimal intervention in delirium, particularly in mitigating short term-outcomes such as delirium severity and duration, however even early detection and intervention has limits in addressing the long-term burden of delirium sequelae (6). Studies have also shown that identifying delirium-prone patients and incorporating delirium prevention strategies are crucial in order to impact significantly on long-term outcomes, such as mortality, cognitive and functional decline (7), however success in achieving this requires systematic and widespread implementation of multifaceted delirium prevention programmes such that delirium is targeted as a serious healthcare issue by clinical leaders, senior hospital management, and healthcare professionals alike.

The under-recognition of delirium is one of the most serious challenges facing delirium care today for many reasons. Firstly, non-detection is associated with particularly poor prognosis, including mortality. Kakuma and colleagues (19) found

that 6-month mortality was significantly increased in older patients discharged from the ED with undetected delirium, compared to those in whom the diagnosis of delirium had been made (19). Secondly, delirium duration is directly related to poor outcomes, such that the longer a patient goes undiagnosed, the greater their risk of adverse sequelae. Gonzalez and co-workers reported an 11% increase in mortality in acute older inpatients for every additional 48 hours of delirium (18) and Kiely and colleagues found that patients with persistent delirium were almost three times more likely to die within one year than those in whom delirium resolved early, independent of other confounders (77). Furthermore, non-detection not only leads to inadequate management of delirium symptoms, but also compounds the distress experienced by relatives and carers who struggle to comprehend the sudden changes in their affected loved one without appropriate explanation from clinical staff (78, 79).

2.5.2. Barriers to Detection

The reasons for under-diagnosis are myriad, not least the complex and fluctuating clinical presentation of delirium, with clinicians potentially being deceived by symptoms that not only vary from patient to patient but also wax and wane characteristically within the same patient over the course of the day. Moreover, the more common and prognostically serious hypoactive form is more subtle to staff than the stereotypical but less prevalent hyperactive agitated form, and hence is commonly mistaken for depression. Another barrier to improved detection is that delirium is often not considered in itself a medical emergency leading to serious

healthcare, economic and personal burden, instead being viewed simply as an expression of underlying illness by medical and nursing staff. Additionally, the conventional misperception that 'confusion' is a natural phenomenon in the ill older adult, or even an element of the normal ageing process, undermines the importance of delirium as a diagnosis and hinders identification across disciplines. Lastly, another obstacle to improving delirium detection rates relates to the lack of robust and systematically applied procedures, even in those at high risk.

2.5.3. Approaches to Improving Detection

2.5.3.1. Identifying the vulnerable patient

The development of strategies for the prevention and early management of delirium has been guided by many studies of factors which increase delirium risk, so that efforts are targeted at those most vulnerable to delirium development. Despite the uncertainty in relation to the exact mechanism driving delirium pathogenesis, multiple predisposing and precipitating factors for delirium in a range of treatment settings and patient groups have been identified (80, 81). The most consistent predisposing factors independent of the underlying cause, are older age and pre-existing cognitive impairment (9). Modifying these risk factors using proactive multifaceted systematic interventions can halve delirium incidence (7), but these strategies are often spread too thinly in our under-resourced health service, as the proportion of inpatients over the age of seventy years rises in tandem with our ageing population.

In 2010, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) published a guidance document on the diagnosis, prevention and management of delirium (5), its main focus being to improve delirium care by promoting a "THINK DELIRIUM" approach for use by all healthcare professionals in their daily work. The guidelines were informed by comprehensive review of the existing literature by delirium experts and advises that all high risk patients should be monitored daily for delirium development, in order to improve detection rates. This includes all those who have any of the following risk factors: being of 65 years and over; having cognitive impairment or dementia; having a current hip fracture; or being severely unwell at risk of decompensation. Unfortunately, this classifies the vast majority of hospital inpatients as being at risk, reflective of the ubiquitous nature of delirium, but making prevention strategies difficult to incorporate in clinical practice. Efforts to refine our ability to identify patients particularly at risk could, therefore, facilitate more focused and efficient approaches towards delirium prevention and detection.

2.5.3.2. Screening and Diagnostic Approaches

Definitive delirium diagnosis is challenging due to its nuanced and commonly complex presentation. Two standard diagnostic systems are used for the diagnosis of delirium, the Diagnostic and Statistical Manual of Mental Disorders criteria (39) and the International Classification of Diseases (ICD)-10 (82). The former is the most commonly used system, both clinically and in the research sphere, as it most accurately reflects the disturbances found in delirium, however neither are easily

applicable in daily practice, requiring specific training and expertise in their use. In order to enhance the feasibility of delirium identification in a practical setting, a two-phase approach to diagnosis is now recommended by experts and advocated by the NICE guidelines (5). The first stage should entail screening for core delirium features in high-risk patients using a short, simple, sensitive instrument, and the second step should incorporate formal assessment by a trained expert of those who screen positive. Although numerous delirium screening tools have been developed, consensus is lacking as to which screening method is best. The NICE guidelines propose a screening approach based on daily monitoring for specific delirium indicators, however this method has not yet been operationalised nor validated for routine clinical use. Identifying an appropriate screening approach depends on many factors, including the clinical setting, but a paramount characteristic is that it should be highly sensitive in order to reduce the possibility of missing delirium cases. Additionally it should require minimal training, and be brief so as to avoid significantly increasing the burdensome workload of ward staff. Below, I have outlined the benefits and disadvantages of many of the existing screening and diagnostic instruments, as well as potential screening approaches which have been studied further in this thesis.

2.5.3.2.1. Confusion Assessment Method (CAM)

The most widely used screening test is the Confusion Assessment Method (CAM, see appendix A) (83, 84), which has been translated into several languages and validated in a wide range of settings, for example, intensive care (85), ED (23, 86) and long-

term care settings (62). This tool is based on DSM-IIIR (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition) criteria and was originally designed as a diagnostic instrument for non-psychiatrists. It tests for the presence or absence of key delirium features: acuity of onset, fluctuating course, inattention, disorganised thinking and altered level of consciousness, incorporating semi-structured patient interview and collateral history. Taking at least five minutes to administer, it lacks the brevity required for routine ward screening. Even more importantly, its diagnostic accuracy depends on the training level of assessors, such that half of cases are missed by minimally trained users (87). A systematic review of its accuracy in research studies reported high specificity (99%, 95% CI 87-100%) but only moderate to high sensitivity (82%, 95% CI 69-91%), cautioning against use of the CAM above best clinical judgement. Recently, an operationalised brief version of the CAM (bCAM), has shown promise as a screening approach in the ED (88), however this version needs further study.

2.5.3.2.2. The Revised Delirium Rating Scale (DRS-R98)

The DRS-R98, see appendix A, is a widely used comprehensive assessment tool which is designed for delirium diagnosis by psychiatrists. With appropriate training, it can be used successfully by other physicians, nurses and psychologists. It is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items which is used to rate symptoms over the previous 48-hour period, with higher scores indicating a greater severity of delirium. It has high interrater reliability, validity, sensitivity and specificity for distinguishing delirium from mixed neuropsychiatric populations

including dementia, depression, and schizophrenia (89, 90). Scores are applied using all available sources of information, including assessment of the patient and discussion with nursing staff and family or caregivers, and hence this instrument is far too time-consuming to be used as a screening tool.

2.5.3.2.3. The 4-AT (The 4 'A's Test)

The 4 'A's Test (4AT) was developed recently for routine use in clinical practice (91). This multidimensional instrument assesses (i) level of alertness; (ii) cognition using the AMT4 (Abbreviated Mental Test-4); (iii) attention using months of the year backwards (MOTYB); and (iv) acuity of onset and / or presence of fluctuations. It has gained traction particularly in the UK where is widely used in the acute setting. It is quick, simple to administer, requires very little training in its use, and has been found to have a sensitivity of 89.7% and specificity of 84.1% in older acute and rehabilitation patients. One disadvantage to its use as a screening test is that collateral history is required to accurately complete the test and although obtaining collateral history is central to delirium diagnosis, reliance on this information as part of a screening step is likely to hinder success in the routine setting.

2.5.3.2.4. The Nu-DESC (The Nursing Delirium Screening Scale)

A number of instruments have been developed for use by nursing staff in an attempt to capitalise on their proximity to patients over a 24-hour period, as well as to address issues with patient fatigability and potential learning effect. These tools tend

to focus on observation for changes synonymous with impending delirium. One such instrument is the Nu-DESC (The Nursing Delirium Screening Scale), an observational five-item scale which (92) measures symptoms of disorientation, inappropriate behaviour and communication, perceptual abnormalities and psychomotor retardation. It has been translated into several languages (93-96) and has been validated in several settings, including medical (92) and surgical units (97), the recovery room (98), and the intensive care unit (99), with high sensitivities and specificities calculated at 83 to 98% and 79 to 92% respectively (using DSM-IV criteria as the reference standard). Another strength is its recognition of the importance of hypoactivity, which can be difficult to detect and associated with poorer outcomes (38). One problem with the Nu-DESC is that it does not include a measurement of attention, nor consideration of the context of symptoms, such as temporal onset, and both of these features are central to delirium diagnosis (100).

2.5.3.2.5. The NEECHAM

The NEECHAM is another nursing based tool used mainly in post-operative patients (101). It incorporates the measurement of physiological markers of illness severity as well as assessment for delirium features. It takes approximately ten minutes to perform and requires training for accurate application.

2.5.3.2.6. RADAR (Recognizing Acute Delirium As part of your Routine)

The RADAR is a recently-developed tool which was devised specifically to improve feasibility in clinical settings and acceptability with nursing staff (102). This tool, which is designed for use during the medication round, contains three simple observation-based items that are intended to detect features which may indicate the presence of delirium (evidence of drowsiness; impaired ability to follow instructions; slow movements). There is no formal patient assessment, which helps to address issues such as patient acceptability, fatigability and learning effect. There is also no requirement for collateral history which ensures the test can be conducted promptly and consistently. Results from early validation studies are relatively promising given the simplicity of the instrument (sensitivity 73%; specificity 67%), although higher sensitivity would be optimum for use as a screening test.

2.5.3.3. Other Potential Screening Approaches

2.5.3.3.1. Attention Testing

Short common bedside cognitive instruments have been considered as potential delirium screening tools, for example the MMSE (Mini-Mental State Examination (103)). However, most generic cognitive screening instruments lack specificity for delirium (9) and cannot differentiate it from other cognitive disorders such as dementia and mild cognitive impairment. Although attention is affected in many disorders, including dementia, depression, and developmental conditions such as attention deficit hyperactivity disorder, it is disproportionately affected in delirium, with deficits being more global and severe. Additionally, given that inattention is a

cardinal and mandatory feature of delirium, it occurs with much greater frequency than other cognitive deficits (42). Hence, theoretically, tests of attention should have utility in ruling out those without delirium at an early stage. Objective measures of attention such as The Edinburgh Delirium Test Box have shown excellent accuracy for differentiating delirium from both dementia and cognitively intact controls (104), however devices such as this are too cumbersome for use as a screening test in a busy clinical setting. Bedside tests of attention are more observer dependent and given that attention is a basic component of cognitive function, performance on attention tests may be influenced by deficits in other domains, for example visual or auditory processing speed and motor execution. Nonetheless, bedside attention tests are simple, brief and generally require little training in their use which enhances their feasibility in busy clinical settings. Furthermore, results from recent studies indicate that they may be useful as a first step in screening for delirium (105-108). Two of the most well-recognised tests are 'WORLD backwards' and 'serial 7's' from Folstein's MMSE (103), however these are known to be particularly sensitive to educational level (109), and have not specifically been tested as delirium screening tests. Other tests such as the Months of the Year Backwards (MOTYB); Digit Span Test, the Spatial Span Forwards (SSF); the Vigilance 'A' Test, and the Digit Cancellation Test have all been found to facilitate delirium detection (105-107, 110). The visual SSF is a pattern recognition test derived from the digit span forwards (111), and may differentiate inattention due to delirium from that caused by dementia (110). The MOTYB, also known as the Months Reverse Test, is a very simple attention test which is widely used for bedside assessment. A recent study by our research group found that the Months of the Year Backwards (MOTYB), a test in

which the subject is asked to recite the months of the year in reverse order starting with December, had a sensitivity of 83.3% and a specificity of 90.8% in detecting full syndromal delirium in general hospital patients (112).

2.5.3.3.2. The Six-item Cognitive Impairment Test (6-CIT)

The 6-CIT, originally called the Six-item Orientation-Memory-Concentration Test (see appendix A), was developed by Katzman et al (113) by shortening Blessed's Mental Status Test (114) as a screening test for dementia. It is also known as the Short Orientation-Memory-Concentration Test and the Short Blessed Test. It involves three tests of temporal orientation (year; month; time of day), two tests of attention (counting backwards from twenty to one; reciting the months of the year in reverse order) and short-term memory (remember a 5-item address). It is scored out of twenty-eight with higher scores indicating more impaired cognition. It has a broad spectrum of use, having been used to screen for dementia in primary care (115); for cognitive screening in the acute setting (116); in research on Alzheimer's disease (AD) (117, 118); and in large epidemiological studies (119). It is quick to perform, requires minimal training, and with its focus on three major cognitive domains affected by delirium, in theory it could have utility as a delirium screening test.

It correlates highly with the MMSE (r^2=- 0.82to -0.926)(115, 116, 120-123), however is much shorter in duration (approximately 2-3 minutes), is less affected by educational attainment (122) and is less culturally biased (124). Other advantages

include that it doesn't require any equipment and it has less potential for interpretive error than other tests such as interlocking pentagons and clock-drawing (122). Because it is completely verbal, it can be also be used in the visually impaired (125), and those with upper limb issues. A study in nursing students showed that scoring accuracy is higher than for the MMSE (126) and another study using the 6-CIT to screen for delirium in the acute setting showed high acceptability by nursing staff (127). A small study by the same group showed that it can be reliably used over the telephone without modification (128) and is also easily translatable into other languages (122). Additionally, of importance where serial testing is required, no significant learning effect has been demonstrated (123). A patient's score on 6-CIT is, however, influenced by increasing age (123), as is seen with other cognitive tests, for example the MMSE (129).

One limitation of the test is that there is no consensus as to the most appropriate cut-off for dementia or cognitive impairment and cut-offs have hence varied from study to study. The most common cut-off proposed for the detection of dementia is 10 / 11 with sensitivities ranging from 82.5% to 90% and specificities from 86.8% to 96% (116, 121-123), however this score was chosen as optimal in these studies by favouring a high specificity over high sensitivity, so as to avoid false-positive dementia diagnoses. This cut-off is in keeping with results from Katzman's original validation study (113), where scores of more than 10 were consistent with dementia, whereas 90% of normal controls had scores of 6 or less. Brooke and Bullock (115) found the best psychometrics using a cut-off of 7 / 8 in a primary care sample of 287

patients (sensitivity 78.6%, specificity 100%) and particularly found it more sensitive than the MMSE in the detection of mild dementia. Other studies have used 8 (128) and 6 (130) respectively as cut-offs for cognitive impairment, and it is generally considered that using lower cut-offs improve sensitivity in detecting milder impairments. The most recent study published assessing the suitability of the 6-CIT as a dementia screening test was performed in primary care patients (131) and interestingly, the results are inconsistent with the other evidence to date. The study involved 72 general practitioners and 3,908 patients and using either a 6-CIT cut-off of 7 / 8 or 10 / 11, sensitivity in detecting dementia was extremely poor at 49% and 32% respectively (specificity was >90% at each cut-off). Despite the large sample, this study was limited by the fact that there was no clinical reference standard for dementia and instead diagnosis was obtained from health insurance records. Additionally, the time of diagnosis was unknown so it was not discernible as to whether the patient had dementia at time of testing with 6-CIT or not. Although, it is therefore difficult to appropriate significance to the authors' findings, these results illustrate that further research is required to assess the utility of the 6-CIT as a screening test for dementia and for other causes of cognitive impairment. Given its theoretical potential for detecting the cognitive deficits of delirium, I was interested to assess if the 6-CIT could be used to characterise the cognitive features of the delirium prodrome (Chapter 8) and also to ascertain if the instrument could be useful in screening for prevalent delirium in the emergency department (Chapter 4).

2.5.3.3.3. The Clock-Drawing Test (CDT)

Bedside tests of visuospatial function are another proposed method of delirium screening, particularly the Clock-Drawing Test (CDT, see appendix A) which is widely used in screening for cognitive impairment and dementia (132). The CDT can be dated back as far as the early 1900's as a test of constructional apraxia, however it is now recognised that performance is associated with ability in other neuropsychological domains, including visuospatial function and also perception; executive function; and verbal and semantic memory (133). There are conflicting reports as to the utility of the CDT in the detection of delirium. Some authors found it reliable for this purpose (134, 135), and others found it unsuitable for delirium screening (133, 136-139). Its advantages include that it is largely unbiased by educational level, ethnicity, language and socio-economic status and it is quick and widely accepted by physicians and patients alike (140, 141). Although multiple scoring methods exist, all of them correlate well with other tests of global cognition (136).

2.5.3.3.4. Interlocking Pentagons test (IPT)

The Interlocking Pentagons Test (IPT, see appendix A), also known as the intersecting pentagons, overlapping pentagons or pentagon copying test, is another well-known visuospatial test which requires the subject to copy a representation of two interlocking pentagons with a quadrilateral figure formed by their overlapping corners. It initially gained popularity as one of a set of nine figures in the Bender-Gestalt test used to assess for specific developmental problems in children (142).

Since then it has been incorporated into other cognitive tests including the MMSE (Mini-Mental State Examination) in which it is scored in a binary fashion (143), and its modified version (Modified Mini-Mental State or 3MS) in which the scoring of the pentagons was altered to a ten-point scale (144). The most commonly applied scoring system remains the binary method. In a study of geometric copying and handwriting tasks in a community-dwelling population of 668 older patients, the IPT was one of the most sensitive tests in detecting small changes in cognition (145). Impairments on the IPT can differentiate between patients with Dementia with Lewy Bodies (DLB) and Alzheimer's Dementia (146-149) and can predict cognitive decline in Parkinson's disease patients with normal cognition and with mild cognitive impairment (150-153). Given the phenomenological similarities between DLB and delirium, it is possible that this test may have utility in detecting delirium, however to our knowledge, no studies have yet examined this.

2.6. Delirium Prodrome (10)

One of the central features of delirium, using any of the available diagnostic criteria, is that it is acute in onset, with symptoms typically appearing over hours to days. However, the concept of a delirium prodrome has been emerging in the literature over the past number of years. The term "prodrome" is defined by the Oxford English Dictionary as "an early symptom indicating the onset of an illness" and is well-recognised in other medical conditions such as migraine, epilepsy, and syncope. In delirium, this phase is thought to represent the emergence of a range of features before the patient meets criteria for a diagnosis of full-syndromal delirium. To date,

there have been very few studies focusing on the delirium prodrome, most designed primarily for other purposes. Other authors have given anecdotal descriptions based on clinical experience. Hence a true understanding of the context and characteristics of the delirium prodrome is limited. One of the first references to this prodromal phase was made by Lipowski in his seminal work “Delirium: Acute Confusional States” published in 1990 (154), in which he suggested that the delirium prodrome was characterised by disturbances in concentration and perception; fatigue and sleep-wake cycle disruption; restlessness; irritability; malaise; as well as hypersensitivity to light and sound (154). Subsequent studies of the prodrome describe a varied range of features, which can broadly be considered in four major categories: cognitive features, non-cognitive neuropsychiatric features, somatic or physical features, and affective or emotional features. The latter two categories can be considered as one category of behavioural features. Some prodromal features are recognised as part of the delirium cluster, however they can occur in the absence of full delirium diagnostic criteria and may be considered elements of a subsyndromal delirium presentation (see below), depending on their nature and severity. Other suggested prodromal symptoms are less related to delirium phenomenology and are more somatic or emotional in nature. Hence, the features of the prodromal phase could be considered even more heterogeneous than the delirium itself, increasing the challenge of detection.

Another aspect of the delirium prodrome which requires clarification is its duration in relation to the onset of delirium. Lipowski suggested that a longer prodrome

preceded delirium secondary to systemic illness or metabolic abnormalities, and that delirium secondary to mechanical or surgical aetiology was likely to be more acute in onset (154). Conversely, studies in hip surgery populations have found that many patients present with prodromal features three to four days before delirium (155, 156). A similar duration has been reported in bone marrow transplant (BMT) patients (157, 158), whereas in general hospital patients, duration ranged from one to nineteen days (159), with a mean of 2.7 days. Prodromal duration is reported as longer in long-term care patients (160), however in this study, patients were only assessed weekly and hence accurate assertions as to the duration of the prodromal phase cannot be made. A consistent observation is that prodromal features tend to increase in number and severity as delirium proximity increases, best illustrated by the findings of Fann and colleagues (157), which shows a precipitous rise in all prodromal features from four days prior to delirium diagnosis. In a study in hip fracture patients by Duppils and co-workers, behavioural changes were different and more repeatedly observed in those with emerging delirium compared to those who remained delirium-free (161). Additionally, the frequency and intensity of behavioural changes increased as delirium approached.

Improved understanding of the characteristics and duration of this prodromal period may facilitate strategies that promote even earlier detection of delirium. It is also possible that intervention in this prodromal period may prevent delirium occurrence, however this hypothesis needs study. Below, I have outlined the various potential aspects of the delirium prodrome, based on the existing literature, considering them

as elements of the four major domains mentioned above. Additionally, characteristics and findings from the existing studies of the delirium prodrome have been outlined in table 1, and the suggestions from case studies and case series are summarised in table 2.

2.6.1. COGNITIVE SYMPTOMS

2.6.1.1. Inattention / clouding of consciousness

Considering the importance of impaired attention span in relation to delirium diagnosis, it is unsurprising that inattention (either distinctly or as an element of the concept known as 'clouding of consciousness') is the most commonly referenced feature of the delirium prodrome. In his 1990 textbook, Lipowski describes how delirium came to be viewed as a disorder of consciousness in the late nineteenth century, highlighting how the term 'clouding of consciousness' evolved to describe disruption in concentration and attention associated with abnormal level of alertness (154). His clinical report of the prodromal state referred to a wide variety of features including poor concentration. Likewise, a subjective experience of the delirious state, written by Crammer, a retired emminent psychiatrist, describes a 'declining awareness of the environment' as delirium emerged (162) and Mermelstein reports a prodrome consisting of 'difficulty focusing' in one patient in a series of three cases of clarithromycin-induced delirium (163).

Studies of hip fracture patients have found that inattention occurs with variable frequency in the prodromal period before delirium development. De Jonghe and colleagues, using the digit span and the Delirium Rating Scale, found that inattention occurred in over half of pre-delirious patients two days before diagnosis, rising to over 80% of cases on the day before delirium onset (155). Similarly, Lee and colleagues found using the Korean version of the Revised Delirium Rating Scale (K-DRS-R98), that inattention occurred as early as four days prior to delirium diagnosis in a Korean cohort of post-operative hip surgery patients (156). Duppils & Wikblad used a patient observation protocol to assess hip fracture patients for the development of behavioural changes in the post-operative period and reported that although clouding of consciousness did not feature prominently in older hip surgery patients, when it did occur it was only in those with emerging delirium (161).

Inattention has also been reported as a frequent prodromal feature in other populations, for example older medical and surgical inpatients and in Bone Marrow Transplant (BMT) patients. Levkoff and coworkers used the Delirium Symptom Interview (DSI) to examine the onset and characteristics of delirium and its prodrome in older hospitalised patients and reported prodromal inattention in 15.9% of 91 cases of delirium in the prodromal phase (159). Fann and colleagues used detailed assessments of mood (Profile of Mood States), pain (numerical pain score ranging from one to ten), and delirium features (DRS and Memorial Delirium Assessment Scale, MDAS) to characterise prodromal features in a population of 90 BMT patients, half of whom went on to have a delirium episode (157). Prodromal

decline in attention span and cognition was observed in the delirium group as delirium approached. Beglinger and co-workers used a comprehensive battery of neuropsychological tests to prospectively examine the cognitive performance of 19 delirious BMT patients compared to 35 non-delirious BMT patients and 10 healthy controls (158). Tests administered at baseline pre-transplantation included Modified Mini Mental State Examination (3MS); Trail-making tests (TMT) A and B; The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); The Wechsler Abbreviated Scale of Intelligence (WASI); and a visual analogue scale of thinking clarity. The groups were comparable for age, education level and WASI IQ at baseline. Subsequently, participants were assessed twice weekly for up to four weeks following transplantation, using an abridged version of the baseline assessment (TMT; 3MS; RBANS List Learning, Coding, Fluency, List Recall and List Recognition subsets). Those who developed delirium demonstrated a steady decline in scores on all measures throughout the post-transplant period, and particularly scores on TMT B, list recall and coding dropped significantly in these patients from the second-last visit to the visit just before delirium was diagnosed. This suggests that a prodromal period consisting of acquired impairments in attention (especially divided attention, complex scanning and visual tracking), psychomotor speed, learning and memory before delirium onset in BMT patients.

2.6.1.2. Disorientation

Disorientation is another frequently observed cognitive feature of emerging delirium, being one of the key prodromal features reported by Levkoff et al in a

prospective study of 325 older general medical and surgical patients (159). Of 91 cases of delirium, 69.2% experienced a prodrome and almost half of these patients experienced disorientation in the prodromal phase, measured using the DSI. Disorientation has been a consistent feature of the delirium prodrome in hip surgery patients. Duppils and Wikblad found that disorientation occurred with significantly higher frequency in patients with imminent delirium in the 48 hours prior to diagnosis, compared to their non-delirious counterparts. Furthermore, disorientation was a prominent feature in these prodromal patients (161). De Jonghe and co-workers found that disorientation preceded delirium development by as early as four days in post-operative hip fracture patients and became increasingly prevalent as delirium approached (155), a finding which was replicated in a similar Korean cohort (156). In addition to these prospective prodromal studies, a 1996 report written by Eden and Foreman described prodromal disorientation in a 69-year old elective renal endarterectomy patient with emerging delirium in the intensive care unit (ICU) (164).

2.6.1.3. Registration and Memory impairment

Deficits in registration and memory have also been described in the delirium prodrome in some of the aforementioned studies. Both short- and long-term memory impairments occurred frequently in the prodrome to delirium in de Jonghe and colleagues' hip fracture cohort (155). Lee and co-workers found that long-term memory deficits appeared first and persisted throughout the prodromal phase, while short-term memory deficits appeared just prior to delirium onset (156). Significant

decreases in immediate recall and long-term memory were recorded during the last assessment prior to delirium diagnosis in BMT patients (158), and in a recent study of long-term care patients, declining performance in registration (measured by requesting immediate recall of three words) was significantly associated with imminent delirium (160). Furthermore, Crammer's report of his subjective experience of delirium describes the onset of retrograde amnesia and impaired registration prior to delirium emergence (162).

2.6.1.4. Visuospatial deficits

Visuospatial impairments seem to be less prevalent and less prominent than other features in the delirium prodrome, however most reports do not give details on how this domain was tested. In the comprehensive neuropsychological study conducted by Beglinger and colleagues, a decline in TMT B in prodromal BMT patients was noted but this may reflect other cognitive domains including poor visuomotor processing speed, attention and working memory, and not necessarily just visuospatial impairment (158). Mild prodromal decline in visuospatial function has been reported in hip surgery patients however the deficit observed was of less magnitude than that in other cognitive domains (156).

2.6.2. NON-COGNITIVE NEUROPSYCHIATRIC FEATURES

This domain includes features which occur as part of the delirium phenomenological spectrum. Almost all recognised non-cognitive neuropsychiatric symptoms have

been reported to varying degrees in the prodromal phase. Perceptual disturbances; psychomotor abnormalities; and sleep-wake cycle disruption are the most prevalent of these features, whereas delusions; affective lability; disorders of speech and thought; and evidence of fluctuations have been reported less frequently.

2.6.2.1. Motor changes

Psychomotor disturbance has long been recognised as central to delirium presentation (40, 42), and hence it is intuitive that motor change would be observed in the prodromal phase. Some studies have described a prodrome characterised by hypoactivity, however, restlessness or hyperactivity has predominated in the prodromal literature. This may be because hypoactivity is more subtle to the untrained eye, does not present the same practical management problems for ward staff that motor agitation causes and hence may be under-reported in some studies.

Levkoff and colleagues reported prodromal psychomotor changes in 54% of older hospitalised patients who went on to develop delirium, (159) and hyperactive features (particularly restlessness), were slightly more prevalent than hypoactive features. Restlessness has featured prominently in case studies or accounts of the prodromal phase, and again this may be because it is more commonly noticed than hypoactivity. Lipowski refers to restlessness in his anecdotal characterisation of the delirium prodrome (154). In Eden and Foreman's ICU case study, it was one of initial harbingers of impending delirium, magnifying in severity as delirium approached

(164). Hip fracture patients have also demonstrated prodromal increases in psychomotor agitation occurring twice as frequently than in non-delirious controls (156, 161). In a study of 20 coronary care unit patients, almost all in the delirium group (n=10) had evidence of hyperactivity during the prodromal phase (165), however the small numbers in this study are limiting. Elective cardiac surgery patients with imminent or early delirium were found to have significantly higher levels of hypoactivity (using wrist actigraphy) in the first 24 hours post-operatively, when compared to those who did not develop delirium, however it was unclear from the report whether the changes were recorded in the early stages of full-syndromal delirium or in the prodromal phase (166).

2.6.2.2. Sleep-wake cycle disturbance

Disruptions in the sleep-wake cycle have also been described in the delirium prodrome, though generally with less consistency. One study of hip surgery patients found that sleep-wake cycle disturbances occurred significantly more frequently in the delirium group, four days prior to delirium onset (156), whereas a similar study found that the meaningful differences between pre-delirious and non-delirious patients only occurred on the day before delirium development (155). A third study in hip fracture patients did not find significant prodromal abnormalities in sleep-wake cycle, although this study differed greatly from the other two with respect to methodology and rather than using formal delirium tools to characterise delirium and its prodrome, employed only observational techniques to assess for prodromal features (161). In a small study of cardiology patients there was a significant

difference between non-delirious and prodromal patients in relation to sleep disturbance (165), and in general hospital patients, Levkoff and colleagues reported that 25.4% of prodromal patients experienced sleep-wake cycle problems, especially in relation to getting to sleep and staying asleep during the night (159). Nocturnal insomnia has also been described in anecdotal reports of the delirium prodrome (154, 164).

2.6.2.3. Perceptual abnormalities

Although other cognitive and non-cognitive features occur with more frequency in the prodromal phase, perceptual disturbance is the most common psychotic feature of the delirium prodrome, and the presence of these abnormalities in this period presents the most convincing evidence for a prodromal phase which is pathological and not simply the manifestation of illness behaviour. Prodromal perceptual disturbances have been reported to varying degrees in studies of older general hospital patients (159); hip surgery patients (156, 161); BMT patients (157); and long-term care patients (160). Lipowski maintained that a spectrum of perceptual abnormalities may occur in the prodromal phase, from mild disorders of perception such as vivid dreams; nightmares; and difficulty differentiating between dreaming and waking imagery to more severe disturbance such as fleeting illusions and disturbing hallucinations. Furthermore, he hypothesised that these latter experiences may contribute to a deterioration in the patient's sense of control over cognitive processes and the ability to comprehend their environment.

2.6.2.4. Other non-cognitive symptoms

Other delirium symptoms have been reported in the prodromal phase but with less consistency. In one case of clarithromycin-induced delirium, 'confused speech' was reported in the prodromal period (163). Incoherent speech and tangentiality occurred respectively in 49.2% and 22% of prodromal hospitalised older patients (159) and incoherence occurred up to four days before delirium onset in one study of hip fracture patients (155). However, in Duppils & Wikblad's study, incoherent speech occurred with practically equal frequency in prodromal and non-delirious hip surgery patients alike (161). Furthermore, speech disturbance was not a significant prodromal feature in the Korean cohort of hip surgery patients. Instead this research group found that that disorganised thinking, delusions and lability of affect occurred in the prodromal phase (156). New-onset disorganised thinking occurred in the prodrome in the long-term care cohort studied by Voyer and co-workers (160), whereas Fann and colleagues reported evidence of fluctuations in BMT patients (157).

2.6.3. SOMATIC OR PHYSICAL FEATURES

A wide spectrum of somatic features have been reported as occurring in the delirium prodrome, however their nature and frequency vary disparately from study to study. Pain or discomfort is reported with the most consistency. In an early study of 100 consecutive cases of delirium referred to liaison psychiatry, Sirois observed retrospectively that unexplained headaches heralded delirium onset in a number of patients (167). Back pain and discomfort at catheter sites has been reported in

prodromal coronary care patients (165). The most robust assessment of prodromal pain was conducted in BMT patients by Fann and colleagues who found that pain (measured using a ten-point Likert Scale) preceded delirium by approximately three days, increasing in intensity as delirium emerged (157). Other somatic prodromal features have been described anecdotally by Lipowski, such as fatigue, malaise and hypersensitivity to light and sound (154), however these features have not been examined in a prospective fashion.

2.6.4. Affective or emotional symptoms

One of the reasons that the delirium prodrome has not yet been fully characterised, despite being mooted as a concept for decades, is that there are elements that challenging to define and quantify. Anecdotally many clinicians, and indeed family members, have noted retrospectively that a patient may have seemed 'not quite him / herself' or 'not quite right' in the days before delirium onset. These observations are usually made with the benefit of hindsight as the signs and symptoms considered are often vague, non-specific and even nebulous, such that detecting or pinpointing them prospectively is difficult. Studying the existing literature, the vast majority of suggested non-specific features include an element of emotional or affective change. These reported emotional changes include irritability (154, 168), anxiety (164, 165), fear (168), and dysphoria (169). Anxiety is the most prevalent, documented in cardiology patients (165), in Eden and Foreman's case study of an ICU patient (164), and prominently in one study of hip surgery patients (161), in which it manifested as 'urgent calls for attention' in the prodromal period. Furthermore, Sirois reported

that complaints of 'general uneasiness' preceded delirium in many cases (167), whereas apathy, dysphoria and withdrawal were noted in the delirium prodrome in children and adolescents in an urban sub-Saharan setting (169). The most comprehensive study of prodromal mood and emotional change was conducted in BMT patients by Fann and colleagues (157), using the Profile of Mood States, a valid and reliable measure of distress and mood disturbance. It has six subscales (Tension-Anxiety; Depression-Dejection; Anger-Hostility; Vigor-Activity; Fatigue-Inertia; Confusion-Bewilderment), from which composite scores of affective distress (the sum of Tension-Anxiety; Depression-Dejection; Anger-Hostility) and fatigue less vigor (Fatigue-Inertia minus Vigor-Activity) can be calculated. In this study, an increase in all negative emotional states, as well as the two composite scores, were observed in the five days before delirium onset and continued to rise for a further number of days into the delirium episode before abating. These results indicate that delirium is preceded by a marked rise in distress and fatigue levels in the prodromal period in BMT patients (157). Further study in this area is required in other clinical populations.

2.6.5. PRODROME OVERVIEW

In summary, the delirium prodrome is suggested to consist of a multitude of features which vary from study to study, hampering efforts to develop a definition. Some features appear consistently across the literature (e.g. inattention), whereas others are observed in only one study (e.g. headaches). Figure 2 is a schematic representation of the proposed prodromal features based on the literature to date.

Given that SSD can occur in the prodromal period as a transitional state towards FSD, some may argue that the delirium prodrome is simply a subsyndromal transitional state, however the prevalence of non-delirium features in the prodromal phase supports the view that the prodrome is a conceptually distinct entity which may include subsyndromal features as part of its presentation. Furthermore, although many of the described somatic and emotional features could be influenced by other patient factors such as illness behaviour, understandable anxiety in relation to prognosis, and low mood caused by reduced function, some studies have found that these features occur more frequently and with more intensity in patients with emerging delirium than those with no delirium. Nonetheless, further work in this area is required to define and characterise the delirium prodrome, particularly in the most vulnerable groups, such as older hospitalised patients.

2.7. SUMMARY

Delirium is a serious, highly prevalent condition which impacts significantly on medical, social and personal outcomes, as well as on increasingly strained health budgets. Our ageing population is manifest across all medical settings, and generates higher case complexity and increased rates of all age-related conditions, especially the 'Geriatric Giants' such as delirium. Delirium shares risk factors with other such frailty syndromes such as falls, and hence, enhanced delirium care is a key factor in delivering better quality healthcare to this growing proportion of older patients. Early identification of those particularly at risk would be helpful in streamlining preventative efforts towards those who need it most, however some risk

stratification methods are over-inclusive for busy clinical workloads and require refining for practical implementation. Delirium prognosis is linked to delirium duration, emphasising the importance of early detection and intervention, yet we are still hindered by poor awareness and understanding of delirium on the ground. Delirium diagnosis requires training and experience, however delirium screening, using simple yet sensitive screening methods, is now recognised as the most efficacious way to improve detection rates. Although a number of diagnostic approaches have been suggested, it is still undecided as to which approach is best.

Even more so than early detection and intervention, strategies to prevent delirium have potential to yield great long-term benefits for patients and healthcare systems but such strategies must be multifactorial, system-wide and imbedded in the philosophy of our institutions in order to be effective. Understanding early indicators of delirium, specifically the prodromal features, may promote the development of targeted approaches to identify those in the early stages of delirium. Although, the existing work in this area has described the landscape, further research is required to definitively characterise this prodromal period, especially in older medical inpatients, a particularly vulnerable group. Once we fully comprehend the clinical nature of the delirium prodrome, we can then move our research focus towards investigating if intervention during this prodromal phase can impact on prognosis. Thus, prospective studies of incident delirium with particular focus on characterising the delirium prodrome are required as a starting point in understanding its clinical significance.

Table 1: Summary of studies of the delirium prodrome (10)

3MS: Modified MMSE; APACHE II: Acute Physiology and Chronic Health Evaluation II; BI: Modified Barthel Index; BC(s): Behavioural change(s); BMT: Bone Marrow Transplant; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; CCU: Coronary Care Unit; DSI: Delirium Symptom Interview; DRS: Delirium Rating Scale; DRS-R98: Revised Delirium Rating Scale; DSM-III: Diagnostic and Statistical Manual for Mental Disorders (3rd Edition); DSM-IIIR: Diagnostic and Statistical Manual for Mental Disorders (3rd Edition)- Revised; DSM-IV: Diagnostic and Statistical Manual for Mental Disorders (4th Edition); EEG: Electroencephalogram; HDS: Hierarchic Dementia Scale; K-DRS-R98: Korean version of the Revised Delirium Rating Scale; LTM: Long-term memory; MDAS: Memorial Delirium Assessment Scale; MMSE: Mini Mental State Examination; MMSE-K: Korean version of the MMSE; ns: not significant; POMS: Profile of Mood States; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; SD: Standard Deviation; STM: Short-term memory; TMT A and B: Trail Making Tests A and B; WAIS: The Wechsler Abbreviated Intelligence Scale

	Study design	Population	No. of cases	Reference standard (delirium)	Assessments used	Frequency of Assessments	Outcomes	Prodromal features	Prodromal duration
Sirois, 1988 (167)	Retrospective cohort study	100 liaison psychiatry referrals	100	DSM-III criteria	Not specified	Not specified	Not specified	Headaches; general uneasiness.	Not specified
Levkoff et al, 1994 (159)	Prospective cohort study	325 older medical and surgical inpatients	91	DSI	DSI	Daily	69.2% of cases experienced a prodrome.	Changes in motor activity, perception, sleep and speech; thought disorder; disorientation; inattentiveness.	Range 1-19 days Mean 2.7 days (SD 3.3)
Matsushima et al, 1997 (165)	Prospective cohort study	20 CCU patients	10	Psychiatry assessment DSM-III-R criteria	MMSE; EEG and eye movement recordings; Assessment of clinical symptoms	Daily on days 1,2,3 and 4 of admission to CCU and a subsequent control recording	Slowing of background EEG activity and increased R and RS group eye movements in delirium group.	Anxiety ($p<0.05$); increased body activity ($p<0.05$); sleep disturbance ($p<0.05$); slowing of background EEG activity ($p<0.005$).	1-3 days

	Study design	Population	No. of cases	Reference standard (delirium)	Assessments used	Frequency of Assessments	Outcomes	Prodromal features	Prodromal duration
Duppils, et al 2004 (161)	Prospective, descriptive observational study	103 older hip surgery patients	32	DSM-IV criteria	Baseline MMSE; structured observation protocol assessing for BC(s)	3 to 8 times daily	BC(s) were more frequent in delirium group.	Disorientation ($p<0.05$); urgent calls for attention ($p<0.05$); increased psychomotor activity (ns); perceptual disturbance (ns).	Up to 48 hours
Fann et al, 2005 (157)	Prospective cohort study	90 BMT patients	45	DRS	DRS, MDAS, POMS, numerical pain score (0-10)	Three times weekly	Factor analysis revealed a 3-factor structure: psychosis-behaviour; cognitive; mood-consciousness, elements of which became apparent in the prodromal phase.	Impairments in attention; perceptual disturbance; changes in cognition; evidence of variability of symptoms; pain; distress symptoms.	5 days
De Jonghe et al (155)	Prospective cohort study	101 older hip fracture patients	66	DSM-IV criteria	MMSE, DRS-R98, Digit span	Daily	Marked increase in mean DRS-R98 scores on the day before delirium.	Disorientation; difficulty concentrating; memory impairment; incoherence.	1-3 days

	Study design	Population	No. of cases	Reference standard (delirium)	Assessments used	Frequency of Assessments	Outcomes	Prodromal features	Prodromal duration
Osse et al, 2009 (166)	Prospective cohort study	70 older elective cardiac surgery patients	38	CAM-ICU	Actiwatch® actigraphy on non-dominant wrist	Continuous data for 1st post-operative day and night	Number of immobility minutes was higher and mean activity level was lower for the delirious group compared to non-delirious group	Lower nocturnal mean activity levels ($p<0.05$); reduced restlessness ($p<0.05$); higher immobility minutes (ns); lower daytime mean activity levels (ns).	Unclear if prodrome or actual early delirium
Beglinger et al, 2010 (158)	Prospective case-control study	54 BMT patients 10 healthy controls	19	Unclear Used DRS; DRS-R98; MDAS	3MS, TMT A and B; RBANS; WAIS; a visual analog scale of thinking clarity	Twice weekly	TMT B, List recall, and coding z-scores (from RBANS) showed a significant drop from the second-last visit to the visit just before delirium.	Deficit in psychomotor speed; impairments in learning, memory, attention Slight increase in DRS and MDAS scores prior to delirium onset.	2-5 days

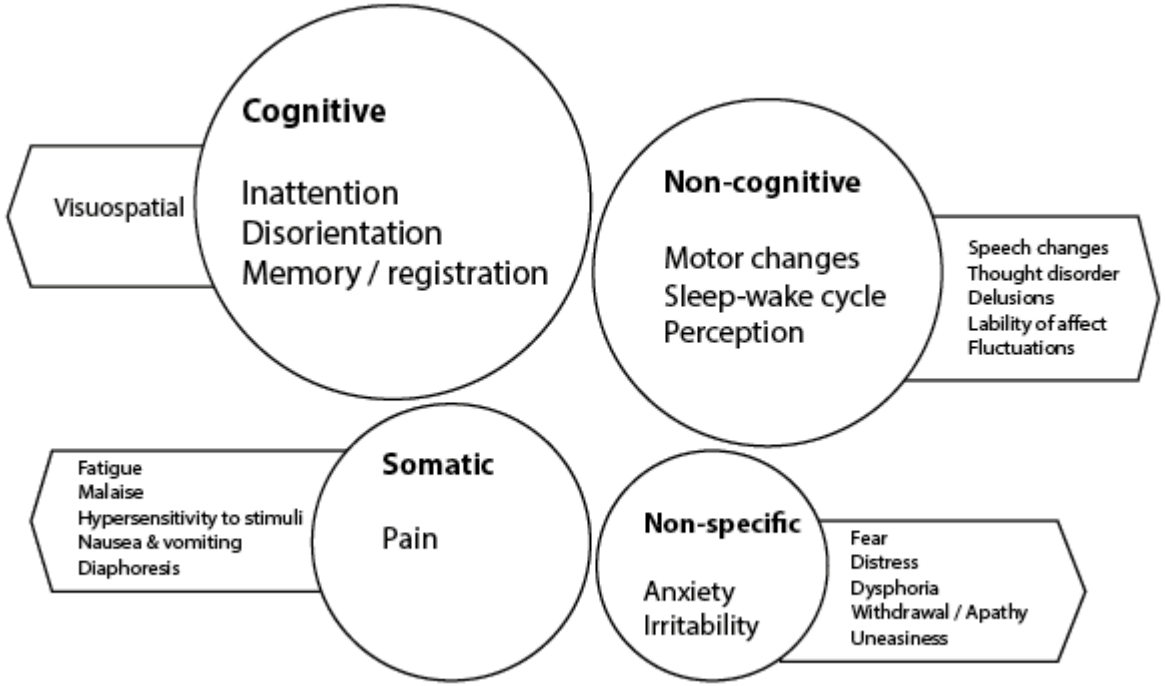
	Study design	Population	No. of cases	Reference standard (delirium)	Assessments used	Frequency of Assessments	Outcomes	Prodromal features	Prodromal duration
Lee et al, 2011 (156)	Prospective cohort study	65 older hip surgery patients	18	DSM-IV and K-DRS-R98	K-DRS-R98; MMSE-K; APACHE III	Daily until day 5 post-operatively.	Increasing K-DRS-R98 symptoms and severity scores as delirium approached with no change in the non-delirious group.	Delirium day -4: sleep-wake, thought process, orientation, attention, LTM impairment; delirium day -3: lability of affect; delirium day -2: perceptual disturbances, hallucinations and visuospatial ability; delirium day -1: delusions, motor agitation, STM impairment.	1-4 days
Voyer et al, 2012 (160)	Nested case-control study	593 LTC patients	85	CAM	MMSE; HDS; BI; CAM	Weekly	There were more new-onset delirium symptoms prior to delirium, but the prevalence was still very low (<15%)	Perceptual disturbances (9.4%); disorganised thinking (8.3%) Impaired registration (14.2%)	<2 weeks

Table 2: Case studies describing an apparent prodromal period (10)

Case Studies	Type of report	Setting or Patient Group	Number of cases	Prodromal features	Prodromal duration
Eden et al, 1996 (164)	Case study	Intensive Care Unit	1	Patient was described as having restlessness, anxiety, nocturnal insomnia, and intermittent disorientation prior to delirium diagnosis.	3 days
Mermelstein, 1998 (163)	Case series	Clarithromycin-induced delirium	3	One patient had a apparent prodrome consisting of difficulty focusing and confused speech.	24 hours
Crammer, 2002 (162)	Case report	Intensive Care Unit (subjective experience)	1	This retired psychiatrist described experiencing retrograde amnesia, a declining awareness of the environment and impaired registration before the onset of delirium.	At least 24 hours
Hatherill et al, 2010 (169)	Prospective case series	Paediatric referrals to consultation liaison psychiatry (Sub-Saharan Africa)	23	22% (n=5) patients presented with an apparent prodrome. Features included apathy, dysphoria and withdrawal.	A few days to a week or more

Figure 2: A schematic representation of the prodromal features of delirium, based on prominence in the existing literature (10)

The most consistent features are in circles, the size of the circle representing the amount of evidence.



3. METHODS

3.1. SETTING

This study was a prospective observational cohort study and was conducted in two acute teaching hospitals in Cork city (Cork University Hospital and Mercy University Hospital). I spent nine months recruiting patients from the Mercy University Hospital (MUH) (Oct 2011- April 2012 and June- July 2012) and 12 months recruiting in Cork University Hospital (CUH) (Aug 2012 – Aug 2013). Recruiting commenced in MUH because, it being the smaller hospital with a fewer number of daily medical admissions, there was more time for me to manage the patient load while refining study processes.

3.2. SELECTION OF THE STUDY POPULATION

3.2.1. INCLUSION AND EXCLUSION CRITERIA

I performed formal delirium assessment on assenting patients admitted under the medical services aged 70 years and older, within 36 hours of admission. This assessment included semi-structured interview with the patient, followed by collateral history from both a nearest relative or caregiver and a member of nursing staff responsible for the care of the patient in question. Patients were excluded from initial assessment if they refused assessment, were admitted electively with a planned length of stay of less than 48 hours, or if their death was considered imminent. All other patients were eligible for initial assessment. In some cases initial

assessment took place but formal delirium assessment was impossible due to severe communication difficulties (e.g. severe dysphasia, severe non-communicative dementia) or coma. These patients were excluded from further assessment, although demographic data was collected from all excluded patients for my records. Patients who were eligible for inclusion were then invited to participate in the study and informed consent was sought.

3.2.2. STUDY SAMPLE

The study sample consisted of non-consecutive patients recruited from Monday to Friday during the recruitment period, however patients were not recruited on every weekday during the study period. Because of the longitudinal nature of the study and the fact that I was working alone, I was only able to assess a certain number of participants at any given time. At points during study recruitment, I would be unable to recruit more patients until current participants either were discharged, withdrew, or completed the study protocol. Hence, recruitment days varied greatly depending on the number of admissions and the proportion excluded following initial assessment.

3.3. STUDY PROCEDURES

3.3.1 RECRUITMENT PROCESSES

Recruitment processes were slightly different in both hospitals. When recruiting in MUH, on a recruitment morning I obtained a list of patients admitted through the

Emergency Department (ED) from the ED administrative staff. This list was manually prepared using patient labels and listed patient details, admitting consultant and current ward. In addition to this list, I also checked for admissions to the Geriatric Medicine ward, as in MUH some emergency patients are admitted directly there. In CUH, the electronic admissions system was more accessible and on recruitment mornings, I accessed the hospital admissions system to ascertain a list of medical patients over the age of 70 years admitted within the previous 36 hours. This list incorporated both emergency and elective admissions. I then approached the patients to invite them to participate in the study.

3.3.2. Screening Assessment

Patients eligible for inclusion were assessed for delirium within 36 hours of admission to detect prevalent delirium on admission. This screening assessment consisted of a semi-structured interview with the patient, using the Confusion Assessment Method (CAM) (83) and the Revised Delirium Rating Scale (DRS-R98) (90) and collateral history from a caregiver or nearest relative, and from nursing staff. Other tests included the Six-item Cognitive Impairment Test (6-CIT); the Spatial Span Forwards (SSF); and tests of visuospatial function including the Clock-Drawing test (CDT); interlocking pentagons (IPT), from the Standardised Mini Mental State Examination (SMMSE) (170); and a set of questions developed to assess visuospatial function verbally (see below). The motor activity profile was defined using the four-item Delirium Motor Subtype Scale-4 (DMSS-4). Potential prodromal symptoms were

ascertained using a novel Prodromal Checklist, the development of which will be described later.

3.3.2.1. Confusion Assessment Method

This tool (see appendix A) has been described in Chapter 2 (Section 2.5.3.2.1). Formal training is required for accurate usage. I had already undergone expert-led CAM training based on the CAM training manual (171) and had conducted two studies using this instrument as an assessment tool, prior to commencement of this study (1, 172). For details on how I scored the individual items in the CAM, please see appendix B.

3.3.2.2. Delirium Rating Scale Revised-98

This instrument (see appendix A) has been introduced in Chapter 2 (Section 2.5.3.2.2.). The DRS-R98 is a widely-used 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. The 13-item severity section can be scored separately from the 3-item diagnostic section; their sum constitutes the severity scale score (0-39). It rates symptoms over the previous 48-hour period and higher scores indicate a greater severity of delirium. The three diagnostic items are used to contextualise the symptoms identified. The score from these three items are then added to the severity scale score to give the DRS-R98 total score. Severity scores of ≥15 and / or total scores ≥18 have been shown to be consistent with a diagnosis of delirium (90). All available sources of information, including assessment of the

patient and discussion with nursing staff and family or caregivers is considered in rating each item. Patient assessment takes approximately 15 minutes. The DRS-R98 is designed to be used by psychiatrists, however with appropriate training in evaluating psychiatric phenomenology in medically ill patients; other physicians, nurses and psychologists can become competent in using it. It has high interrater reliability, validity, sensitivity and specificity for distinguishing delirium from mixed neuropsychiatric populations including dementia, depression, and schizophrenia (110). In July and August 2011, I underwent specific training in this tool with Prof. David Meagher in Limerick, based on the DRS-R98 administration manual written by Prof. Paula Trzepacz, the instrument's creator (173) and learned how to elicit evidence of abnormalities when present. Please see appendix B for details on how I scored each item throughout the study.

3.3.2.3. Delirium Motor Subtype Scale-4 (DMSS-4)

The Delirium Motor Subtype Scale-4 (DMSS-4, see appendix A) is a four-item data-derived scale developed by Prof. David Meagher (38). Further detail on its development is available in Chapter 2 (Section 2.3). It is used to classify whether a patient meets criteria for one of the delirium motor subtypes, which are categorised as hypoactive, hyperactive, mixed or no subtype. A patient is considered to fit the hypoactive subtype if they have at least one hypoactive feature present and no hyperactive features. Conversely, to fit the hyperactive subtype, the patient must have at least one hyperactive feature and no hypoactive features. If a patient presents with one or more features from each group, they have a mixed profile and

if they have no feature from either group, they are considered not to have a motor subtype. In this study, the DMSS-4 was scored by questioning the nursing staff, allowing for observations made during patient interview. The DMSS-4 was used to assess all patients on a daily basis irrespective of their delirium status.

3.3.2.4. The Six-item Cognitive Impairment Test (6-CIT)

The 6-CIT is discussed in detail in Chapter 2 (Section 2.5.3.3.2.) (113). It involves three tests of temporal orientation (year; month; time of day), two tests of attention (counting backwards from twenty to one; reciting the months of the year in reverse order) and short-term memory (remember a 5-point address), see appendix A.

3.3.2.5. Spatial Span Forwards

The visual Spatial Span Forwards (SSF) is a pattern recognition test based on the digit span forwards (111), and has recently shown utility in identifying inattention in patients with delirium versus those with dementia (110). The SSF is performed using an A5-sized piece of white card with eight red squares (each measuring 1.5cm^2) evenly spaced over three rows (configuration three, two, three; landscape; see appendix A). Predetermined sequences are tapped out for the patients to replicate. The test begins with a sequence of two squares and the sequence increases in number with each correct iteration, up to a maximum sequence of seven. Two attempts are allowed at each level using different predetermined sequences. In

general, patients who are unable to correctly repeat a sequence of five are considered to have failed the test.

3.3.2.6. Clock-Drawing Test

The Clock-Drawing Test (CDT, see appendix A) has also been described in Chapter 2 (Section 2.5.3.3.3.). There are multiple methods for scoring the CDT. In this study, we used a 15-point scoring method from the QMCI (Quick Mild Cognitive Impairment screen), a tool developed to differentiate between mild cognitive impairment and normal controls (174). Using this method, the subject is given a pre-drawn circle and is requested to draw in the numbers and set the time at 'ten past eleven'. A transparent template, designed to facilitate inter-rater reliability, is used to guide scoring of the placement of the numbers and hands (175), see appendix A. The score ranges from 0 to 15 with lower scores indicating greater degree of impairment.

3.3.2.7. Interlocking Pentagons Test (IPT)

The Interlocking Pentagons Test (IPT, see appendix A), described in Chapter 2 (Section 2.5.3.3.4) can be scored either in a binary fashion, as in the MMSE (143) or on a ten-point scale (144), utilised in the Modified Mini Mental State. The most commonly applied scoring system remains the binary method, in which the patient must draw two pentagons intersecting to form a four-sided figure in order to pass the test.

3.3.2.8. Environmental Visuospatial Questions Test (EVSQ)

Visuospatial ability is commonly impaired in delirium (75) and is one of five cognitive domains assessed using the DRS-R98. Many visuospatial tests are unsuitable for those with fine motor or visual impairment as they require that the subject reproduce a figure using pen and paper. We developed a series of questions (EVSQ or the Environmental Visuospatial Questions Test, see appendix A) relating to the patient's surroundings. We hypothesised that these questions would at least partly assess their visuospatial function. Each patient was asked five questions daily, from a pool of eight possible questions and questions were rotated to minimise learning effect. One mark was given for each correct answer and the test was scored out of five.

3.3.3. IDENTIFYING PREVALENT DELIRIUM

Prevalent delirium was defined by a DRS-R98 severity score of ≥ 15 and / or total score of ≥ 18, based on assessment and symptoms described over the previous 48 hours. Patients with prevalent delirium were excluded from the longitudinal study, because in these patients, a prospective assessment of prodromal features (the main study objective) would not be possible. Hence, patients with prevalent delirium on admission underwent limited assessment only and demographic data was collected, as with all excluded patients. Occasionally, some patients with prevalent delirium were followed daily which was unplanned. This occurred when collateral history from a family member (suggesting prevalent delirium) was not available until later in the admission. Data pertaining to patients with late-identified prevalent delirium on

admission who consented or assented (see ethical procedures) to study participation, was included in the analysis for Chapter 4 which relates to the efficacy of screening methods for prevalent delirium.

3.3.4. BASELINE ASSESSMENT

In the first few weeks of the study, full baseline assessment was performed on consenting patients on the first assessment day, however, this proved to be very time inefficient as many soon-to-be excluded patients were being assessed in full, for example, those with prevalent delirium and those who would be discharged the following day. Hence from approximately week 4 onwards, baseline assessment was completed on day 2 of the study.

Baseline assessment included the following (see Appendix A for samples of the instruments used and appendix C for a copy of the baseline data collection file):

- Demographic information including age, sex, time from ED arrival to ward admission.
- Social History: Marital status, place of residence, social support, highest level of education, alcohol history (units per week) and smoking history (pack year history).
- Screening for visual and hearing impairment: Simple bedside assessment of hearing and vision was used. A person was considered hearing impaired

either if they used one / two hearing aids; if they answered no to the question 'Can you hear me?'; if they stated they had hearing problems; if hearing impairment was documented in their chart; or if there was evidence of hearing impairment during the interview. A person was considered visually impaired if they were unable to identify either a pen or a watch or read a sentence (font 28) while wearing appropriate spectacles if required. Literacy was taken into account for this assessment.

- Standardised Mini Mental State Examination (SMMSE) (170)
- Modified Barthel Index (BI) (176)
- Mini-Nutritional Assesssment - Short Form (MNA-SF) (177)
- ABCDS Depression Score (178) [+/- 15-item Geriatric Depression Scale (GDS) (179)]
- Medical history, including medication history was recorded from the medical notes and the Modified Cumulative Illness Rating Scale (M-CIRS) was calculated.

3.3.4.1. SMMSE (Standardised Mini-Mental State Examination)

The SMMSE (see appendix A) is based on the original Mini-Mental State Examination (MMSE) published in 1975 by Folstein (143). The MMSE was developed as a short screening test to detect cognitive impairment, and was primarily indicated for clinical use, however, evolved to become a commonly used screening test to evaluate patients' suitability for inclusion / exclusion in clinical trials, and additionally

as an outcome measure in such studies. It measures several cognitive domains, including orientation to time and place; registration; short-term memory; attention; language; constructional and visuospatial ability; and ability to follow commands. The original test had few instructions for scoring which led to wide variability in scoring methods between raters and hence reduced test reliability. This led to efforts to improve inter- and intra-rater reliability by standardising the scoring system. The SMMSE, published in 1991 (170) was developed and tested in order to decrease variability and improve the reliability of the MMSE, by providing clear and well-defined scoring and administration instructions (180). When reliability was compared with the original MMSE, intra-rater variance was improved by 86% and inter-rater variance by 76% when SMMSE was used. Intra-class correlation for the SMMSE was 0.90, and for the MMSE 0.69. Additionally the duration of the test was shortened when using the SMMSE (mean duration 10.47 minutes v. 13.39 minutes for the unstandardised version) (180). In this study, if a patient was unable to complete certain items due to, for example severe vision impairment or dominant hand paresis, an adjusted SMMSE score was calculated by dividing the patient's score by their total possible score and multiplying the numerator by 30, as in other similar studies (181). Additionally, scores were adjusted for advanced age and low level of educational attainment as recommended by Prof. Will Molloy (the developer of the SMMSE) and by other research groups (109, 182). In patients of 80 years and older, one point was added to their final SMMSE score and in those whose education did not go beyond primary school, one point was also added to their final score. During the baseline assessment in which the SMMSE was performed, items common to the SMMSE and the 6-CIT were only asked once.

3.3.4.2. Modified Barthel Index

The Modified Barthel Index (BI, see appendix A) was originally developed in 1965 as an instrument to assess level of disability in inpatients with neuromuscular and musculoskeletal conditions (183). It scores ten variables out of a total score of 20, with lower scores indicating greater levels of functional dependence. It has been recommended by the Royal College of Physicians for the routine assessment of functional ability in older adults (184).

3.3.4.3. Short-form Mini-Nutritional Assesssment (MNA-SF) (177)

The Mini Nutritional Assessment (MNA) was developed in the early 1990's as a nutrition screening tool in the elderly (177). Since then it has become the most established and most widely used tool for this purpose and has been translated into multiple languages. In order to shorten the duration of the assessment, an abridged version (MNA-SF) was developed. This was based on item correlation with total MNA score and with clinical nutritional status, as well as internal consistency; reliability; completeness; and ease of administration of each item (185). This shortened version correlated very well with the full version (r=.945) and has now superseded its predecessor due to its improved feasibility. The test is scored out of 14, with lower scores indicating worse nutritional status. Scores of 12 to 14 indicate normal nutritional status, whereas scores of 8-11 signal patients at risk of malnutrition, and scores of 0-7 signify a state of malnourishment (see appendix A).

3.3.4.4. Screening for depression

3.3.4.4.1. The AB Clinician Depression Screen ABCDS (178)

The ABCDS (see appendix A) is a short screening tool for depression, which takes less than two minutes to complete. It was developed by correlation of items from the 30-point Geriatric Depression Score (GDS-30) with diagnosis of depression (defined as GDS-30 of 14 or more). Sensitivities, specificities, positive predicted values (PPV) and negative predicted values (NPV) were calculated and receiver operating characteristic (ROC) curve analysis was performed. The resulting top five correlates were developed into a two-step screening process, with the best correlate used as a single question in step one ("Do you often feel downhearted or blue?", NPV 96%). A negative response to question 1, hence negates the need for further questioning, as it rules out depression with 96% certainty. In the setting of a positive response, the four other highly correlated questions are asked and an overall score out of five is calculated. Scores of one or two indicate low risk of depression, whereas scores of four or five suggest current depression. A score of three is inconclusive and requires further testing with the Geriatric Depression Scale.

3.3.4.4.2. The 15-item Geriatric Depression Scale (GDS-15)(179)

In this study, if the ABCDS was scored as three (inconclusive), the patient underwent further testing for depression using the GDS-15, see appendix A. This is a fifteen item scale developed from the long form of the Geriatric Depression Scale (GDS-30)(186) by item correlation with diagnosis of depression. This shorter form has been shown to correlate well with the original GDS (179), however is more feasible in the

physically ill and in those with mild dementia, as their attention spans may be short and / or they may fatigue easily. In general, GDS-15 scores of 0-4 are considered normal, whereas 5-8 suggest mild depression and 9-15 indicating more severe depression.

3.3.4.5. The Modified Cumulative Illness Rating Scale (M-CIRS)

The Cumulative Illness Rating Scale (CIRS) was initially developed in 1968 by Linn and colleagues in order to quantify comorbidity in older patients, such that meaningful comparisons could be drawn between patients in relation to medical burden (187). In the intervening years, it has been modified and updated to improve feasibility, as well as to have additional applicability in older patients with complex medical histories, and to allow successful inclusion of acute medical conditions. The most current version is the Modified CIRS (M-CIRS) (188), which scores each of thirteen categories (based on organ systems) from 0 to 4 (higher scores indicating greater levels of morbidity). The individual scores are then added to give a cumulative score.

3.3.4.6. Frailty

Frailty is a concept which is difficult to fully define however it is commonly thought of as an increased vulnerability to stressors, which usually occurs as a person ages, due to impairments in multiple inter-related systems. Collecting data pertaining to frailty was also considered, given the population under study, however ultimately this element was excluded for two reasons. Firstly, a number of different frailty

instruments have been validated over the years, including rules-based definitions, the summation of deficits, and clinical judgement scores, however all these tools have been validated in community-based samples because frailty is considered to pertain to a person's baseline state rather than how a person presents in the setting of acute illness. Only one instrument, the Reported Edmonton Frail Scale, has been used in hospital inpatients (189). This tool which is based on the Edmonton Frail Scale (190), using self-reports rather than objective measures, has only been validated in one small Australian study of acute older hospitalised inpatients. This study compared the Reported Edmonton Frail Scale to a reference standard of experienced clinican impression only, without any data collected pertaining to outcomes (189). Given the expected cognitive vulnerability of the population in our study, we felt that using a self-reported quesionnaire would be unreliable, especially given that it had not yet been definitively validated. We also felt that the other frailty instruments, having not been designed nor validated for use in the acute setting, would not be appropriate for use in this study. Furthermore, we had decided to use the MNA-SF to ascertain nutritional status (see above and appendix A), which has been validated for use in the acute setting. This instrument comprises many elements considered central to the measurement of frailty (cognition, weight loss, appetite, psychological stress, mobility) and hence we felt that to also measure frailty would introduce a variable very similar to, and potentially collinear with the MNA-SF.

3.3.5. COLLATERAL HISTORY

Obtaining accurate collateral history from a close relative or next-of-kin (NOK), or others, for example nursing home staff, is a cornerstone of delirium assessment. If there are obvious symptoms present, it is important to ascertain the acuity of onset of these features, temporal relationship to illness or other potential precipitants, and presence of fluctuations. If there are mild or no obvious symptoms present, it is still important to speak with a relative to investigate if there were any recent delirium features that have resolved since arrival to hospital or that are still fluctuating in severity. Furthermore, speaking to a relative or NOK is also key to ascertaining pre-morbid cognitive status (see later) as cognitive assessments in the acute setting cannot be relied upon, especially in the setting of delirium. Additionally, collateral informants were questioned in relation to the presence or absence of potential prodromal features using a novel prodromal checklist (see below). Hence, the collateral history included questions relating to delirium phenomenology; the Prodromal Checklist (see later); and the IQCODE-SF (Informant Questionnaire for Cognitive Decline in the Elderly-Short Form, see below) (191).

3.3.5.1. Identifying premorbid dementia

Identifying premorbid dementia is highly relevant in the assessment of patients for delirium, given that it is one of the strongest independent risk factors for delirium. Moreover, many features of the two conditions can overlap and confound diagnosis and, as a result, delirium is often mistaken for dementia. Ascertaining premorbid cognition can be very challenging, especially in patients with acute illness, delirium,

poor cooperation, communication problems and additionally in those with limited education. Particularly in the acute setting, patients may underperform on cognitive assessment tools for a number of possible reasons. They may have delirium or more subtle subsyndromal delirium or may be too ill to participate. Hence, I investigated for pre-existing dementia by examining the medical notes and used an informant questionnaire called the IQCODE-SF (Informant Questionnaire for Cognitive Decline in the Elderly-Short Form) (191) to ascertain pre-admission cognitive status (see below). Sometimes collateral history was not available and in these cases, if the corrected SMMSE (see above for SMMSE scoring) was 27/30 or above, these patients were considered not to have pre-existing cognitive impairment, in keeping with similar studies (181, 192). If the SMMSE was lower than 27/30, allowing for poor education and advanced age, it was unclear whether the lower score was due to an acute, subacute or chronic problem and hence premorbid cognitive status could not be applied. Patients with scores that were borderline or who had discordant SMMSE and IQCODE-SF were discussed with my supervisors and a consensus decision on pre-morbid cognitive status was made.

3.3.5.1.1. Informant Questionnaire for Cognitive Decline in the Elderly - Short Form (IQCODE-SF)

The IQCODE or Informant Questionnaire for Cognitive Decline in the Elderly was developed in order to facilitate assessment of pre-morbid cognitive function by using informant reports comparing current cognitive function to that of approximately ten years previously. The initial instrument consisted of 39 items. This was then

consolidated to the 16-item short form which correlated 0.98 with the full form and had comparative validity with respect to clinical diagnosis. This short form is now the most commonly used form and has been translated into many languages (193). The informant is asked to grade the patient's current cognitive status as 'much improved'; 'a bit improved'; 'not much change'; 'a bit worse'; or 'much worse', compared to ten year's previously (see appendix A). The answers for each item are assigned scores of 1 to 5, from 'much improved' to 'much worse'. In an older cohort of patients, the majority of scores lie between 3 and 5 for each item, as improvement is unusual in these circumstances. The scores for each item are then added together and divided by 16 to calculate the final mean score. There is no unanimous IQCODE-SF cut-off used for dementia screening, and in general, cut-offs have been lower in dementia screening in the community than in hospital samples. In a review of its use (193), a table of studies summarise the IQCODE-SF cut-off scores used in a variety of studies and the review authors recommend that those intending to utilise the tool for study purposes should choose a cut-off from a study closest in composition to the population in their own study. Hence, in this study a cut-off of 3.5 or above was used to indicate premorbid dementia, reflecting the cut-offs used in other older medical inpatient cohorts (194-196). There are some limitations to the IQCODE-SF. Firstly, in patients with anxiety or depression, occasionally the test may be falsely positive. This may be due to an effect of depression on cognitive function or an inability on the informant's part to distinguish anxiety and depression from cognitive decline. Secondly, the IQCODE-SF score can be influenced by informant characteristics such carer anxiety and / or depression as well as the quality of the relationship between the patient and the informant (193).

Hence, where IQCODE-SF scores were incongruous with the rest of the assessment, consensus decision on pre-morbid dementia was made with my supervisors, based on all available information.

3.3.6. Longitudinal Assessments

Patients who were eligible for inclusion in the longitudinal study of delirium prodrome and who gave informed consent (see ethical procedures), were reviewed daily for the first seven days of admission and then weekly thereafter until discharge. Patients whose admissions were shorter than one week were assessed daily until discharge. These longitudinal assessments included both patient and staff interview. Daily patient assessment included CAM; DRS-R98; 6-CIT; MOTYB; SSF; CDT; IPT; EVSQ. Daily interview with nursing staff included questions relating to CAM and DRS-R98 items; the Prodromal Checklist and the DMSS-4. Those who were discharged within three days without delirium were excluded from the study, as we could not confidently outrule delirium development within the week after admission in these patients. Patients who were assessed for at least four consecutive days post-admission and who remained delirium-free were considered controls and were reviewed weekly until discharge. Patients who developed delirium during the first week were considered cases and were reviewed daily as tolerated until delirium resolved or the patient was discharged. In patients in whom delirium resolved, assessments continued on a weekly basis until discharge. Delirium resolution was defined as three consecutive days with DRS-R98 scores in the subsyndromal or normal range, taking into account the patients' pre-delirium scores.

3.3.7. THE DELIRIUM ETIOLOGY CHECKLIST (DEC)

The Delirium Etiology Checklist (DEC) (27) was completed for all patients who developed delirium (see appendix A). This is a commonly used research tool which is used to attribute etiology to the delirium episode. It includes twelve categories: drug intoxication; drug withdrawal; metabolic / endocrine disturbance; traumatic brain injury; seizures; intracranial infection; systemic infection; intracranial neoplasm; systemic neoplasm; cerebrovascular; organ insufficiency; other central nervous system problems; and other systemic problems. The presence and suspected role of multiple potential contributors are rated according to the degree of attribution to the delirium episode, ranging from 0 (ruled out / not present / not relevant) to 4 (definite cause).

3.3.8. DEVELOPING THE PRODROMAL CHECKLIST

Because it is not yet known exactly what symptoms comprise the prodrome to delirium, there has been no instrument developed to detect it. Hence, in order to investigate for prodromal symptoms in this study, it was necessary to develop a tool designed to identify prodromal symptoms. In the first instance, in order to identify potential prodromal symptoms, I performed a preliminary literature search on PubMed, PsycInfo, CINAHL, Science Direct and Web of Knowledge using the search terms “delirium” or “confusion” (title / abstract) and “prodrom*” or “early indicat*” (all fields). Following review of abstracts and subsequently of potentially relevant articles, eight studies of the delirium prodrome (155, 157-159, 161, 165-167) and five publications of case studies / case series referring to the prodromal phase (162-

164, 168, 169) were considered relevant (of note, when this search was updated in 2013, two further studies were discovered (156, 160), see tables 1 and 2 in Chapter 2). These articles were reviewed for methods used in the investigation of prodromal features and also for the symptoms measured. Additionally, we sought opinions from two experts in this field (Dr. Dimitrios Adamis and Dr. Jos de Jonghe) as to other potential features.

In consultation with my supervisors, we decided to devise a checklist of symptoms, known as the Prodromal Checklist, for use during interview with relevant nursing staff. The questionnaire had to encompass all potential prodromal symptom domains, however had to be relatively short in duration and acceptable to busy nursing staff. It was clear that assessment for prodromal features would be required on a regular basis, and because of staff changeover twice in a 24-hour period on hospital wards, ideally these assessments would take place during each shift. However, for feasibility purposes, as I was the sole researcher, my supervisors and I decided that the assessments would take place daily, including weekends. The assessments would involve using the Prodromal Checklist to ascertain from relevant staff nurses if there was any evidence of emerging symptomatology over the previous 24 hours. Rather than scoring the features on the checklist in a binary way (present / absent), we deemed it more appropriate initially to score each item as 0 (not present), 1 (possibly present / somewhat present) or 2 (definitely present). This was because the checklist is very subjective and some features are difficult to define, hence we wished to ensure sensitivity in detecting all potential prodromal features.

The checklist, following a few iterations based on suggestions from my supervisors, was additionally reviewed for face validity by Prof. Paula Trzepacz, an international delirium expert and creator of the DRS-R98. Some minor modifications were subsequently made and the final checklist can be found in appendix A. To ascertain any prodromal features at admission, the patients' caregivers / nearest relative was interviewed using the prodromal checklist and presence of features over the previous week were sought. On subsequent assessments, the relevant nursing staff were questioned and in this situation the presence of features over the previous 24 hours were sought.

3.4 OUTCOMES

In addition to recording the course of the delirium during the hospital stay, the in-hospital patient outcomes were examined using the hospital electronic system, including mortality, length of stay and discharge destination. I also gathered data pertaining to outcomes at six-months using the hospital electronic system. Patients were also invited to come for re-assessment at a dedicated research clinic held in the Assessment and Treatment Centre (ATC) in St. Finbarr's Hospital (SFH). Although multiple parameters were measured at this research clinic (including cognitive and functional status; depression; and nutrition), these results will be reported elsewhere as they are beyond the scope of this thesis. Six-month outcomes reported in this thesis include a composite adverse outcome of mortality and institutionalisation. If I was unable to reach individual participants at six months, I contacted their General Practitioners to ascertain these outcomes. Composite

adverse outcomes at discharge and at six months were compared between those who developed incident delirium and those who did not using both univariate and multivariable logistic regression (Chapter 10).

3.5. Sample Size Estimation

As aforementioned, the primary objective of this study was to characterise the delirium prodrome, particularly the behavioural features. Hence, we attempted to power the study to meet this objective, but because this was an exploratory study using a novel instrument, accurate power calculations were challenging. Given that there were 31 major behavioural features separated into 6 different domains, it was anticipated that we would identify approximately 8 to 12 unique prodromal features, using factor analysis. Hence, for this analysis it was considered that between 80 and 120 cases of incident delirium would be required. It was also expected that we would use regression analysis to identify which symptoms were most predictive of delirium development. In this analysis, for an effect size of 0.35, alpha 0.05, and power 0.95, and 12 predictor variables, a sample size of 86 is considered sufficient. Hence to ensure good power for both analyses, a sample size of 85 to 120 would be recommended. The prevalence of delirium in older medical inpatients is known to be approximately 42% and the in-hospital incidence in this population between 8 and 12% (197). If we assume an incidence of 10%, this means that between 850 and 1200 patients would need to be screened in order to detect enough cases of incident delirium, which would not be feasible in the given time-frame for a solo researcher. Thus, because the study was exploratory, and that often power estimations are not

reliable, in consultation with my supervisors (DM, ST) and another expert in the field, Dr. Dimitrios Adamis, we agreed that sixty incident cases of delirium would be sufficient for this study.

3.6. Data Collection and Data Management

Data collection commenced in October 2011 using individual paper data collection files which covered the baseline and longitudinal assessments for each participant. Basic demographic data was also collected for excluded patients. Each recruited patient was assigned a study number which was used to pseudo-anonymise the data. The patient identifiers were kept in separate folder and locked away. Hence, the names and / or medical record numbers of participants did not feature on any document concerning the research and all research documents were kept securely in a locked office. In April 2012, electronic data collection was commenced using the filemaker pro programme (version 11) on iPad. This made data collection much more efficient and easier to manage electronically. The file that was used for data collection was again pseudo-anonymised and did not include any patient identifiers. All databases used to analyse the data excluded patient identifiers and all electronic documents with any patient identifier was password-encrypted.

3.7. Statistical Analysis

The majority of the analyses were conducted using SPSS version 20, however for recurrent event survival analyses Stata version 11 was used. Delirium was defined as a DRS-R98 severity score of ≥15 and / or a total score of ≥18 for all analyses. In Chapter 5, in which the utility of the NICE-based questionnaire in detecting delirium is investigated, we conducted an additional analysis, considering CAM as the reference standard for delirium diagnosis: CAM positive indicating presence of delirium and CAM negative indicating its absence. For all analyses, except that conducted in Chapter 8 on subsyndromal delirium (SSD), normal controls were considered to have a DRS-R98 severity score of <15 and a total score of <18. In Chapter 8, patients were considered to have SSD if they had a DRS-R98 total score ≥6 and <18 with scores of at least 1 for each of items 10 (attention) and 14 (temporal onset of symptoms) on the DRS-R98, see Chapter 8 for further detail. Hence in this analysis only, normal controls were those who had DRS-R98 total scores <6, or those with total scores ≥6 and <18 who scored 0 on either / both of the above items.

Demographic data were expressed as means ± standard deviation (SD) or medians and interquartile ranges (IQR), depending on the distribution of the data. Comparisons of groups were made using a χ^2 or Fisher Exact test for differences in proportions, a t-test or ANOVA (Analysis of Variance) for differences in means or Mann Whitney U non-parametric tests for differences in mean ranks. In Chapter 5, univariate logistic regression was used to assess if various baseline predictor variables were associated with incident delirium. Subsequently, multivariable logistic

regression (including variables with $p<0.05$ on univariate analysis) was used to identify which screening tests predicted the occurrence of prevalent delirium. Final multivariable regression models were assessed using -2 log likelihood and goodness of fit was examined using the Hosmer-Lemeshow (C_{HL}) test.

In the analysis of screening tests in the detection of prevalent delirium (Chapter 4), Receiver Operating Characteristic (ROC) analysis was conducted and the Area Under the Curve (AUC) was calculated for tests rated on a continuous scale, whereas 2 x 2 tables were used to calculate sensitivities, specificities and positive and negative predictive values with 95% confidence intervals for tests with binary outcomes. Stepwise discriminant analysis was utilised to investigate how the screening tests distinguish delirium, dementia and normal controls using all the screening tests as independent variables. In Chapter 6, outlining the efficacy of the NICE-based questionnaire in the detection of delirium, stepwise discriminant analysis was also used to identify the elements of the questionnaire which discriminate delirium from no delirium. In this chapter, as aforementioned, separate analyses were conducted using the DRS-R98 and CAM respectively as the reference standard for delirium diagnosis. To evaluate the correlations between the elements of the NICE-based questionnaire and the individual items of the CAM and DRS-R98, Spearman's Rho was used.

In chapters 7, 8, and 9, recurrent event survival analysis was used to examine the association between various prodromal features and the development of delirium. Cox proportional hazards models adjusted for age, sex, comorbidity, functional status and cognitive status were utilised and the proportional hazards assumptions were checked using extended Cox models with time-dependent covariates (see chapters 7, 8, and 9 for more detail on the selection of confounding variables). If any of the variables varied across time, extended proportional hazards models were used for the analysis. Log likelihood and the AIC (Akaike Information Criterion) were used to assess model fit. Hazard ratios with confidence intervals of 95% are reported in the results.

The Generalised Estimating Equation (GEE) method was utilised to analyse longitudinal data for the relationship over time between motor subtypes and independent variables in Chapter 10. The GEE method allows for the fact that within subject observations are correlated and estimates the population average across time (expressed as coefficients). The estimated coefficients depict the relationship between the independent predictors and motor subtype status at each time point, rather than comparing motor profile groups based on longitudinal course. This allowed each available score for every included patient to be incorporated in the analysis, taking into account the correlation between scores for each respective participant.

3.8. Ethical Considerations and Procedures

3.8.1. Informed Consent

People with delirium and / or dementia are potentially vulnerable and hence the most rigorous ethical principles apply to any research involving such patients. By the very nature of the condition, many patients with delirium lack capacity to give informed consent to participation in studies. Currently, in Ireland, there is no legal provision for another adult to give consent on behalf of an incapacitated adult. If all patients who lack capacity were excluded, however, a very significant sample bias would occur (198). Hence, as with previous studies, informed consent was requested from those who had the capacity to give it and assent to participation was sought from patients who were incompetent to consent, as well as approval from a 'nearest relative'. Participants were informed both verbally and in writing about the nature and purpose of the research. In addition, patients and relatives were informed that participation in the research was voluntary and that should they choose not to participate, no negative penalty would apply. A patient information leaflet was supplied, outlining the purpose and procedures of the study, and that all participation was voluntary. A copy of the consent form and patient information leaflet is supplied in appendix D. If at any point during assessment, questioning distressed the patient, the interview was discontinued immediately and nursing staff were made aware of the patient's condition. A facility was provided by Dr. Suzanne Timmons (PI) for follow-up of patients / carers to discuss any issues that arose during the study, however this facility was never requested. The study involved the

collection of routine clinical data and no additional phlebotomy or investigations were performed.

3.8.2. CONFIDENTIALITY

This study involved assessing patients across multiple domains on several occasions as well as gaining access to confidential information such as demographic data and medical history. All data collected was kept in a password-encrypted database and only the lead researcher and research staff had access (see 'data collection and management' above).

3.8.3. PATIENT CARE

If I detected that a patient had delirium, I informed the responsible nurse verbally and I put a note in the chart outlining the subtype of delirium and any aetiological and precipitating factor I considered contributory. I also left my phone number in the notes, should one of the medical team wish to contact me to discuss. The decision as to what course of action was appropriate was made by the medical team looking after the patient just as they would do if a relative or nurse noticed a patient had possible delirium outside of the study. A copy of the standard note for medical charts is supplied in Appendix D, however in most cases I wrote extra information which I felt would be helpful to the medical team.

3.8.4. Ethical Approval

Formal ethical approval was granted by the Cork Research Ethics Committee (CREC). A copy of the letter of approval from CREC is available in appendix D.

3.9. Delivering Objectives

In the following section, methodology specific to the individual objectives of this thesis are summarised. More detail is available in the respective results chapters.

3.9.1. Chapter 4: The Six-item Cognitive Impairment Test as a Screening Test for Delirium.

Objective (iv) To identify the prevalence of delirium on admission and establish the diagnostic accuracy of screening tests in delirium detection.

This was one of the secondary aims of the study. Medical inpatients were identified through the processes described above. Patients were approached and assessed for study eligibility unless they were terminally ill. Those approached who refused participation, or in whom assessment was impossible (e.g. coma, stupor) were excluded, as were those in whom full formal assessment was attempted but impossible due to communication problems (e.g. muteness or severe dysphasia). All other patients who consented or assented according to our protocol were included in this element of the study. This study was cross-sectional in nature. I used the DRS-R98 to formally assess for presence of prevalent delirium within 36 hours of admission (and usually within 24 hours). Patients were considered to have delirium if

the DRS-R98 severity score was ≥15 and / or the total score was ≥18. Patients also underwent a series of cognitive tests (also conducted by me) at the same time as the delirium assessment. These tests included the 6-CIT; CDT; IPT; MOTYB; SSF; and EVSQ (see above). The IQCODE-SF was used to ascertain if premorbid dementia was present in a subgroup of patients. We assessed the psychometrics of the screening tests in detecting the presence of prevalent delirium as described in the statistics section above. Given the challenges in differentiating delirium from dementia in the acute setting, we also used discriminant analysis to assess if any of the tests had utility in discriminating these two conditions in this cohort.

3.9.2. Chapter 5: Making NICE Nicer- A Suggested Approach Towards Targeting the Most Vulnerable.

Objective (v): To determine the incidence of delirium in older medical inpatients and identify predictors of incident delirium in this group.

The recent NICE guidelines propose that all patients who meet one of the following criteria should be assessed daily for delirium: age 65 years or older; cognitive impairment; current hip fracture; or severe illness at risk of decompensation. In the introduction, I have outlined how this risk stratification method may be difficult to implement in clinical practice, so in this chapter I attempted to identify other features which may help to further risk stratify older medical patients, so that screening approaches can be targeted towards the most vulnerable. As described above, patients were assessed within 36 hours of admission, using the DRS-R98 for evidence of prevalent delirium. Those who were non-delirious and who consented to

inclusion, were then assessed daily for the development of incident delirium. Incident delirium was diagnosed if a patient reached a severity score of ≥15 and / or a total score of ≥18 on the DRS-R98. Risk factors for delirium were assessed using logistic regression and included age; alcohol history; premorbid dementia; poor functional status; comorbidity burden; history of depression; current depression; hearing and visual impairment; polypharmacy; and use of deliriogenic medications pre-admission, see Chapter 5 for detail. Other potential risk factors were also assessed including sex; place of residence; social support; level of education; smoking; and poor nutritional status on admission.

3.9.3. Chapter 6: The NICE Screening Recommendations: Clinical Efficacy and Relationship to Delirium Phenomenology

Objective (vi): To examine the clinical utility of the screening recommendations made by the NICE guidelines in detecting incident delirium.

The recent NICE guidelines (5) propose 'indicators of delirium' which should be checked daily in all high-risk hospitalised groups (see above). These indicators focus on changes or fluctuations in usual behaviour in the following domains: cognitive function: "for example, worsened concentration, slow responses, confusion"; perception: "for example, visual or auditory hallucinations"; physical function: "for example, reduced mobility, reduced movement, restlessness, agitation, changes in appetite, sleep"; and disturbance of social behaviour: "for example, poor cooperation, withdrawal, or alterations in communication, mood and/or attitude". This screening tool has been developed by expert consensus opinion, however its

clinical utility had not previously been formally assessed. I designed a questionnaire for interviewing nursing staff based on the NICE guidance (see appendix A). The exact phraseology of the guidelines was used when possible, in order to ensure that the questionnaire was as close as possible to being an operationalised version of the guidance document. The questions used were reviewed by my supervisors to ensure that proximity to the original guidance was optimised. Researchers (Dr. Maeve Davis, Dr. Mary Buckley, Dr. Annmarie Hannon, Dr. Theva Jayaraman) were trained to ask these questions in a standardised way and used the questionnaire to then independently survey the relevant nursing staff about the presence or absence of these 'indicators of delirium'. I was not made aware of the results of the questionnaire and the researchers were blinded to the delirium status of the patients assessed throughout the study. The accuracy of these nurse-observed delirium indicators in predicting presence of delirium was then assessed. We also investigated which elements of the questionnaire correlated with formally assessed elements of delirium phenomenology, in order to identify to which features of delirium the nursing staff were most attuned.

3.9.4. Chapters 7, 8 and 9: Delirium is Preceded by a Behavioural Prodrome in Older Medical Inpatients; Cognitive Impairment Heralds Delirium Onset Independent of Dementia; Delirium Features Occur in the Delirium Prodrome

Objectives (i), (ii), and (iii): Characterising the Prodromal Features of Incident Delirium in Older Medical Inpatients: Behavioural Features; Cognitive Features; and Delirium Features.

This was the primary aim of the study and hence three chapters have been devoted to this important aspect. These three chapters outline the prodromal features, respectively the behavioural features; cognitive features; and features of delirium phenomenology, found to predict delirium onset in this cohort of older medical inpatients. To date, the studies in this area have varied considerably in methodology, assessments used and treatment setting. We aimed to use all available information from the existing literature on delirium prodrome to define the prodromal period in older medical inpatients. Patients underwent a series of assessments on a daily basis to investigate for prodromal features, including cognitive assessment, delirium assessment and observation for behavioural features. Relevant nursing staff were interviewed using the novel Prodromal Checklist (see above and appendix A) to assess for objective evidence of any behavioural features in the previous 24-hours. Additionally, any prodromal behaviour noticed by me during daily interview with the patient that was missed by the nursing staff, was marked as present appropriately. The family member / next-of-kin / carer who provided collateral history for the delirium assessment was also questioned using the Prodromal Checklist, to assess for evidence of prodromal features in the week prior to admission (only new symptoms / exacerbation of previous symptoms in the previous week were eligible

for inclusion). This information was then pooled with the nursing responses on the screening day so that all available information on potential prodromal features in the lead-up to admission was utilised on day 1. Cognitive tests employed were the 6-CIT (incorporating MOTYB, 20-1, temporal orientation and short-term memory); tests of visuospatial function (including the CDT; IPT; and EVSQ); and tests of attention (including the SSF and MOTYB). Patients underwent these tests on a daily basis and hence we were able to use longitudinal analysis to assess if impairments on these tests predicted development of incident delirium, independent of pre-morbid dementia. We used the DRS-R98 daily to assess the delirium status of our participants and similar to the study in Korean hip fracture patients published by Lee et al (199), we used longitudinal analysis to identify which delirium phenomenological features predicted the emergence of delirium.

3.9.5. Chapter 10: Motor Profile of Incident Delirium in Older Medical Inpatients: Frequency; Stability; and Predictors

Objective (vii): To assess the prevalence and stability of motor subtypes of incident delirium in older medical inpatients.

Patients were assessed daily for delirium and additionally for objective evidence of motor features. Motor subtyping is not only the most common and most objective way to classify delirium, but it also has the most evidence for meaningful differences between subgroups based on aetiology, pathophysiology and prognosis (38). The Delirium Motor Subtype Scale - 4 (DMSS-4) was used to ascertain the motor profile for each patient in the initial stages and throughout the course of the delirium (see

above and appendix A). This scale allows for categorisation of the delirium as either hyperactive, hypoactive, mixed subtype or no subtype. As patients were assessed in a longitudinal fashion, we were able to apply longitudinal motor subtypes to each patient with delirium, based on the subtypes expressed during a delirium episode, similar to studies in palliative care patients (11, 54). Five longitudinal categories were possible, four stable and one variable: hypoactive subtype throughout; hyperactive subtype throughout; mixed subtype thoughout; no subtype throughout; and variable profile (see Chapter 10 for detail). From these data, we were able to examine the frequency and stability of motor subtypes in this population.

3.9.6. Chapter 11: Motor Profiling can Differentiate Older Medical Patients with Subsyndromal Delirium from those with No Delirium

Objective (viii): To characterise the phenomenology and motor profile of subsyndromal delirium in older medical inpatients.

Subsyndromal delirium is a state in which a patient presents with certain delirium features, however does not meet criteria for full delirium diagnosis. It is important clinically because it leads to adverse outcomes at rates intermediate between patients with delirium and those with no delirium spectrum disorder. However, many patients without any delirium spectrum disorder, particularly in the acute hospital setting, present with individual delirium features, for example sleep-wake cycle abnormalities. Although recent studies have shown that subsyndromal delirium is phenomenologically more similar to delirium than no delirium, it can be challenging to discern what specifically distinguishes patients with no delirium from

those with the more prognostically significant subsyndromal delirium. Additionally, we do not understand if motor subtypes have any role in subclassifying subsyndromal delirium. In this study, patients were assessed daily for delirium and additionally for objective evidence of motor features. The DRS-R98 and DMSS-4 were used to provide in-depth characterisation of the phenomenology and motor profile of both full- and subsyndromal delirium (FSD, SSD) and longitudinal motor subtypes were applied. Frequency and stability of subtypes was evaluated. In relation to phenomenology, mean scores of each item on the DRS-R98 were compared between normal controls, patients with SSD and those with FSD and certain features were found to differentiate between the groups.

4. THE SIX-ITEM COGNITIVE IMPAIRMENT TEST AS A SCREENING TEST FOR DELIRIUM

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4.1. INTRODUCTION

Delirium is a complex neuropsychiatric condition which occurs in the setting of acute illness. It is highly prevalent across clinical settings (1), and is independently associated with adverse outcomes including increased mortality and accelerated cognitive and functional decline (3, 17). Although studies indicate that early recognition and intervention can impact positively on prognosis (18, 19, 200, 201), delirium remains largely unrecognised across settings (1, 23, 202), particularly in older patients (2) and those with pre-existing dementia (20). Understanding delirium is challenging to the untrained eye. The variable and fluctuating symptom profile with periods of lucidity can often be misleading, and the more common and prognostically serious hypoactive form is less visible to staff than the stereotypical but less prevalent hyperactive agitated form. Furthermore, the conventional

misperception that ‘confusion’ is a natural occurrence in the setting of acute illness in the older adult, or even an element of the normal ageing process undermines the significance of delirium as a diagnosis and impedes identification across disciplines.

In view of its seriousness and scale, all at-risk patients should be regularly assessed for delirium development. However, this poses a significant challenge given that formal diagnosis requires thorough and often time-consuming assessment by a trained and experienced clinician. The most feasible approach, advocated by the NICE guidelines (5), incorporates two steps: firstly, screening for core delirium features using a simple, short test, followed by formal assessment in those who screen positive. Identifying an appropriate initial assessment depends on the clinical setting amongst other factors, but in general, a useful delirium screening tool should be highly sensitive, require minimal training, and be brief so that it does not add much to the existing burdensome workload of ward staff. There are numerous screening tools available but there remains no consensus as to which should be used.

The most widely used delirium instrument is the Confusion Assessment Method (CAM) (83, 84), based on DSM-IIIR (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition) criteria. It tests for the presence or absence of key delirium features: acuity of onset, fluctuating course, inattention, disorganised thinking and altered level of consciousness, and includes semi-structured patient interview as well

as informant history. Although it is considered the most robust short bedside test (203), has been validated in several languages and adapted for multiple settings (85), its potential as a routine screening test is hampered by its administration time of approximately five minutes and low sensitivity in untrained hands (87). However, an operationalised brief version of the CAM (bCAM), has shown promise as a successful screening approach in the Emergency Department (88). A more recently developed multidimensional tool, the 4 'A's Test (4-AT), was designed for routine use in clinical practice (91). It incorporates assessment of (i) level of alertness; (ii) cognition using the AMT4 (Abbreviated Mental Test-4); (iii) attention using Months of the Year Backwards (MOTYB); and (iv) acuity of onset and / or presence of fluctuations. It is widely used clinically, brief and simple to administer, and a study of diagnostic accuracy conducted in acute and rehabilitation geriatric medicine units in an independent centre found a sensitivity of 89.7% and specificity of 84.1%. Like the CAM and bCAM, collateral history is required to complete the test with accuracy, and although obtaining accurate collateral history is central to formal delirium diagnosis, this often time-consuming, and sometimes impossible, step may hinder the success of a screening test in practice. Other screening instruments based purely on patient observation do not require informant reports nor cognitive testing, are acceptable to nursing staff and initial studies of their use are encouraging, yet further studies are required to validate results (92, 102).

Common bedside cognitive tests have also been suggested for screening, however these tools tend to lack specificity for delirium (9) unless they focus upon deficits in

cognitive domains (e.g. attention) which are disproportionately affected in delirium when compared to normal ageing and dementia (105-108). Attention tests such as the MOTYB and Spatial Span Forwards (SSF), amongst others, have been found to be delirium sensitive (105-107). The SSF is a visual pattern recognition test based on the digit span forwards (111), and may discriminate the inattention of delirium from that caused by dementia (110). The MOTYB is a simple test of attention which is widely used for bedside assessment. It is sensitive in detecting delirium in acute hospital inpatients, particularly in older patients (105). The Six-item Cognitive Impairment Test (6-CIT) is a cognitive screening test which incorporates tests of attention with evaluation of temporal orientation and short-term memory (113), three of the main cognitive domains affected in delirium. It hence has potential as delirium screening test. Because it is a completely verbal test, it can be also be used in the visually impaired (125) and those with upper limb issues. It requires minimal training and has high acceptability among nursing staff (127). Additionally, of importance where serial testing is required, no significant learning effect has been demonstrated (123). Its applicability as a delirium screening test has not yet been studied and thus there are no suggestions as to an appropriate cut-off in this setting. Bedside tests of visuospatial function are another proposed method of delirium screening, particularly the Clock-Drawing Test (CDT), which is widely used in screening for cognitive impairment and dementia (132). As well as visuospatial function, it assesses constructional praxis, executive function; and verbal and semantic memory (133). There are conflicting reports as to the utility of the CDT in the detection of delirium. Some authors found it reliable for this purpose (134, 135), and others found it unsuitable for delirium screening (133, 136-139). Its advantages include that

it is largely unbiased by educational level, ethnicity, language and socio-economic status and it is quick and widely accepted by physicians and patients alike (140, 141). Another well-known visuospatial test is the Interlocking Pentagons test (IPT), which initially gained popularity as one of a set of nine figures in the Bender-Gestalt test used to assess for developmental problems in children (142). Since then it has been incorporated into other cognitive tests including the MMSE (Mini-Mental State Examination) (143). Impairments on the IPT can differentiate between patients with Dementia with Lewy Bodies (DLB) and Alzheimer's Dementia (146-149) and can predict cognitive decline in Parkinson's disease patients (150-153). Given the phenomenological similarities between DLB and delirium, it is possible that this test may have utility in detecting delirium, however to our knowledge, no studies have yet examined this. Thus, the aim of this study was to assess the utility of several simple bedside assessments in the detection of prevalent delirium in older medical patients on admission. The tests we assessed were the 6-CIT; MOTYB; SSF; CDT; IPT and a set of verbal visuospatial questions (see below).

4.2. METHODS

This cross-sectional study was part of a larger longitudinal study of delirium conducted in two hospitals in Cork city, Ireland (Cork University Hospital and the Mercy University Hospital) between October 2011 and August 2013. Patients of 70 years and older who were admitted medically were eligible for inclusion. Patients were excluded for many reasons: refusal to participate; being terminally unwell or comatose; or due to severe communication issues (e.g., advanced non-

communicative dementia; severe dysphasia). Patients were assessed for prevalent delirium within 36 hours of presentation to the emergency department using the Delirium Rating Scale Revised ’98 (DRS-R98). They also concurrently underwent testing with six other cognitive screening methods as described below and in figure 3.

4.2.1. ASSESSMENTS

4.2.1.1. Delirium Rating Scale-Revised ’98 (DRS-R98)

This is a 16-item scale incorporating 13 severity items (rated from 0 to 3) and 3 diagnostic items (rated from 0 to 2 or 3), with a total possible score range of 0 to 46. It is used both as a diagnostic tool and additionally to evaluate phenomenology and symptom severity over the previous 24-hour period. It has high inter-rater reliability, validity, sensitivity and specificity for distinguishing delirium from other neuropsychiatric disorders including dementia and depression (90, 204, 205). In keeping with guidelines for its use (173), in this cross-sectional study DRS-R98 defined delirium was denoted by a severity score ≥15 or total score ≥18.

4.2.1.2. Six-item Cognitive Impairment Test

The Six-item Cognitive Impairment Test (6-CIT), originally called the Six-item Orientation-Memory-Concentration Test was developed by Katzman et al (113) as a screening test for dementia. It involves three temporal orientation questions; two tests of attention; and a test of short-term logical memory (see figure 3). It is scored out of twenty-eight with higher scores indicating greater degree of impairment.

4.2.1.3. Spatial Span Forwards

The Spatial Span Forwards (SSF) is performed using an A5 card with eight red squares (each measuring 1.5cm^2) evenly spaced over three rows (formation three, two, three; landscape) on a white background, see appendix A. Predetermined sequences are tapped out for the patient to repeat, beginning with a sequence of two and up to a maximum of seven. Two attempts are allowed at each level and subjects unable to correctly repeat a sequence of five are generally considered to have failed the test. Because it is non-verbal, it can be used in those cannot speak (e.g. intubated patients / tracheostomy patients), or have expressive aphasia (e.g. stroke patients).

4.2.1.4. Months of the Year Backwards

The Months of the Year Backwards (MOTYB), can be scored using several methods, either dichotomised into a positive or negative result in a variety of different ways, or using a scale of accuracy performance based on the number of errors (206). In this study, as in previous studies from our research group (1, 105, 181), subjects were first invited to say the months of the year forward from January to December and subsequently asked to recite the months backwards from December to January. Those who reached July without error were considered to have passed the test.

4.2.1.5. Environmental Visuospatial Questions Test

Visuospatial ability is commonly impaired in delirium (75) and is one of five cognitive domains assessed using the DRS-R98. Many visuospatial tests require that the

subject reproduce a figure and are unsuited to those with fine motor or visual impairments. We devised a series of questions (EVSQ or Environmental Visuospatial Questions Test) relating to the patient's environment which we hypothesised would at least in part reflect their visuospatial function. From a pool of eight questions, five were asked daily of each patient (see figure 3). The questions were rotated in order to minimise learning effect. A mark was given for each correct answer and the test was scored out of five.

4.2.1.6. Interlocking pentagons test

The Interlocking Pentagons Test (IPT) requires the subject to copy a representation of two intersecting pentagons with a quadrilateral figure formed by their overlapping corners, see figure 3. It can be scored either in a binary fashion as in the MMSE (Mini-Mental State Examination) (143) or as a ten-point scale (144). The most commonly applied scoring system remains the binary method, which was applied in this study.

4.2.1.7. Clock-Drawing Test

The Clock-Drawing Test (CDT) can be scored by a variety of different methods, all of which correlate well with other tests of global cognition (136). In this study we used a 15-point scoring method from the QMCI (Quick Mild Cognitive Impairment screen), a tool developed to differentiate between mild cognitive impairment and normal controls (174). Using this method, the subject is given a pre-drawn circle and is

requested to draw in the numbers and set the time at 'ten past eleven'. A transparent template is used to guide scoring of the placement of the numbers and hands, see appendix A.

4.2.2. Assessment of previous cognitive status

Medical charts were examined for an indication of a previous diagnosis of dementia by an appropriately trained physician. The Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) was also used to ascertain a prior dementia history (mean cut-off ≥3.5) through a standardised interview of carers / next-of-kin (193). In borderline cases, diagnosis was reached by consensus opinion of experts (ST, DM). In those with no known diagnosis or available informants, a score of ≥27 /30 on the SMMSE (Standardised Mini Mental State Examination) was considered normal, in keeping with other studies (181). In subjects with lower SMMSE scores and with no available collateral history, premorbid cognition was considered "unknown".

4.2.3. Ethical procedures

This study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The nature and purpose of the study was discussed with participants and informed consent was obtained. Because of the nature of the study, it was anticipated that many participants would not have capacity to give informed consent and so, consistent with similar studies and in accordance with the Helsinki

Guidelines for Medical Research involving human subjects (207), ethical approval was granted to augment patient assent in those lacking capacity with approval from a nearest relative or next-of-kin.

4.2.4. STATISTICAL ANALYSIS

Statistical analyses were conducted using SPSS version 20. Demographic data were expressed as means ± SD or medians and IQR, depending on the distribution of the data. Delirium was defined as a DRS-R98 severity score of ≥15 and / or a total score of ≥18. Comparisons of categorical variables were made using a χ^2 test and for continuous variables parametric or non-parametric tests were used dependent on their distribution. Also Receiver Operating Characteristic (ROC) analysis, and the Area Under the Curve (AUC) were calculated for the tests which were rated on a continuous scale. Subgroup analysis evaluating test performance in patients with and without dementia was also performed. Spearman's Rho was used to investigate the relationship between the six screening tests. Multivariable logistic regression, using a backwards stepwise method, was used to identify which screening tests significantly predicted occurrence of prevalent delirium. Model fit was assessed using -2 Log likelihood and goodness of fit using the Hosmer-Lemeshow (C_{HL}) test. Stepwise discriminant analysis was utilised to investigate how the screening tests distinguish delirium, dementia and normal controls using all the screening tests as independent variables.

4.3. RESULTS

Of 555 patients approached, 470 had full delirium assessments performed and 184 (33.2% of those approached) met criteria for delirium. The median age of the cohort was 81 years (range 70-99; IQR 10) and 50.4% (n=237) were female, see table 3. Comorbid dementia status was known in 320 patients (68% of those included), and 79 patients had premorbid dementia. Patients with delirium were slightly older and were more likely to have pre-existing dementia than those without. The correlations between performance on the six screening tests were assessed using Spearman's rho coefficients (see table 4). Correlations between 6-CIT and the other scales are all negative (- sign), as higher scores on the 6-CIT indicate more impaired cognition, whereas the opposite is the case for the other scales. The binary tests (MOTYB and IPT) were coded 0 for fail and 1 for pass, hence these also have negative correlation with the 6-CIT.

Tables 5 and 6 show the performance of the six tests in detecting delirium. The AUC for continuous variables is shown in table 5, as is the best cut-off with sensitivity, specificity, NPV (Negative Predictive Value), PPV (Positive Predictive Value) and 95% confidence intervals for each scale using DRS-R98 diagnosis as the reference standard. These values have been calculated for the overall group and also for those with and without pre-morbid dementia. Figures 4 to 7 show the respective ROC curves for each test. Table 6 shows sensitivity, specificity, NPV and PPV with 95% confidence intervals (95% CI) for each binary test, also divided into subgroups. Caution must be used when interpreting these results, particularly the NPV and PPV,

given that the sample was not consecutive and hence the prevalence rate may not be completely accurate. In the diagnosis of prevalent delirium, the most robust test was the 6-CIT with an AUC of 0.88 (95% CI 0.84-0.91). For the whole group, a cut-off point of 11 / 12, was found to have the best match between sensitivity and specificity at 83.5% (95% CI 76.6-88.8) and 76.0% (95% CI 70.3-81), respectively ($p<0.001$). However when screening for a serious condition with high prevalence, favouring sensitivity and NPV over specificity and PPV is advised, in order to reduce the risk of missed cases. With this in mind, the accuracy of other cut-offs were explored and using a cut-off of 8 / 9 for the whole group, sensitivity was 89.9% (95% CI 83.8-93.9) and NPV was 91.2% (95% CI 85.8-94.7), whereas specificity was 62.7% (56.5-68.5) and PPV was 59.2% (95% CI 52.6-65.4). This optimal cut-off did vary depending on dementia status, see table 5.

Logistic regression analysis was conducted to assess which tests most accurately predicted delirium occurrence. All six screening tests were entered into the initial model, with dementia and age as covariates, and forced entry method was used to arrive at the best model, as shown in table 7. This model correctly classified 82.7% of participants, 60.8% with delirium and 92% without. In order to identify which test specifically distinguished delirium from dementia and from normal controls, we performed a stepwise discriminant function analysis with the categorical variable (delirium / dementia / no neurocognitive disorder) as the dependent variable and all six screening tests as independent variables. We found that only the 6-CIT significantly predicted correct classification, with 78.1% of the original grouped cases

correctly classified (Wilks' Lambda=0.748, F=62.15, df1:1, df2:1, df3:184, p<0.001). Using statistically more rigorous cross-validation, in which each case was re-classified by the functions derived from all other cases, results were similar. We then compared the mean scores on the 6-CIT between the different neurocognitive groups, using Kruskall-Wallis test, and found that they differed significantly from each other (see table 8). Controls scored significantly lower (i.e. performed significantly better) than those with either dementia or delirium, with a median score of 6 (IQR 7, range 0-22). Patients with dementia only were more impaired, with a median score of 14 (IQR, range 2-28), but delirium patients scored significantly much higher, their median score being 19 (IQR 11, range 0-28), p<0.001. Figure 8 illustrates median 6-CIT scores for the three groups.

4.4. DISCUSSION

We found that the 6-CIT is a robust method of screening for prevalent delirium on admission in older medical inpatients, with high overall sensitivity and NPV, and an optimum cut-off for delirium screening of 8 / 9. We also found that the 6-CIT can distinguish patients with delirium from those with dementia (and no delirium) and also from those with neither diagnosis. Being the first time this test has been investigated for utility as a delirium screening test, our suggested cut-off of 8 / 9 for delirium screening is the first such proposed cut-off. In previous studies of its use in screening for dementia, several cut-off scores have been suggested, the most common one being 10 / 11 with sensitivities ranging from 82.5% to 90% and specificities from 86.8% to 96% (116, 121-123). In these studies, a high specificity

was emphasised over high sensitivity, so as to minimise false-positive dementia diagnoses. Other studies have used 7 / 8 (128) and 5 / 6 (130) respectively as cut-offs for the non-specific term 'cognitive impairment', and it is generally considered that using lower cut-offs improves sensitivity in detecting milder impairments.

The individual tests of attention, MOTYB and SSF, were also sensitive to the presence of delirium, but specificity was low for both these tests particularly in patients with dementia. A previous study conducted by our research group found that MOTYB had high sensitivity and specificity in detecting delirium, and was particularly useful in older patients (≥69 years) with a sensitivity of 83.8% and a specificity of 89.6% (105). In this more recent study, sensitivity was similar (84.6%), but specificity was lower at 58.4%. The reasons for this are unclear however, it may relate to differences in study methodology. The former study was part of a large point prevalence study of delirium in all adult inpatients (aged 17 to 95 years) in a general hospital, whereas this latter study concentrated only on medical inpatients of 70 years and older at the point of admission. There were, thus, more patients with pre-morbid dementia in the current study which may have contributed to the difference in findings. The 6-CIT incorporates a version of the MOTYB as one of its measures of attention, and it may be that its accuracy improves with the addition of tests of other core cognitive domains affected in delirium.

This was the first study to examine the performance of IPT in detecting delirium, and

although it missed very few cases, it seemed to detect a more generalised impairment in cognition, rather than that specifically due to delirium. The CDT performed well in the overall analysis and in the non-dementia group, however the results in the dementia group were poor and not statistically significant. This test was also associated with delirium occurrence on multivariable logistic regression but was unable to distinguish between delirium and dementia on discriminant analysis which is in keeping with more recent studies of its use (133, 136-139). Our environmental questions (EVSQ) designed to identify visuospatial deficits in those who could not use a pen, were not useful in delirium detection. Although the correlations between EVSQ and the CDT and IPT respectively were statistically significant, the correlation coefficients were low. Thus, it is likely that the EVSQ also detects impairments in cognition other than in visuospatial function. Interestingly the 6-CIT correlated highly with all the other tests.

The tests which independently predicted the diagnosis of delirium were 6-CIT, SSF and CDT. However on stepwise discriminant analysis only the 6-CIT differentiated between delirium, dementia (without delirium) and normal controls, an important finding given that delirium is commonly mistaken for dementia and attempting to distinguish between the two in an acute setting is challenging. A systematic review conducted by Morandi and colleagues in 2012 indicated that the CAM and CAM-ICU were most useful for detecting delirium superimposed on dementia but studies using these tools were not designed specifically to distinguish between patients with delirium and those with dementia only (208). Other studies identify that sustained

visual attention (104); bedside measures of attention (110, 209) and deficits in visual perception (210) can differentiate the two conditions. Previous work by Meagher and co-workers has highlighted that the SSF can distinguish between delirium and dementia as well as between comorbid delirium-dementia and dementia but did not discriminate between both delirium groups (110). Our results do not replicate this finding, and the differing results may be due to a variety of reasons. Firstly, the previous study by Meagher et al involved palliative care patients with a younger age range, whereas our cohort were older medical patients. Furthermore, unlike previous work, we did not separate the delirium cases into those with dementia and those without, as we did not have dementia diagnosis available in all of the delirium cases. Lastly, we did not discern dementia severity in our cohort which may have impacted on results. Importantly, although our results show that patients with delirium score significantly higher on the 6-CIT than those with dementia only (who in turn score higher than normal controls), figure 8 demonstrates that the boxplots overlap, hence we cannot discern an accurate cut-off to distinguish the two from our data.

The strengths of this study include that delirium was diagnosed by a trained experienced rater using a well-validated sensitive instrument. There were a high number of delirium cases included (n=184) and six bedside cognitive tests were assessed, although one limitation is the potential for bias given that the same investigator conducted the delirium assessments and the cognitive testing. A study strength is that dementia status was determined using the IQCODE-SF, which is a

well-recognised and validated tool for studies such as this. On the other hand, IQCODE-SF scores were not available for all those included. The issue of identifying pre-morbid dementia at the point of admission is commonly challenging in day-to-day practice, when collateral history can often be difficult to obtain, and dementia is also vastly under-recognised in the community and in the hospital sector. In a study of dementia prevalence in the acute hospital setting, one-quarter of patients had dementia, yet only approximately one-third of these had a prior diagnosis (181). In the acute setting, in order to expedite delirium diagnosis and hence facilitate appropriate intervention strategies, a simple quick method to screen for delirium is crucial and although collateral history, supported by appropriate diagnostic instruments, remains the first line in attempting to identify if a patient with a cognitive deficit is acutely compromised with delirium or chronically impaired with dementia, it should not be a rate-limiting step in the screening process. This study suggests that early in admission, the 6-CIT is a useful screening tool to detect prevalent delirium and our results also indicate that it may distinguish between patients with delirium and those with dementia only. Further studies in larger populations with more defined neurocognitive groups are needed to verify these results. Of particular importance for future work in this area is the identification of an accurate method to differentiate delirium from dementia using the 6-CIT. The question as to whether or not the 6-CIT can differentiate between patients with delirium superimposed on dementia from those with delirium alone, is less clinically relevant, given the urgency of detecting delirium, not dementia.

Figure 3: Description of screening tests included in the study

*QMCI = Quick Mild Cognitive Impairment Screen. It includes a template for scoring the clock-drawing test.

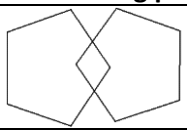
A.	**The Six-item Cognitive Impairment Test (6-CIT)**	**Scoring**
	1. What year is it?	Score 4 if incorrect
	2. What month is it?	Score 3 if incorrect
	Repeat after me: "John / Smith / 42 / High Street / Bedford." I want you to try to remember that name and address. I will ask you about it later.	(not scored)
	3. About what time is it?	Score 3 if more than 1 hour wrong
	4. Count backwards from 20 down to 1	Score 2 if one error Score 4 if two or more errors
	5. Say the months of the year in reverse order, starting with December	Score 2 if one error Score 4 if two or more errors
	6. What was that name and address you repeated after me earlier?	Score 2 for each error Maximum score 10 for 5 errors
		Total score = ____/ 28
B.	**Spatial Span Forwards (SSF)**	Subject must repeat sequences of squares of increasing difficulty tapped out by the examiner. Correctly repeating a sequence of 5 squares is generally considered the criteria to pass the test.
C.	**The Months of the Year Backwards (MOTYB)**	Subject must get back as far as July without error in order to pass the test.
D.	**Environmental Visuospatial Questions (EVSQ)**	
	1. Where is the toilet? 2. Where is the nurses' station? 3. Where is the way out? 4. Which is bigger, ……* or …….*? 5. Which is closer to you, the window or the door? 6. Which of my hands is closer to you? 7. Which is taller, ….. *or ……*? 8. Which is closer to you, ……* or …….*?	Five of these questions were asked daily and the subject was given a mark for each correct answer. The test was scored out of five. *Objects in room or on bedside table are used here
E.	**Interlocking pentagons (IPT)**	
		Score 1 if entirely correct Score 0 if any mistake
F.	**Clock-Drawing Test (CDT)**	The patient is given a pre-drawn circle. They are instructed to fill in the numbers to make it look like a clock, and to draw the hands at 'ten past eleven'. The test is scored according to the QMCI*, out of 15 with lower scores indicating a greater degree of impairment.

Table 3: Demographics of patients included in the study of delirium screening tools

	Total (n=470)	Delirium (n=184)	No Delirium (n=286)	sig.
Age (years), median (IQR)	81 (10)	82 (15.25)	80 (9)	<0.001
Sex (% female)	50.4	50	50.7	0.882
Dementia status (n=320)		(n=80)	(n=240)	
Dementia, n (%)	79 (24.7)	43 (53.8)	36 (15.0)	<0.001

Table 4: Correlations between different approaches to screening for delirium

6-CIT= Six-item Cognitive Impairment Test; SSF = Spatial Span Forwards; EVSQ = Environmental Visuospatial Questions; MOTYB = Months of the Year Backwards; IPT = Interlocking Pentagons Test; CDT = Clock Drawing Test. All correlations are significant at the level <0.001, except for those marked □, which are significant at the level <0.01

		6-CIT	SSF	EVSQ	MOTYB	IPT	CDT
6-CIT	Correlation coefficient	*1.000*	-0.569	-0.446	-0.548	-0.419	-0.576
SSF	Correlation coefficient	-0.569	*1.000*	0.385	0.345	0.378	0.422
EVSQ	Correlation coefficient	-0.446	0.385	*1.000*	0.245	0.136□	0.298
MOTYB	Correlation coefficient	-0.548	0.345	0.245	*1.000*	0.227	0.346
IPT	Correlation coefficient	-0.419	0.378	0.136□	0.227	*1.000*	0.414
CDT	Correlation coefficient	-0.576	0.422	0.298	0.346	0.414	*1.000*

Table 5: AUC with 95% confidence intervals for each continuous screening test.

This is shown for the whole group and then divided into those with and without dementia. The most efficient cut-off score for each scale based on the coordinates of the curve is also shown. *Cut-off score that optimises sensitivity and Negative Predictive Value

6-CIT= Six-item Cognitive Impairment Test; SSF = Spatial Span Forwards; EVSQ = Environmental Visuospatial Questions; CDT = Clock Drawing Test; NPV = Negative Predictive Value; PPV = Positive Predictive Value; AUC = Area under the Receiver Operating Characteristic Curve; CI = confidence interval

Screening test	Subgroup	AUC (95% CI)	sig.	Best cut-off score*	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
6-CIT	Overall	0.88 (0.84-0.91)	<0.001	**8 / 9**	89.9 (83.8-93.9)	62.7 (56.6-68.5)	91.2 (85.8-94.7)	59.2 (52.6-65.4)
	No dementia	0.80 (0.71-0.88)	<0.001	**7 / 8**	84.8 (67.3-94.3)	61 (53.5-67.9)	95.8 (90-98.4)	27.7 (19.5-37.7)
	Dementia	0.67 (0.55-0.79)	0.013	**11 / 12**	80.5 (64.6-90.6)	31.2 (16.8-50.1)	55.6 (33.3-77.6)	60 (45.9-72.7)
SSF	Overall	0.79 (0.74-0.81)	<0.001	**4 / 5**	90.2 (84.1-94.2)	40.9 (35.1-47)	88.3 (81.1-93.1)	45.8 (40.1-51.7)
	No dementia	0.73 (0.63-0.82)	<0.001	**4 / 5**	87.9 (70.9-96)	42.3 (35.4-49.6)	95.4 (88-98.5)	20.4 (14.3-28.2)
	Dementia	0.65 (0.52-0.77)	0.028	**4 / 5**	89.7 (74.8-96.7)	25.1 (2.7-42.5)	69.2 (38.8-89.6)	56.5 (43.3-68.8)
EVSQ	Overall	0.71 (0.66-0.76)	<0.001	**4 / 5**	72 (64.3-78.5)	56.1 (50-61.9)	77.3 (70.8-82.8)	49 (42.5-55.4)
	No dementia	0.59 (0.47-0.70)	0.110					
	Dementia	0.60 (0.48-0.73)	0.126					
CDT	Overall	0.80 (0.76-0.85)	<0.001	**9 / 10**	80.9 (72.1-87.5)	63. 1 (56.7-69)	88.2 (82.3-92.4)	49.2 (41.7-56.7)
	No dementia	0.82 (0.69-0.82)	<0.001	**9 / 10**	86.7 (68.9-95.6)	65 (57.4-71.9)	96.6 (91.1-98.9)	29.5 (20.5-40.4)
	Dementia	0.54 (0.39-0.69)	0.591					

Table 6: Performance of binary screening tests in the detection of delirium

MOTYB = Months of the Year Backwards; IPT =Interlocking Pentagons Test; CI = Confidence Interval; NPV = Negative Predictive Value; PPV = Positive Predictive Value

Screening Test		Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)	sig.
MOTYB	Overall	84.6 (77.7-89.7)	58.4 (52.4-64.2)	87.4 (81.6-91.6)	52.8 (46.4-59.1)	<0.001
	No dementia	75 (56.6-87.9)	61.9 (54.8-68.5)	94 (88.1-97.2)	23.8 (16.1-33.5)	<0.001
	Dementia	83.3 (68-92.5)	33.3 (19.1-51.1)	63.2 (38.6-82.8)	59.3 (45.8-71.7)	0.08
IPT	Overall	92.7 (86.3-96.4)	39.8 (33.9-46)	92.1 (85.1-96.1)	42 (36.1-48.1)	<0.001
	No dementia	90.6 (73.8-97.5)	40.9 (33.8-48.3)	96.2 (88.5-99)	20.8 (14.6-28.7)	<0.001
	Dementia	87.1 (69.2-95.8)	14.7 (5.5-31.8)	55.6 (22.7-84.7)	48.2 (34.8-61.8)	0.561

Table 7: Multivariable logistic regression model of screening tests which were significantly predictive of prevalent delirium status

-2 log likelihood 258.27; Hosmer-Lemeshow test p=0.288, β= coefficient, OR = odds ratio, CI = confidence interval

82.7% cases correctly classified (60.8% of delirium cases, 92% of no delirium cases)

	β	OR	95% CI for OR	sig.
6-CIT score (per unit increase)	0.145	1.157	(1.09-1.22)	<0.001
CDT score (per unit increase)	-0.111	0.895	(0.83-0.96)	0.002
SSF score (per unit increase)	-0.324	0.731	(0.55-0.97)	0.028
constant	-0.564	0.569		

Table 8: Comparison of 6-CIT scores for each neurocognitive group

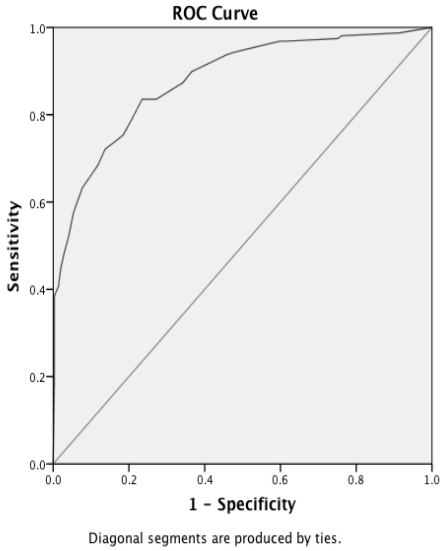
6-CIT = Six-item Cognitive Impairment Test; IQR = interquartile range

*Kruskall-Wallis Test was used as distribution was non-parametric

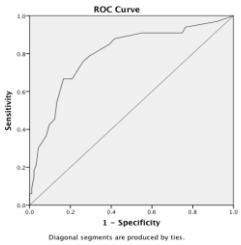
	Controls (n=132)	**Dementia only** (n=32)	**Delirium** (n=158)	**sig.**
6-CIT score median ± IQR	6 ±7	14 ±8	19 ±11	<0.001 for all comparisons*

Figure 4: Receiver Operating Characteristic Curves for 6-CIT: a) overall group; b) patients without dementia; c)patients with dementia

4 a)



4 b)



4 c)

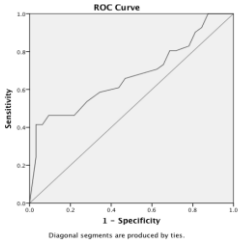
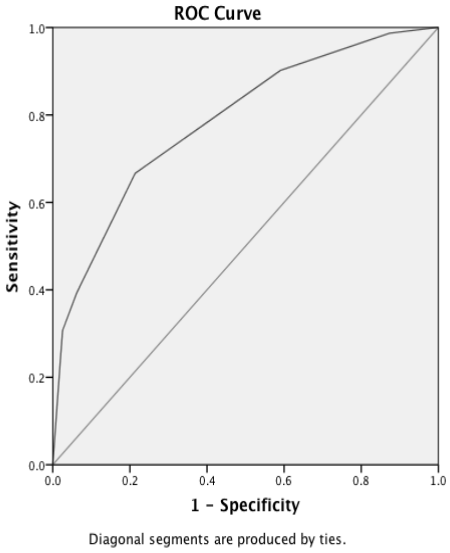
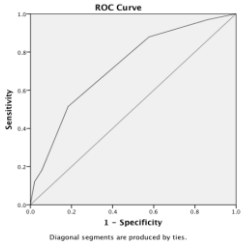


Figure 5: Receiver Operating Characteristic Curves for SSF: a) overall group; b) patients without dementia; c) patients with dementia

5 a)



5 b)



5 c)

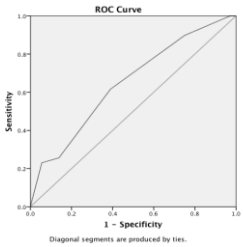
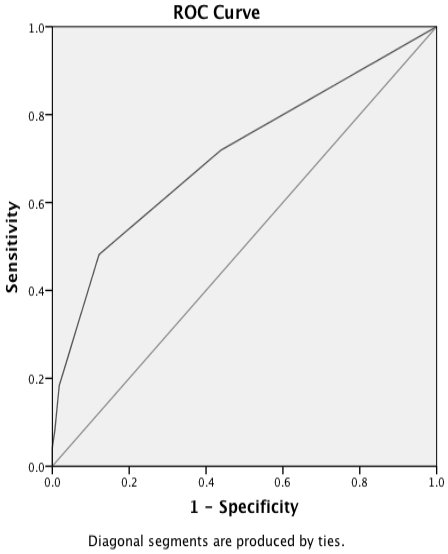
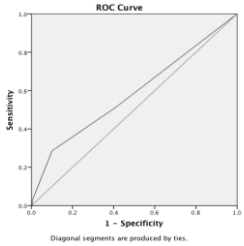


Figure 6: Receiver Operating Characteristic Curves for EVSQ: a) overall group; b) patients without dementia; c) patients with dementia

6 a)



6 c)



6 d)

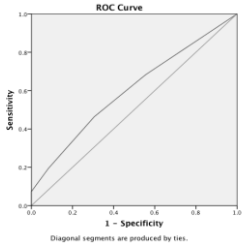
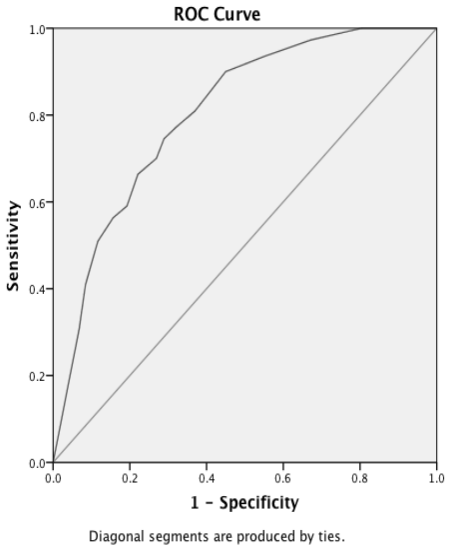
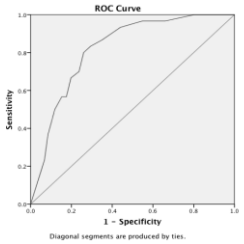


Figure 7: Receiver Operating Characteristic Curves for CDT: a) overall group; b) patients without dementia; c) patients with dementia

7 a)



7 c)



7 d)

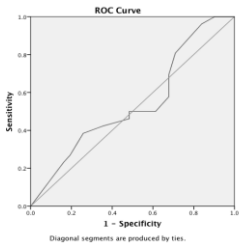
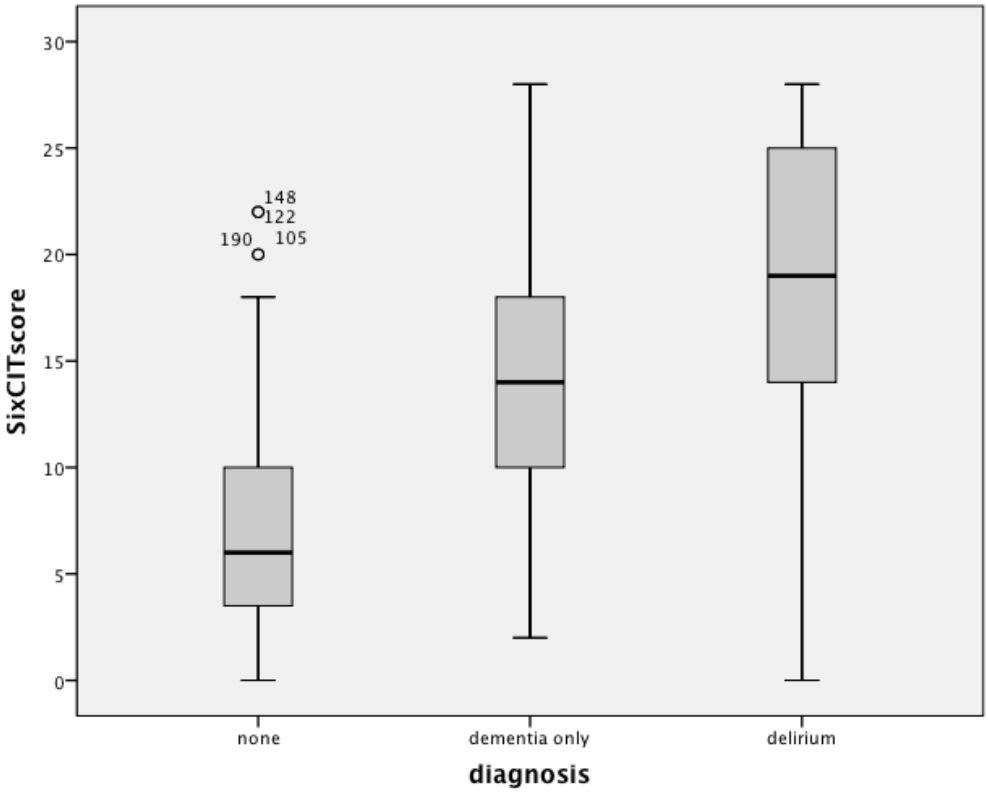


Figure 8: Boxplots of the distribution of total 6-CIT scores for the different neurocognitive groups



5. MAKING NICE NICER- A SUGGESTED APPROACH TOWARDS TARGETING THE MOST VULNERABLE.

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5.1. INTRODUCTION

Delirium is a complex neuropsychiatric syndrome caused by underlying illness or injury which presents with an acute change in cognition and attention (3). It is highly prevalent, occurring in approximately 20% of hospital inpatients (1) and up to 60% in frail hospitalised older adults (211). It is a serious condition which leads to increased mortality (14); more prolonged hospital stays (15) with higher readmission rates (16); and increased cognitive (17) and functional decline (16). Early identification and management is key to minimising these adverse outcomes (212), yet delirium remains seriously underdetected across clinical settings (20, 23, 213).

The pathophysiology of delirium remains unclear and although it is often caused by direct brain insults such as trauma, hypoxia, metabolic abnormalities, stroke and

drug effects, it can also be the result of an aberrant stress response where there is an exaggerated physiological reaction to apparently mild peripheral illness or injury, particularly in those with a vulnerable brain (28). Despite the uncertainty in relation to the precise mechanisms of delirium pathogenesis, multiple predisposing and precipitating factors have been identified (80, 81). Modifying these risk factors through proactive multifaceted systematic interventions has been shown to halve delirium incidence (7).

In 2010, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) published guidance on the diagnosis, prevention and management of delirium (5) based on comprehensive review of the existing literature by experts in the field. Given the poor recognition of delirium, they recommend that patients at risk should undergo daily screening for the emergence of delirium, with full formal assessment by a trained, experienced clinician in those who screen positive. Patients considered at high risk included patients with any one of the following characteristics: being of 65 years and over; having cognitive impairment or dementia; having a current hip fracture; or having a severe illness at risk of decompensation. This broad categorisation includes the vast majority of hospital inpatients, reflective of the pervasiveness of delirium across hospital settings, however as a risk-stratification tool, it does not help to target delirium detection programmes towards the most vulnerable and hence does not assist in making screening more feasible and acceptable to busy clinical staff. In order to achieve this, it is necessary to identify

more specifically which of these patients are at sufficiently high risk to warrant more intense (e.g. daily or more frequent) screening.

Several clinical prediction tools have been developed (214) in order to assist with risk stratification, however these can include elements which are not easily assessed at presentation (215) or involve complex calculations that are poorly suited to the demands of busy real-world everyday practice (216). In this study, we aimed to focus the NICE criteria in order to tailor screening to the most vulnerable groups based on information that would be readily available and easily recordable at the point of hospital admission.

5.2. METHODS

5.2.1. SETTING AND PARTICIPANTS

This was a prospective observational cohort study conducted in two hospitals in Cork city, Ireland (Cork University Hospital and the Mercy University Hospital) between October 2011 and August 2013. Patients of ≥70 years of age admitted medically through the emergency department were screened for study eligibility within 36 hours of admission (and usually within 24 hours). Patients who refused, who were gravely ill or dying, or who were admitted to the intensive care unit (ICU) were excluded from screening assessment. Following initial assessment, patients with prevalent delirium on admission; and those in whom formal delirium assessment was impossible due to severe communication difficulties (e.g. severe dysphasia,

severe non-communicative dementia) or coma were excluded from longitudinal assessment. Patients who were eligible for inclusion were then invited to participate in the prospective study and informed consent was sought. Consenting participants underwent daily assessment for the development of delirium for at least seven days or until discharged. Patients who were discharged early without delirium (within 3 days of admission) were excluded from the study due to inability to confidently outrule incident delirium post-discharge.

5.2.2. ASSESSMENTS USED

5.2.2.1. Delirium

A trained delirium assessor (NO'R) performed all delirium assessments using the Revised Delirium Rating Scale (DRS-R98). This diagnostically precise scale comprises 16-items; 13 of which grade severity of individual features (rated from 0 to 3) and 3 contextual items (rated from 0 to 2 or 3). The scores from each severity item are added to give a severity score and the scores from the diagnostic items are then added to the severity score to give a cumulative or total score (range 0 to 46). It is validated for discriminating delirium from other neuropsychiatric diagnoses, with high inter-rater reliability, sensitivity and specificity (90, 205). It can also be used to assess symptom severity over the previous 24-hour period and hence can be used to evaluate delirium phenomenology. In this study, delirium was diagnosed using a cut-off of ≥15 on the severity scale and / or ≥18 using the total score, in keeping with the guidelines for its use (173).

5.2.2.2. Potential delirium predictors

Potential predisposing and precipitating factors in medical inpatients were identified by reviewing the existing literature, including the NICE guidelines published in 2010 (5). We included only baseline factors which can be easily identified and are typically recorded routinely in hospital admission notes. We did not include vital signs or laboratory values. Demographic data and social history factors were recorded including age, sex, marital status, place of residence, social support, level of educational attainment and alcohol and smoking history. Excess alcohol intake was defined as drinking more than 14 units per week for females and more than 21 units per week for males (217). Comorbidity burden was calculated using the Modified Cumulative Illness Rating Scale for Geriatrics (M-CIRS) and medication use was recorded (see below). Prior history of depression was obtained from the medical chart and ascertainment of prior history of dementia is also described below. The Modified Barthel Index (BI) was used to assess functional status on admission and the Mini-Nutritional Assessment – Short Form (MNA-SF) graded nutritional status. Simple screening assessments of hearing and sight were performed at the bedside. A modified version of the Geriatric Depression Scale, the ABCDS (AB Clinician Depression Screen), was used to screen for current depression. See appendix A for copies of the instruments used.

5.2.2.3. Medications and Polypharmacy

A list of admission medications was compiled, including those taken regularly or on a PRN (as required) basis. This included those prescribed by a patient's general

practitioner or another doctor for recent illness. The term polypharmacy refers to the use of multiple medications by a patient, however there is no international consensus as to what the cut-off should be (5). Hence, in this study we considered the two cut-offs cited in the NICE guidance: three or more; and five or more medications. Additionally we collated a list of potentially deliriogenic medications (see table 9) based on the existing literature (218) and on the NICE guidelines (5) and identified patients who were in receipt of any one or more of those culprit medications.

5.2.2.4. Assessment of previous cognitive status

The Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) was used to assess for pre-admission cognitive impairment and decline. This is a 16-item scale scored by a caregiver or close relative. In this study, a mean item cut-off score of ≥3.5 was used to diagnose dementia in keeping with similar study cohorts (193). In borderline cases, diagnosis was reached by consensus discussion (with ST and DM). The medical case notes of each patient were also reviewed and in patients with no available collateral history / IQCODE-SF, a patient with documentation of pre-morbid dementia made by an appropriately trained physician was considered to have dementia. In the absence of an IQCODE-SF / collateral history / previous diagnosis, ascertaining dementia status was challenging. Those patients who scored ≥27 /30 on the SMMSE were considered not to have dementia, due to findings from another hospital-based study in which dementia prevalence was 2% in older patients with MMSE scores ≥27 /30 (192). Premorbid

cognition was recorded as “unknown” in participants with SMMSE scores < 27 / 30 without collateral history / IQCODE-SF (n=2).

5.2.3. ETHICAL PROCEDURES

The nature and purpose of the study was discussed in detail with participants and written information was supplied. However, it was anticipated that many participants would not be capable of giving informed written consent due to cognitive impairment at study entry. Therefore, in keeping with former studies, informed consent was obtained from patients capable of providing it, and assent to participation was sought from those who were incompetent to consent (based on informal assessment during the consent process), as well as support from a nearest relative or carer. Formal ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. Due to the non-invasive nature of the study, ethics committee approval was granted to augment patient assent with proxy consent from next of kin where possible, or a responsible caregiver, in accordance with the Helsinki Guidelines for Medical Research involving human subjects (207).

5.2.4. STATISTICAL ANALYSES

Demographic data were expressed as means ± SD or medians and IQR, depending on the distribution of the data. Comparisons of groups (delirium, no delirium) were made using a χ^2 or Fisher Exact test for differences in proportions, a t-test for differences in means or Mann Whitney U non-parametric tests for differences in

mean ranks. Univariate logistic regression was used to assess if various baseline predictor variables were associated with incident delirium. Variables with $p<0.05$ were included in a multivariable logistic regression model, using a simple "enter" method, where all significant variables were entered in the model together, as well as age and sex. The final model was assessed using the Hosmer-Lemeshow (C_{HL}) test for goodness of fit, and fitted the data well ($p>0.05$). Multicollinearity with the independent variables was investigated using the variance inflation factor (VIF) and tolerance statistic and where there was collinearity between variables, the most clinically relevant variable was included in the model, so that all the remaining variables had a VIF less than 10 and a tolerance statistic more than 0.1. Analyses were conducted using SPSS version 20.

5.3. RESULTS

A total of 191 patients were included in the final analysis (see figure 9 for a detailed explanation of flow of patients through the study). The median age of the included patients was 80 (IQR 10), 52.9% (n=101) were male and 16.9% (n=32) had premorbid dementia (see table 10 for a full report of the baseline characteristics of the cohort). We identified *a priori,* from the existing literature and using clinical judgement, factors which had the potential to increase delirium risk. Table 11 reports the odds ratios of important variables in relation to incident delirium development. Those who developed delirium were slightly older and more likely to have pre-morbid dementia, depression and hearing impairment. They also had higher comorbidity and functional dependence and were more likely to be undernourished. Patients

with incident delirium were also more likely to have either family support or formal social support. This was felt to be a surrogate marker for functional dependence, and not in itself likely to be a delirium risk factor so we did not include this factor in multivariable analysis. Using multivariable logistic regression (table 12), we identified variables that were independently predictive of incident delirium in this cohort and found that M-CIRS, BI and premorbid dementia with adjusted Odds Ratios (OR) of 1.15 (95% CI 1.06-1.25, per 1 unit M-CIRS increase); 1.13 (95% CI 1.06-1.25, per 1 unit BI decrease); and 2.54 (95% CI 1.01-6.43) respectively predicted delirium development independent of confounders.

5.4. Discussion

The NICE guidelines recognise the importance of regular delirium screening in vulnerable inpatients. They propose a risk stratification method which appears overly inclusive and which lacks routine applicability in many real world settings. Tailoring the approach more specifically to focus upon those most at risk would be more manageable in the busy hospital setting. Delirium is known to be a multifactorial condition, with more than one causative factor evident in most episodes (219). Multiple risk factor studies have shown a diverse range of predisposing and precipitating factors, however many studies do not differentiate between incident and prevalent delirium, which is crucial in order to ascertain which factors predated delirium development. Additionally, many risk factor studies report factors that involve excessive complexity in delirium risk stratification, for example delirium predictors which require laboratory sample analysis, such as serum urea

(81, 220, 221) and serum albumin (222, 223), or predictive models which involve a mathematical calculation (216). Our aim was to identify clinically relevant risk factors for delirium which could be easily established on the patient's arrival to the emergency department and which may target those who are at significantly higher risk of incident delirium during their hospital stay. In this prospective study, having examined multiple baseline factors, we identified three independent risk factors for incident delirium: high comorbidity; pre-morbid dementia; high functional dependence on admission. These risk factors have been identified in other studies, pre-existing cognitive impairment being one of the most consistently recognised delirium risk factors across clinical settings (224-226).

Co-morbid illness has also been shown in several studies to be independently predictive of delirium development. A study of 667 older hospitalised patients in Mexico, using the Cumulative Illness Rating Scale (CIRS) to evaluate comorbidity burden, found an adjusted OR for delirium development of 1.16 for each unit CIRS increase (95% CI 1.04-1.3, p=0.006), independent of other factors, findings very similar to ours (223). Inouye and colleagues found that high comorbidity indicated by a Charlson Comorbidity Index (CCI) score of >4 was independently predictive of delirium diagnosis at discharge from hospital (OR 1.7; 95% CI 1.1-2.6) in older medical patients. This effect of comorbidity has also been shown in surgical patients, again using either CIRS (227) or CCI (228).

Functional dependence has also been found in previous studies to be an independent risk factor for delirium development. Martinez and colleagues identified high level of dependency as one of three predictive factors in a model developed to classify delirium risk in patients on internal medicine wards (229). Another study conducted by Carrasco and co-workers found that older patients with good functional status who are not dehydrated on admission are highly unlikely to develop incident delirium, independent of increasing age (216). This predictive model requires laboratory measurement of serum urea and creatinine, along with BI measurement of function, with a subsequent calculation to infer delirium risk. Markers of dehydration, for example increased urea, or urea / creatinine ratio have been shown to be a risk factor in other studies (81, 220), however we did not include laboratory values in our analysis, given that our aim was to investigate risk factors that can be ascertained either by the referring doctor or immediately on presentation to the ED.

As well as functional dependency, the predictive model developed by Martinez and colleagues included two other risk factors: age >85 years old and being on centrally acting drugs, including antipsychotics (229). We chose to assess medication burden in a variety of ways. We assessed polypharmacy using cut-offs of both ≥3 or ≥5 medications (as outlined in the NICE guidance). We created a list of potential deliriogenic medications on admission (see table 9) and analysed this variable in two ways. Firstly, using a binary approach we identified if a patient was or was not on one or more potentially deliriogenic medication, and secondly we calculated the

number of potentially culprit medications each patient was in receipt of and entered this variable as a scale. We compiled this list to include medications identified in a recent systematic review by Clegg et al (218) as associated with higher risk of incident delirium, as well as those for which there is uncertainty regarding the risk of delirium. We also included additional medications outlined in the NICE guidance as being potentially deliriogenic (5). Martinez and colleagues included antipsychotics as a culprit medication, however the evidence regarding this drug class is mixed, with one high quality RCT in hip fracture patients showing that haloperidol was not associated with increased delirium risk (230) and other studies finding an independent association between antipsychotic use and delirium development (224, 231). Additionally, it appears that using antipsychotics prophylactically peri-operatively may reduce post-operative delirium incidence (232). Nonetheless, we repeated the analysis including antipsychotics as a culprit medication and our results did not differ. Non-steroidal anti-inflammatory drugs (NSAIDs) are another medication group in which there remains uncertainty in relation to delirium risk (218), however given that cyclo-oxygenase inhibition may have a protective effect in mouse models (233), we excluded NSAIDs from our list of potentially culprit medications. We did also repeat the analysis including NSAIDs and there remained no significant association with incident delirium. It is unclear why medication burden was not predictive of delirium development in this cohort, when the literature suggests increased risk with many medications. It is possible that our study was underpowered to detect a significant effect of medications. We did not examine medication doses, and although we were careful to exclude inhaled and topically administered preparations given the low likelihood of systemic absorption, all

patients on either low or high doses of a potentially culprit medication were treated the same. Although we only recorded admission medications, given that the majority of cases developed delirium on the second day of assessment, it is probable that the effect of post-admission prescriptions is negligible.

Older age was not an independent predictor of incident delirium in our cohort, despite being one of the most consistent risk factors throughout the literature (5), however like in Inouye's study in 1993 (220), using an age cut-off of >70 years for study inclusion may mean that we had *a priori* adjusted for age. A recent systematic review of risk factors for incident delirium in older medical inpatients found on pooled analysis that dementia, illness severity, visual impairment, polypharmacy, urinary catheterisation, low albumin, and length of hospital stay were statistically significantly associated with delirium (226). In general, only the first four of these factors are readily identifiable at presentation. Our study similarly identified dementia, comorbidity burden, as well as functional dependence. We also assessed for the effect of visual impairment, polypharmacy and malnutrition (using the MNA-SF), however found no significant independent association.

A study limitation is that we only considered older medical inpatients, and hence our findings cannot be generalised to surgical or intensive care patients, or to younger patients. The small sample size is another important limitation of our study. We did not investigate any of the in-hospital risk factors, as we were focusing on variables

which are readily available at presentation to the emergency department, however we appreciate that these additional factors play an important role in precipitating delirium. Our view is that those who are stratified as high risk at the hospital front door, should all then be commenced on a delirium care pathway aiming to minimise the in-hospital precipitants.

Despite these limitations, our study has many strengths, including the prospective design, the performance of daily assessments throughout the first week of hospitalisation, as well as the use of a highly sensitive and standardised delirium diagnostic instrument performed by a trained and experienced assessor. There were few exclusion criteria and hence our cohort is likely to be representative of real world older medical inpatient populations. The patients were carefully assessed for pre-morbid dementia; functional dependence; comorbidity; medication burden; and for other risk factors, focusing on clinically relevant and easily identifiable risk factors. We found that functional and cognitive impairment as well as comorbidity burden were independently predictive of delirium development within the first week of admission, highlighting that delirium occurrence is a marker of general vulnerability, sharing risk factors with other geriatric syndromes, such as falls.

The NICE guidance risk stratification approach incorporates cognitive impairment, older age, illness severity and current hip fracture. Our study was conducted in older medical inpatients and did not include hip fracture patients. We agree that all hip

fracture patients and all dementia patients should undergo frequent delirium screening as these groups are especially delirium-prone with incidence rates of up to 62% in the former and up to 89% in the latter (234). Additionally, all severely unwell patients should be monitored regularly for complications, including delirium. However, our study has shown that older patients can be further risk stratified, based on their burden of comorbidity and their functional level on admission. Hence, we propose a modification of the NICE criteria regarding older patients, so that only those with higher comorbidity and lower functional status on admission should undergo intense (e.g. daily or more frequent) delirium screening, once assessed to be delirium free on admission. In busy, and often under-resourced health services, risk stratifying older patients in this way may assist in targeting delirium screening and preventative strategies to those who are most vulnerable, making this important process more feasible for routine application in every day practice.

Figure 9: Flow of patients through the prospective study

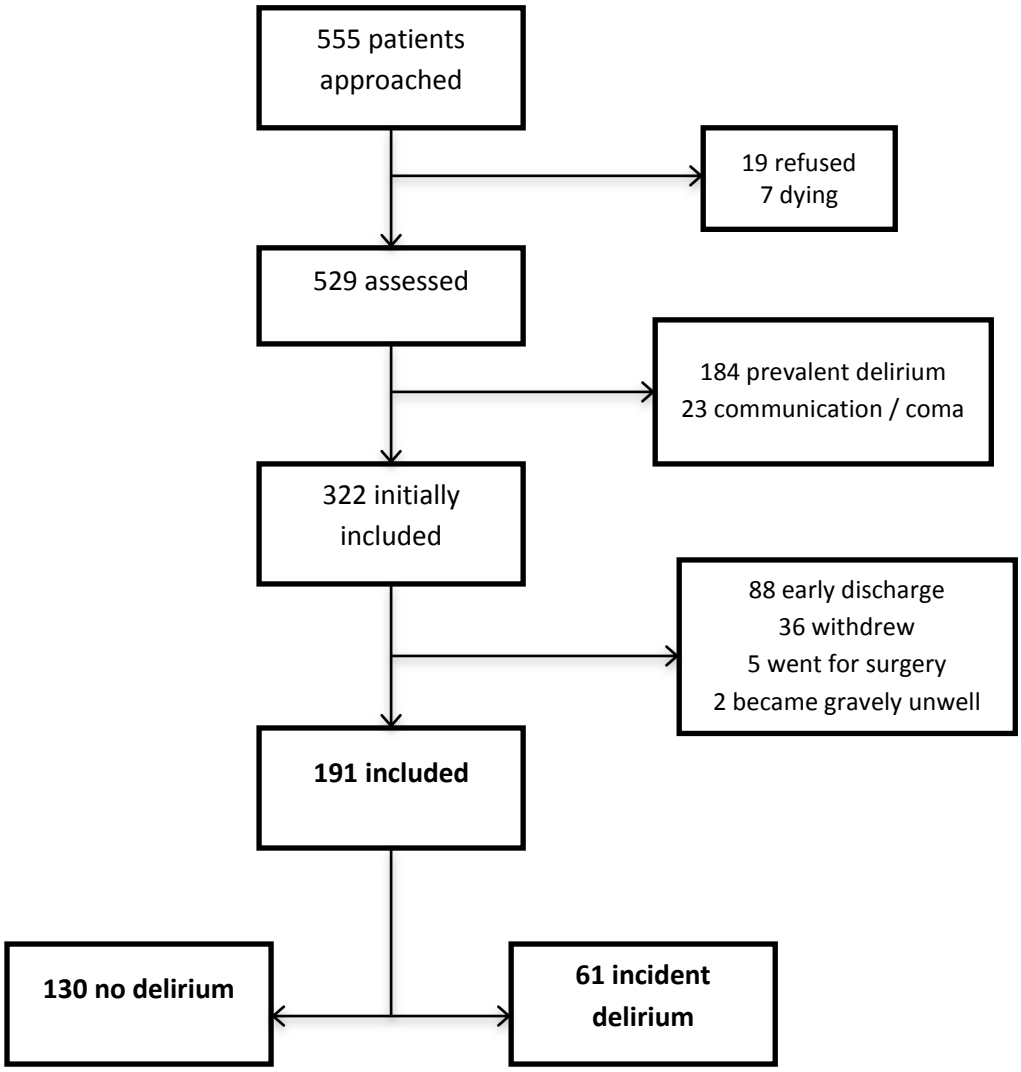


Table 9: List of medications included as potentially deliriogenic

*I also repeated the analysis including antipsychotic medications, however there remained no significant association on multivariable analysis. Similarly, I repeated the analysis including NSAIDs as potentially culprit medications. Given that both antipsychotics and NSAIDs may have a protective effect in relation to delirium development, the analysis reported includes neither of these medications classes (see text).

Benzodiazepines
Opioids
Dihydropyridines
Tricyclic antidepressants
Anticholinergics (excluding inhaled / topical)
Steroids (excluding inhaled / topical)
H2-receptor antagonists
Antihistamines (H1 receptor antagonists)
Drugs for Parkinson's disease
Zopiclone / zolpidem

Table 10: Baseline characteristics of the cohort separated into groups based on incident delirium status

*t-test for continuous data and Chi-squared test for categorical data unless otherwise specified.

[+]Social support= any level of formal support (home help / home care package) or practical support from a relative.

Variables	**Delirium (n=61) Means (SD) n (%)**	**No Delirium (n=130) Means (SD) n (%)**	**Shapiro Wilk's Del**	**NoDel**	**sig.***
Demographics:					
Age	81.4 (6.3)	79.4 (5.5)	.088	.012	0.03
Ln (Age)			.124	.021	**0.03**
			Equal variance both for Age and Ln Age		
*Sex (*female)	30 (49)	60 (46)			0.70
Marital Status					
Single	9 (15)	15 (12)			0.18
Married	20 (33)	61 (47)			
Widow	32 (52)	54 (41)			
Residence on admission					
1. Home alone	19 (31)	48 (37)			
2. Home with spouse/partner	18 (30)	59 (45)			
3. Home with relatives, others, sheltered	19 (31)	20 (15)			Fishers exact test**: 0.008**
4. Nursing home	5 (8)	3 (2)			1 cell has expected count less than 5
Social Support (excluding Nursing home patients)[+]	37 (67) (missing=6)	55 (44) (missing=4)			**0.003**

Variables	Delirium (n=61) Means (SD) n (%)	No Delirium (n=130) Means (SD) n (%)	sig.* Shapiro Wilk's Del NoDel
Alcohol excess			
1. No history	45 (76)	110 (85)	
2. Previous history of excess	11 (19)	10 (8)	
3. Current history of excess	3 (5)	9 (7)	0.085
	(missing =2)	(missing =1)	1 cell has expected cell count less than 5
Smoking history			
1. Never	26 (44)	56 (43)	
2. Ex-smoker	29 (49)	56 (43)	
3. Current smoker	4 (7)	17 (13)	0.410
Education			
Primary education or less	28 (52)	59 (47)	0.57
	(missing=7)	(missing=5)	
Premorbid Dementia	18 (30)	14 (11)	**0.001**
	(missing=1)	(missing=1)	
Depression			
1. Current screen positive for depression	6 (11)	6 (5)	Fisher's exact test: 0.188
(ABCDS and / or GDS)	(missing=5)	(missing=3)	1 cell with expected count <5
2. Previous history of depression	20 (33)	24 (19)	**0.028**
Sensory Impairment:			
1. Hearing impairment	38 (62)	59 (45)	**0.029**
2. Visual Impairment	11 (18)	22 (17)	0.811
	(missing=1)		

Variables	Delirium (n=61) Means (SD) n (%)	No Delirium (n=130) Means (SD) n (%)	sig.*
Barthel Index (median, IQR)	11 (6)	16 (6)	**<0.001** (Mann-Whitney U-test)
MNA-SF category			
1. Malnourished 0-7	23(39)	36(30)	
2. At Risk 8-11	35(59)	68(56)	**0.022**
3. Normal 12-14	1(2)	18(15)	
	(missing=2)	(missing=8)	
Admission culprit medication			
• On at least 1 deliriogenic medication on admission	41 (68) (missing = 1)	80 (62) (missing=1)	0.4
• Total number of deliriogenic medications on admission, median (IQR)	1 (1)	1 (1)	0.23
Polypharmacy			
• ***≥3 medications on admission***	55 (96) (missing =4)	105 (88) (missing =11)	0.075
• ***≥5 medications on admission***	50 (89) (missing =5)	92 (79) (missing =14)	0.106

Table 11: Odds Ratios for clinically relevant variables in relation to incident delirium development

β= coefficient, OR = odds ratio, CI = confidence interval; BI = Modified Barthel Index; M-CIRS = Modified Cumulative Illness Rating Scale; MNA-SF = Mini Nutritional Assessment – Short Form.

Residence was recoded as the binary variable 'nursing home resident yes / no'; Alcohol excess was recoded as 'current alcohol excess yes / no.

Variables	β	OR	95% CI (OR)	sig.
Female sex	-0.121	0.886	(0.48-1.63)	0.696
Age (per 1 unit increase)	0.06	**1.06**	(1.01-1.12)	**0.027**
Premorbid dementia	1.259	**3.52**	(1.61-7.7)	**0.002**
BI (per 1 unit decrease)	0.200	**1.22**	(1.13-1.32)	**<0.001**
M-CIRS (per 1 unit increase)	0.150	**1.16**	(1.09-1.24)	**<0.001**
MNA-SF score (per 1 unit decrease)	0.179	**1.2**	(1.04-1.37)	**0.012**
≥1 Deliriogenic medication on admission	0.279	1.32	(0.69-2.53)	0.4
Number of deliriogenic medications on admission	0.210	1.23	(0.83-1.83)	0.298
Polypharmacy (≥3 medications)	1.299	3.67	(0.8-16.71)	0.093
Polypharmacy (≥5 medications)	0.777	2.17	(0.83-5.67)	0.112
Nursing home resident	1.330	3.78	(0.87-16.37)	0.075
Hearing impairment	0.687	**1.99**	(1.07-3.71)	**0.03**
Visual Impairment	0.097	1.1	(0.5-2.45)	0.812
Previous history of depression	0.768	**2.15**	(1.08-4.31)	**0.03**
Current alcohol excess	-0.336	0.71	(0.19-2.74)	0.624
Primary education or less	0.186	1.2	(0.64-2.28)	0.568

Table 12: Association (multivariable logistic regression) between independent variables and incident delirium.

History of depression was excluded due to collinearity with premorbid dementia (-2 log likelihood 174.164; Hosmer-Lemeshow test p=0.75, β= coefficient, OR = odds ratio, CI = confidence interval)

Variables	β	OR	95% CI (OR)	sig.
Female sex	-0.215	0.81	(0.37-1.75)	0.586
Age (1 unit increase)	0.01	1.01	(0.95-1.08)	0.756
Premorbid dementia	0.934	**2.54**	(1.01-6.43)	**0.048**
BI (1 unit decrease)	0.142	**1.15**	(1.06-1.25)	**0.001**
M-CIRS (1 unit increase)	0.124	**1.13**	(1.05-1.22)	**0.001**
Hearing impairment	0.41	1.5	(0.69-3.27)	0.303
MNA-SF score (1 unit decrease)	0.073	1.08	(0.91-1.28)	0.409

6. THE NICE SCREENING RECOMMENDATIONS: CLINICAL EFFICACY AND RELATIONSHIP TO DELIRIUM PHENOMENOLOGY

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6.1. INTRODUCTION

Delirium is a common, serious neuropsychiatric condition occurring in one-fifth of acute hospital inpatients with higher rates in older patients and those with pre-existing cognitive impairment (1). Delirium independently predicts poor outcomes including increased mortality, institutionalisation and cognitive decline (3, 17). Despite this, delirium remains widely under-diagnosed across clinical settings, even though studies indicate an understanding of its importance among physicians (235, 236). Early recognition can improve outcomes (201) and, conversely, delayed diagnosis compounds their severity, most starkly highlighted in one study which found that each 48-hour delay in diagnosis resulted in an 11% increase in mortality (18). The causes of under-detection are myriad, not least due to its characteristically fluctuating nature and varying symptomatology. It is commonly missed or mistaken for other neuropsychiatric diagnosis (202) by those without expert training and

experience, particularly when it occurs in older patients (2), those with comorbid dementia (20) or psychiatric diagnoses (25) and in those with a hypoactive motor profile (21, 22).

Given its prevalence and prognostic implications, all patients at risk of developing delirium should be frequently and routinely assessed using systematically implemented sensitive tools. This is challenging as formal diagnosis is time-consuming and requires expert assessment using validated delirium assessment instruments. The Confusion Assessment Method (CAM) (83) is the most widely used diagnostic tool, having been designed initially for non-psychiatrists. It has been validated in multiple languages and clinical settings (84), but notwithstanding its broad scope and appeal, without appropriate training it lacks sensitivity, missing up to 50% of cases (87). It takes approximately 5 minutes to administer, but can take longer. More comprehensive assessment tools are more time-consuming and require an even greater level of expertise but are more diagnostically precise (89, 90). Other instruments based on patient observation have been developed, in order to address issues with patient fatigability and potential learning effect (92, 102), as well as to improve acceptability with nursing staff on the ground. Although these instruments show great promise, further studies are required to verify results.

In 2010, the UK National Institute for Health and Clinical Excellence (NICE) launched guidelines on the diagnosis, assessment and management of delirium, its key focus

being to improve delirium detection and management by promoting the adoption of a “THINK DELIRIUM” approach by all healthcare professionals in their day-to-day work (5). The guidelines highlighted the importance of identifying particularly vulnerable patients and advocated a two-stage screening and diagnostic approach in the at-risk population. A two-stage approach (incorporating a highly sensitive, brief and usable “rule-out” screening test followed by more detailed “rule-in” assessment in those who screen positive) is now widely recognised as the most feasible method of improving detection (88, 212), and multiple approaches have been suggested (88, 91, 105). The NICE guidelines, developed by a panel of experts, make recommendations as to how to monitor for emerging delirium on a daily basis as unfortunately there was (and still is) no consensus on the best detection method for routine ward use by staff untrained or minimally trained in delirium. The recommendations prompt staff to observe for changes or fluctuations in a series of delirium indicator symptoms divided into four domains: cognitive function; perception; physical function; and social behaviour (see table 13). There is no doubt that these indicators reflect aspects of the core features of delirium and, hence have face validity, however a specific method of application is lacking in the guidelines. Given the nuances of delirium presentation, it is likely that success in following these recommendations would require a level of clinical skill in delirium detection which is only gleaned from experience and training. Whether or not this is the case remains unknown, as to date this screening approach has not been validated in the clinical setting.

Given the protean nature of delirium features, another interesting question pertaining to these guidelines is to which aspects of delirium phenomenology do the individual indicators relate? We now know that certain delirium features are central to diagnosis (for example inattention), and some features occur consistently but not universally (such as psychomotor disturbance), whereas other symptoms occur more sporadically (for example, perceptual abnormalities, delusions and affective lability) (40). The inter-relationship of these delirium features has been analysed in various studies by either examining correlations between individual symptoms or their relationship through factor analysis (41). Cross-sectional and longitudinal studies have identified that delirium comprises a three-factor structure (42, 43), divided into attention / other cognitive; circadian (psychomotor and sleep-wake cycle disturbances); and higher level thinking (disorders of language, thought process and executive function). This work helps to illuminate the inter-relationship between certain features and should facilitate improved understanding of delirium neuropathogenesis, amongst other areas (41).

As aforementioned, certain patient groups are more prone to under-detection than others, but interestingly, there is also evidence to support the notion that different healthcare disciplines are more attuned to differing symptomatology as it presents. For example, work from our research group shows that doctors tend to identify delirium in the presence of inattention and short-term memory, whereas delirium visibility to nursing staff was increased in the setting of delusions and affective lability, as well as inattention and long-term memory impairment (1). Consequently,

the aims of this study were firstly to assess the clinical utility of an operationalised approach to the NICE screening recommendations in a routine ward setting (compared to two gold-standard tests, namely CAM and DRS-R98), and secondly to examine the relationship between the NICE indicators and the various components of delirium phenomenology (using the DRS-R98).

6.2. METHODS

6.2.1. SETTING AND PARTICIPANTS

This study was nested within a larger prospective observational cohort study of delirium prodrome which was conducted in two hospitals in Cork city, Ireland (Cork University Hospital and the Mercy University Hospital) between October 2011 and August 2013. Patients of ≥70 years of age admitted medically were eligible for inclusion. Patients who refused or who were gravely ill or dying were excluded, as were those with severe communication difficulties (e.g. severe dysphasia, severe non-communicative dementia) or coma.

6.2.2. ASSESSMENTS

6.2.2.1. Delirium Rating Scale-Revised '98 (DRS-R98)

This is a 16-item scale which includes 13 severity items (rated from 0 to 3) and 3 diagnostic items (rated from 0 to 2 or 3), with a total possible score range of 0 to 46. It is a diagnostic tool and is also used to assess symptom severity over the previous 24-hour period. It has high inter-rater reliability, validity, sensitivity and specificity

for distinguishing delirium from other neuropsychiatric disorders including dementia and depression (90, 204, 205). In this study, in keeping with guidelines for its use (173), DRS-R98 defined delirium was considered if the total score was ≥18.

6.2.2.2. Confusion Assessment Method

The Confusion Assessment Method (CAM), as stated above, is most broadly used delirium instrument (83, 84). It was based on DSM-IIIR (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition) criteria. The sensitive short-form and most commonly used version of this tool consists of five items: 1A) Acute onset; 1B) Fluctuating course; 2) Inattention; 3) Disorganised thinking; and 4) Altered level of consciousness, where the presence of 1A or B *and* item 2 *and either* item 3 or 4 gives a diagnosis of delirium.

6.2.2.3. NICE-based questionnaire

The NICE guidelines recommend screening for delirium on a daily basis, by assessing patients for changes in four domains: cognitive function; perception; physical function; and social behaviour. I developed a novel questionnaire based on these recommendations incorporating seventeen questions which reflected the key areas described in the guidelines (see table 13). These questions were divided into the four domains outlined in the guidelines. The first question in each domain is designed to introduce the major area under observation in that domain (e.g. Has there been a recent change or any fluctuations in the patient's cognition?) and the following

questions are more specific, focusing on a particular aspect of that domain. Each question is designed to be as close as possible in wording to that of the guidelines, and where possible the exact wording is used. The questionnaire was developed and revised in consultation with my supervisors (ST, DM).

A trained experienced delirium researcher (NO'R) conducted the delirium assessments, while a group of other researchers questioned the nursing staff independently using the NICE-based questionnaire. These researchers underwent a training session in which I instructed them to ask the questions in the order shown in table 13 (see appendix A for the relevant excerpt from the NICE guidance together with a copy of the questionnaire used). The researchers were blinded to the results of the delirium assessments and I was blinded to the results of the questionnaire.

6.2.3. ETHICAL PROCEDURES

This study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The nature and purpose of the study was thoroughly discussed with participants and written information was supplied. Informed consent was then obtained from capable participants. Due to the nature of the study, it was anticipated that many subjects would not have capacity to give written consent and hence, consistent with former studies, ethical approval was granted in these cases to bolster patient assent with approval from a nearest relative or next-of-kin in

accordance with the Helsinki Guidelines for Medical Research involving human subjects (207).

6.2.4. STATISTICAL ANALYSES

Statistical analyses were conducted using SPSS version 20 and Stata version 11 software packages. Descriptive statistics were reported as means ± SD for continuous variables and as proportions and percentages for categorical variables. In order to evaluate the components of the NICE-based questionnaire in terms of differentiating delirium from no delirium, a stepwise discriminant analysis was performed, using the data from assessment day two as this was the day with most delirium cases. The CAM and the DRS-R98 were respectively used to define delirium in two separate models, entered as the dependent variable with the individual components / domains of the NICE-based questionnaire entered respectively as the independent variables. The CAM and DRS-R98 were considered as binary variables (CAM positive / negative; DRS-R98 total score ≥ 18 /<18). A p-value of less than 0.05 was considered significant. The psychometrics of the final models were assessed by calculating sensitivity; specificity; positive and negative likelihood ratios, Positive Predictive Value (PPV), and Negative Predictive Value (NPV). Confidence intervals of 95% were utilised and are reported in the results. Cronbach's alpha was used to evaluate the consistency of questionnaire. Because the components of each assessment tool were categorical / binary, Spearman's Rho was used to assess the correlations between the elements of the NICE-based questionnaire and the individual items of the CAM and DRS-R98.

6.3. RESULTS

The highest number of dual assessments were conducted on assessment day two (n = 70), and hence we included only data collected on the second day of assessment for each patient. The mean age of this cohort was 79.7 (± 5.5) years, 61.4% (n= 43) were male and ten patients (14.3%) had pre-morbid dementia (see Chapter 3 for details on how pre-morbid dementia was identified). Nine patients (12.9%) had delirium on day two using the DRS-R98 for assessment; and fourteen (20%) using CAM. Twenty-nine patients (41.4%) screened positive using the NICE-based questionnaire (i.e. at least one of the 17 questions was answered positively by nursing staff). Twenty screened positively for physical changes, ten for changes in cognition, ten for changes in social behaviour and two for perceptual change. There was low agreement using Kappa statistic between a delirium diagnosis using the NICE-based questionnaire and either CAM (κ=0.247) or DRS-R98 (κ=0.149). Cronbach's alpha for the 17-item questionnaire was 0.740.

Discriminant analysis was then used to identify which of the questions from the NICE-based questionnaire would discriminate between those who had delirium and those who did not. Only fifteen of the seventeen questions were included in our initial model, as the three questions pertaining to perceptual change were collinear (see table 13). The analysis was performed using firstly the CAM and subsequently the DRS-R98 as the dependent variable, these two analyses producing differing results (see table 14), likely reflecting the known discordance in diagnosis between these two tools (as evidenced again here by almost twice the diagnosis rate with

CAM than DRS-R98, 12.9% v.s 20%) . We then repeated the analysis, this time entering into the model the four domains of change as described by the NICE guidelines: *cognitive change; perceptual change; changes in physical function;* and *changes in social behaviour* (see table 13). If any question(s) in an individual domain was positive, change in that domain was considered present. The only domain in which changes significantly predicted delirium / not delirium classification, using either the CAM or the DRS-R98 as the dependent variable, was *cognitive change* (see table 15, p=0.001; p=0.031 respectively). Using the CAM as the dependent variable, 82.9% of participants were correctly classified, and 77.1% were correctly classified when the DRS-R98 was used. The diagnostic accuracy of this approach was calculated, such that any positive response on the cognitive domain section was considered a positive screen. Sensitivity; specificity; Likelihood Ratios (positive LR+ and LR-) both conventional as well as weighted by prevalence (wLR); and positive and negative predictive values (PPV; NPV) are shown in table 16. Despite the high percentage of correct classification on discriminant analysis, the sensitivity of the NICE-based domains for delirium identification was low, particularly for DRS-R98 defined delirium at 33% (95% CI 9-69.1), see table 16. Sensitivity for CAM-defined delirium was slightly higher at 41.7% (95% CI 0.16.5-71.4), whereas specificity was high using both diagnostic methods for diagnosis (CAM 92.9%, 95% CI 81.9-97.7; DRS-R98 88.5%, 95% CI 77.2-94.9).

This approach is not how the guidelines were meant to be utilised however. The NICE guidelines state that evidence of any of the delirium indicators outlined should

alert staff to the possibility of delirium. In relation to our questionnaire, this means that a positive response to at least one question in any of the four domains should indicate a positive screen. Table 16 also outlines the psychometrics of the NICE-based questionnaire using each respective delirium diagnostic method as the dependent variable. With this approach, sensitivity is improved using either the CAM or the DRS-R98 as the reference standard, however at 64.3% (CAM, 95% CI 35.6-86.0) to 66.7% (DRS-R98, 95% CI 30.9-91.0), it is still too low for the questionnaire to be considered a useful screening test. It is important to stress that these results must be interpreted with great caution due to the low agreement between the NICE-based questionnaire and each of the diagnostic methods, as outlined above.

Spearman's Rho was used to examine the correlations between the individual questions from the NICE-based questionnaire and the components for the CAM and the DRS-R98. The significant correlations are shown in tables 17 and 18. Some items on the NICE-based questionnaire correlate well with corresponding similar items on the CAM / DRS-R98, for example NICE-based question 1a ("Has there been a recent change or any fluctuations in the patient's cognition?") correlates highly with CAM item 1B (fluctuating course) and DRS-R98 item 15 (severity of fluctuations); question 2a ("Has the patient had any perceptual disturbances?") correlates highly with DRS-R98 item 2 (perceptual disturbances and hallucinations); and question 3d ("Has there been any change in their sleep pattern?") correlates somewhat with item 1 on the DRS-R98 (sleep-wake cycle abnormalities). Other items from the NICE-based questionnaire which would be expected to map onto related items from the CAM

and / or DRS-R98, do not show any significant correlation with these items. For example, question 1b *"Does it seem harder for them to focus on what you're saying or on a task?"* is a question commonly used to identify from an informant whether or not a subject has informally demonstrated inattention over the time period. This question would hence be expected to correlate with CAM item 2 and DRS-R98 item 10 which evaluates for inattention, however it did not. In fact it did not correlate with any cognitive item on the DRS-R98. Inattention on the CAM and DRS-R98 instead correlated with other questions from the cognitive domain of the NICE-based questionnaire, for instance, question 1b *("Has the patient been more confused than usual in the last 24 hours?")*, indicating that nursing staff recognise "confusion" but not inattention per se. No other cognitive item from the DRS-R98 correlated with any of the cognitive domain questions from the NICE-based questionnaire.

Questions directed towards the identification of hyperactivity and hypoactivity did not correlate with their counterparts on the DRS-R98, yet DRS-R98 item 7 (motor agitation) correlated well with questions pertaining to cognitive function, social behavior and changes in sleep pattern. The only question from the NICE-based questionnaire which did not correlate with any CAM / DRS-R98 item was the question *"Have they become less active or have they slowed down in general?",* which is unremarkable, given that it is well-documented that hypoactive delirium is the most unrecognised form. Instead, motor retardation correlated somewhat with questions related to perception and social behavior. DRS-R98 item 14 (temporal onset of symptoms) somewhat correlated with question 1a ("Has there been a

recent change or any fluctuations in the patient's cognition?"); question 1b ("Has the patient been more confused than usual in the last 24 hours?"); and question 4a ("Has there been any changes in their social behaviour?"), whereas its counterpart on the CAM (item 1A, acuity of onset) correlated with question 3d ("Has there been any change in their sleep pattern?"), indicating that meaningful changes in cognition, sleep pattern and social behaviour may be identified by nursing staff.

6.4. Discussion

Our results indicate that the sensitivity of a questionnaire based on the NICE indicators of delirium is too low for the tool to be safely used as a screening test. When the questionnaire is used such that any positive answer reflects a positive screen, sensitivity is approximately 65%. On discriminant analysis, changes in the cognitive domain significantly predicted whether or not a patient was delirious, correctly classifying up to 82.9% of patients, whereas changes in other domains did not. Using the cognitive domain, a high proportion of patients were labelled falsely negative, however, and thus sensitivity was even lower at 33.3-41.7%. Neither approach would hence be suitable as the first step in a two-stage delirium screening process, where the initial phase requires high sensitivity to minimise the occurrence of missed cases. The concept of a two-stage screening method has gained traction in recent years as more insights are gained into barriers to delirium detection on the ground. Such a concept is utilised successfully in many other clinical scenarios, for example the use of D-Dimers to help ascertain which patients require further investigation for venous thromboembolism (VTE). Importantly, in this example, a

patient presents with a clinical feature suggestive of the diagnosis of concern, thus prompting a diagnostic algorithm. When a patient develops delirium, it most commonly does not announce its arrival. Affected patients, by its very nature, are unaware of unfolding cognitive and neuropsychiatric change, and relatives and healthcare professionals alike often normalise 'confusion' in the setting of an older person with acute underlying illness. Hence when it comes to delirium screening, we need a 'track and trigger' approach (not unlike the concept of the National Early Warning Score for physical illness (237)), where a 'cognitive vital sign' is recorded as routinely as physical observations, and further assessment is indicated in the setting of results outside an accepted range.

By examining the correlations between the NICE indicator features with the individual constituents of the CAM and DRS-R98, we explored which formal tool-identified delirium features were detected by nurses in the routine ward setting (tables 17 and 18). Questions on the NICE-based questionnaire which correlated well with corresponding items on the formal tests include those pertaining to perceptual abnormalities and sleep-wake cycle disturbance, indicating that these features are likely to be highly visible to untrained nursing staff. Caution must be exercised when interpreting this, however, as only two patients screened positive in this study for perceptual change. In any case, psychotic symptoms only occur in approximately half of delirium presentations (42) and hence reliance on detecting perceptual abnormalities in screening for delirium would miss too many cases. Although the sleep-wake cycle is consistently affected in delirium, studies indicate that mild

changes occur very frequently in non-delirious patients, with more moderate to severe disruption being associated with subsyndromal and full-syndromal delirium (76). Thus, depending on recognising changes in sleep pattern is likely to be overly non-specific. As aforementioned, inattention is a cardinal feature of delirium, however, to those less schooled in delirium presentation, inattention on the CAM or DRS-R98 did not correlate with the NICE-based question designed for this purpose (question 1b *"Does it seem harder for them to focus on what you're saying or on a task?")*. Other cognitive questions did however correlate with formally diagnosed inattention, which perhaps suggests that the concept of inattention, although recognised as a component of cognition, is poorly understood. Questions on the NICE-based questionnaire pertaining to physical function would have been expected to be associated with motor items on the DRS-R98, but this was not the case. Instead both psychomotor agitation and retardation correlated highly with indicators of change in social behaviour. Motor agitation correlated also with questions pertaining to sleep pattern and cognition. The former finding may reflect a tendency for nursing staff to be particularly alert to nocturnal agitation due to the ensuing care issues as well as the effect on neighbouring patients. The overly broad use of the umbrella term 'confusion', which can refer to the presence of any one of various different phenomena from disorientation to disorganised thinking to delusions, including agitation, may account for this correlation. Unsurprisingly psychomotor retardation correlated with fewer questions on the NICE-based questionnaire and indeed the only question not to correlate with any of the CAM / DRS-R98 formally diagnosed features was the one designed to detect hypoactivity (question 3b, *"Have they become less active or have they slowed down in general?").* This reflects the subtle

presentation of hypoactive delirium and corresponds with previous work reporting poor detection rates in this group (21, 22).

In another study, aiming to shorten the duration of CAM assessment, Yang and colleagues (238) used item response theory to identify the most efficient set of items to determine the presence or absence of each of the CAM features in 4,598 patients enrolled in a randomised controlled trial of a Delirium Abatement Program (611 with delirium) (239). Although the methodology of this large study contrasts greatly with ours, it examines a similar concept and some of their results are mirrored in our findings. Investigators report the top five delirium indicators for each CAM feature positive subgroup, both on direct interview and by observation, so that each CAM feature was related to ten indicators. Features indicating CAM item 1 positivity included a subjective feeling of confusion over the past day; and evidence of sleep disturbance. In our much smaller study, the NICE-based questions directed at these features ("*Has there been a recent change or any fluctuations in the patient's cognition?"; "Has the patient been more confused than usual in the last 24 hours?";* and *"Has there been any change in their sleep pattern?")* also correlated with item 1 A or B on the CAM. Yang and colleagues identified that formal and informal assessment of orientation and attention corresponded to CAM item 2 on the CAM. Our work found that the only cognitive items to correlate with this item were questions relating to general cognitive change rather than inattention per se, as described above. In contrast to the work by Yang and colleagues, in our study none of the NICE-based questions correlated with CAM items 3 or 4, however none of

them targeted these aspects definitively and only two questions could be considered related in some way to these features: respectively "*Has there been any changes in their level of communication with you?";* and *"Has there been any change in their sleep pattern?".* The reasons for any discrepancies between the two studies are clear. The two studies methodologies are vastly different, our study purely identifying correlations between various features of delirium using different methods of assessment in a small cohort of older medical inpatients. In the study by Yang and co-workers, there was significant *a priori* conceptualisation by a panel of delirium experts as to which symptom dimensions and features would likely be related to each CAM item. The data was drawn from a multicentre interventional study of delirium with 611 cases of CAM-defined delirium. Additionally, it is likely that assessments in this study were made by clinicians trained in delirium assessment, whereas the staff nurses who participated in our work were for the most part without any delirium training. Nevertheless, there are some interesting parallel findings between the two studies.

Despite our small numbers, our study has many strengths. Firstly, to our knowledge, it is the first attempt to investigate the clinical utility of these guidelines as recommended by NICE and we developed a novel questionnaire based on the guidelines for this purpose. Furthermore, we utilised this questionnaire as an innovative method to ascertain which delirium features are recognised by staff with minimal or no training and which features are not detected. Secondly, formal delirium assessment was conducted by a trained and experienced delirium assessor

using two well-validated delirium assessment tools. The researchers utilising the NICE-based questionnaire were blinded to the delirium status of the patients and operated completely independently of the delirium assessor. The cognitive domain was the most significantly predictive of delirium / no delirium group membership using both DRS-R98 and CAM as the dependent variable indicating validity of the results. Limitations of our study include the small number of delirium cases included and as this was a study in older medical inpatients only, this may affect the generalisability of the results. Also our novel questionnaire was based on our interpretation of the guidelines only, and hence we cannot be certain that our results definitively answer the question as to the clinical utility of the guidelines.

Approaches to delirium screening must take into account the type of clinical setting for implementation, the time available and expertise of staff who will conduct the screening, as well as the availability of experts in the area. In general hospitals, particularly with increasing demands and staff shortages, it is imperative that a screening instrument be brief and easy to apply with minimal training. Approaches that require significant training are costly, particularly considering the additional opportunity cost of removing staff from duty. Given the prevalence of delirium across the general hospital with associated increased healthcare costs and other poor outcomes, the initial screening test must be sensitive in order to reduce the risk of missing cases. The best, most efficient initial screening method has yet to be confirmed, although many approaches have been suggested and initial results are encouraging. The NICE guidelines give recommendations to healthcare staff to

observe for indicators of delirium in at-risk patients. Similar screening approaches designed for nursing staff use and based on monitoring for observed changes include two instruments developed in Canada: the NuDESC (92) and the RADAR (102). The NuDesc (Nursing Delirium Rating Scale) is a five-item observational test which assesses for disorientation; inappropriate behaviour; inappropriate communication; perceptual abnormalities and psychomotor retardation. It takes less than one minute to perform and takes into account reduced activity which occurs with illness. Preliminary studies show a sensitivity of 85.7% and a specificity of 86.8%, using DSM-IV as the reference standard (92). Designed to be administered during medication rounds, the RADAR (102) prompts nursing staff to observe patients for evidence of drowsiness, poor concentration / comprehension, and psychomotor retardation. It has at best acceptable sensitivity and specificity (at 73% and 67% respectively) against DSM-IV-TR (and also DSM5) criteria for delirium when administered four times daily, but its major strengths are its brevity and simplicity. Taking only seven seconds to administer, the authors assert that it detects 73 times more cases of delirium per minute than the CAM. Other advantages include its acceptability to nursing staff and a concise training programme. Given the difficulty in picking up subtle but highly prevalent hypoactive delirium, it is likely that a formal test of attention and / or cognition is also required to buttress these observational methods and improve sensitivity.

In conclusion, screening for delirium across clinical settings is important, yet greater clarity is required as to the best approach for each environment. The NICE guidelines

recommend screening for changes in four domains which can be affected in delirium, however our study highlights that minimally trained staff have at best modest accuracy in delirium detection by applying a questionnaire based on these guidelines. It is likely that a simpler approach is warranted in the acute hospital setting. Further studies are required to elucidate which approach is most effective for this purpose.

Table 13: NICE guidelines with the questionnaire embedded

[1]These two questions were excluded from the discriminant analysis, as they were considered collinear with question 2a.

Excerpt from NICE guidelines on screening		**Questionnaire based on these guidelines**	
At presentation, assess people at risk for recent (within hours or days) changes or fluctuations in behaviour. These may be reported by the person at risk, or a carer or relative. Be particularly vigilant for behavior indicating hypoactive delirium (marked*). These behavior changes may affect:			
Cognitive function	*for example:*	1.a	Has there been a recent change or any fluctuations in the patient's cognition?
	confusion	1.b	Has the patient been more confused than usual in the last 24 hours?
	worsened concentration*	1.c	Does it seem harder for them to focus on what you're saying or on a task?
	slow responses*	1.d	Are their responses to you slower than before?
Perception	*for example:*	2.a	Has the patient had any perceptual disturbances?
	visual or auditory hallucinations	2.b	Have they complained of any hallucinations?[1]
		2.c	Does it seem that they are responding to things that are not there?[1]
Physical function	*for example:*	3.a	Has there been any changes in the patient's physical function?
	reduced mobility*, reduced movement*	3.b	Have they become less active or have they slowed down in general?
	restlessness, agitation	3.c	Have they been restless or agitated at all?
	sleep disturbance	3.d	Has there been any change in their sleep pattern?
	changes in appetite*	3.e	Have they lost their appetite?
Social behaviour	*for example:*	4.a	Has there been any changes in their social behaviour?
	withdrawal*	4.b	Have they become withdrawn or disinterested?
	lack of cooperation with reasonable requests	4.c	Have they become less cooperative / need more prompting than usual?
	alterations mood and/or attitude	4.d	Have there been any changes in their mood / attitude towards you?
	alterations in communication	4.e	Has there been any changes in their level of communication with you?

Table 14: Results from discriminant analysis of 15 NICE-based questions using a) the CAM and then b) the DRS-R98 as the dependent variable
Significant findings shown

a) CAM as dependent variable

NICE-based question	Wilks' Lambda	F	df1	df2	sig.
1.b. Has the patient been more confused than usual in the last 24 hours?	.933	4.574	1	64	.036
3.d. Has there been any change in their sleep pattern?	.850	11.260	1	64	.001
3.e. Have they lost their appetite	.888	8.095	1	64	.006
4.a. Has there been any changes in their social behaviour?	.933	4.574	1	64	.036
4.c. Have they become less cooperative / need more prompting than usual?	.928	4.998	1	64	.029
4.e. Has there been any changes in their level of communication with you?	.928	4.998	1	64	.029

b) DRS-R98 as dependent variable

NICE-based question	Wilks' Lambda	F	df1	df2	sig.
3.d. Has there been any change in their sleep pattern?	0.868	9.423	1	62	0.003
3.e. Have they lost their appetite?	0.914	5.812	1	62	0.019

Table 15: Results from discriminant analysis of 4 NICE-based domains of change using a) the CAM and b) the DRS-R98 as the dependent variable

(+Could not be computed as it was a constant in the analysis)

a) CAM as dependent variable

NICE-based domain	Wilk's Lamda	F	df1	df2	sig.
cognitive change	.849	11.724	1	66	.001
perceptual change	+				
changes in physical function	.984	1.039	1	66	.312
changes in social behaviour	.982	1.217	1	66	.274

82.9% of cross-validated grouped cases correctly classified

b) DRS-R98 as dependent variable

NICE-based domain	Wilk's Lamda	F	df1	df2	sig.
cognitive change	.932	4.843	1	66	.031
perceptual change	+				
changes in physical function	.973	1.847	1	66	.179
changes in social behaviour	.945	3.858	1	66	.054

77.1% of cross-validated grouped cases correctly classified

Table 16: Sensitivity, specificity, likelihood ratios and positive and negative predictive values for delirium (CAM / DRS-R98 defined) using the NICE-based questionnaire.

Firstly, results pertaining to the NICE-based questionnaire in totality as a screening approach (any question answered positive = positive test are shown and secondly, the NICE-based cognitive domain of change (any cognitive domain question answered positive = positive test).

In brackets [95% confidence intervals]. LR+= Positive Likelihood Ratio, LR-= Negative Likelihood Ratio, wLR+= Positive Likelihood Ratio weighted by prevalence, wLR-= Negative Likelihood Ratio weighted by prevalence, PPV= Positive Predictive Value, NPV= Negative Predictive Value

	Sensitivity (%)	Specificity (%)	LR+	LR-	wLR+	wLR-	PPV (%)	NPV (%)
NICE-based questionnaire								
CAM as reference standard	64.3 (35.6-86.0)	64.3 (50.3-76.3)	1.8 (1.06-3.04)	0.56 (0.27-1.14)	0.45 (0.25-0.82)	0.14 (0.06-0.32)	31.0 (16.0-51.0)	87.8 (73.0-95.4)
DRS-R98 as reference standard	66.7 (30.9-91.0)	62.3 (48.9-74.1)	1.77 (1.01-3.11)	0.54 (0.21-1.37)	0.26 (0.12-0.54)	0.08 (0.03-0.24)	20.7 (8.7-40.3)	92.7 (79.0-98.1)
NICE-based cognitive domain								
CAM as reference standard	41.7 (16.5-71.4)	92.9 (81.9-97.7)	5.83 (1.83-18.56)	0.63 (0.39-1.02)	1.25 (0.49-3.19)	0.13 (0.07-0.27)	55.6 (22.7-84.7)	88.1 (76.5-94.7)
DRS-R98 as reference standard	33.3 (9.0-69.1)	88.5 (77.2-94.9)	2.9 (0.91-9.24)	0.75 (0.47-1.2)	0.43 (0.15-1.2)	0.11 (0.05-0.24)	30 (8.1-64.6)	90 (78.8-95.9)

Table 17: Significant correlations between the NICE-based questionnaire and the CAM using Spearman's Rho (sig.)

Each CAM item is scored as present or absent. Dis. Thinking = Disorganised Thinking; LOC= Level of consciousness. Correlations between related items shaded. Items which are somewhat related but do not correlate in lined shading; *p<0.05; **p<0.005, ***p<0.001

	CAM 1A Acute onset	CAM1B Fluctuating Course	CAM 2 Inattention	CAM 3 Dis. Thinking	CAM 4 Altered LOC
Cognitive function				No correlations	No correlations
1.a. Has there been a recent change or any fluctuations in the patient's cognition?		0.475 ***	0.37 **		
1.b. Has the patient been more confused than usual in the last 24 hours?		0.404 **	0.334 **		
1.c. Does it seem harder for them to focus on what you're saying or on a task?					
1.d. Are their responses to you slower than before?		0.356 **			
Physical function					
3.d. Has there been any change in their sleep pattern?	0.304 **	0.312 *			
3.e. Have they lost their appetite?		0.376 **			
Social behaviour					
4.a. Has there been any changes in their social behaviour?		0.289 **	0.242 *		
4.b. Have they become withdrawn or disinterested?			0.291 **		
4.c. Have they become less cooperative / need more prompting than usual?			0.291 **		
4.e. Has there been any changes in their level of communication with you?					

Table 18: Significant correlations between the NICE-based questionnaire and the DRS-R98 using Spearman's Rho (sig.)

Each DRS-R98 item is graded from 0-3 (items 1-14) or 0-2 (items 15 & 16), higher scores indicating greater severity / intensity. Item 1 sleep: Sleep-wake cycle disturbance; Item 2 perc: Perceptual disturbances and hallucinations; Item 3 del: Delusions; Item 4 affect: Lability of affect; Item 5 lang: Language; Item 6 thoug: Thought process abnormalities; Item 7 agit: Motor agitation; Item 8 retar: Motor retardation; Item 9 orient: Orientation; Item 10 attent: Attention; Item 11 stm: Short-term memory; Item 12 ltm: Long-term memory; Item 13 visuo: Visuospatial ability; Item 14 onset: Temporal onset of symptoms; Item 15 fluct: Fluctuation of symptom severity; Item 16 phys: Physical disorder

Correlations between related items in bold; *p<0.05; **p<0.005, ***p<0.001

	DRS-R98 item 1 sleep	**DRS-R98 Item 2 perc**	**DRS-R98 item 3 del**	**DRS-R98 item 4 affect**	**DRS-R98 item 5 lang**	**DRS-R98 item 6 thoug**	**DRS-R98 item 7 agit**	**DRS-R98 item 8 retar**	**DRS-R98 item 9 orient**	**DRS-R98 item 10 attent**	**DRS-R98 item 11 stm**	**DRS-R98 item 12 ltm**	**DRS-R98 item 13 visuo**	**DRS-R98 Item 14 onset**	**DRS-R98 Item 15 fluct**	**DRS-R98 Item 16 phys**
Cognitive function																
1.a. Has there been a recent change or any fluctuations in the patient's cognition?					0.325 **		0.371 ***			0.321 **				0.238 *	0.406 ***	0.214 *
1.b. Has the patient been more confused than usual in the last 24 hours?							0.412 ***			0.314 **				0.268 *	0.246 *	0.239 *
1.c. Does it seem harder for them to focus on what you're saying or on a task?							0.335 **								0.225 *	
1.d. Are their responses to you slower than before?					0.312 **		0.262 *								0.446 ***	
Perception																
2.a. Has the patient had any perceptual disturbances?		0.522 ***						0.251 **								
Physical function																
3.a. Has there been any changes in the patient's physical function?	0.229 *															

Table 18 continued

	DRS-R98 item 1 sleep	DRS-R98 Item 2 perc	DRS-R98 item 3 del	DRS-R98 item 4 affect	DRS-R98 item 5 lang	DRS-R98 item 6 thoug	DRS-R98 item 7 agit	DRS-R98 item 8 retar	DRS-R98 item 9 orient	DRS-R98 item 10 attent	DRS-R98 item 11 stm	DRS-R98 item 12 ltm	DRS-R98 item 13 visuo	DRS-R98 Item 14 onset	DRS-R98 Item 15 fluct	DRS-R98 Item 16 phys
3.b. Have they become less active or slowed down?																
3.c. Have they been restless or agitated at all?			0.448 ***	0.267 **					0.226 *			0.219 *				
3.d. Has there been any change in their sleep pattern?	0.276 *		0.298 *			0.241 *	0.354 **		0.327 **	0.283 **	0.259 *		0.228 *		0.337 **	0.470 ***
3.e. Have they lost their appetite?			0.263 *						0.404 ***	0.282 **	0.383 ***	0.374 ***	0.256 *	0.3 *	0.387 ***	0.396 ***
Social behaviour																
4.a. Has there been any changes in their social behaviour?	0.269 *						0.389 ***	0.287 **	0.292 *				0.273 *	0.276 *	0.5 ***	0.326 **
4.b. Have they become withdrawn or disinterested?							0.241 *			0.242 *			0.216 *		0.377 ***	
4.c. Have they become less cooperative / need more prompting than usual?			0.25 *				0.306 **		0.288 **		0.225 *		0.209 *			0.247 *
4.d. Have there been any changes in their mood / attitude towards you?			0.346 ***				0.249 *		0.346 **							
4.e. Has there been any changes in their level of communication with you?			0.25 *	0.236 *			0.306 **			0.238 *	0.3 **	0.275 **	0.209 *			0.247 *

7. PRODROMAL FEATURES PREDICT DELIRIUM ONSET IN OLDER MEDICAL INPATIENTS.

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7.1. INTRODUCTION

Delirium is a complex neuropsychiatric syndrome caused by a variety of factors including acute illness, medication toxicity or injury. It is associated with adverse outcomes, such as mortality, loss of independence and cognitive decline (3), which relate not only to the underlying aetiology but also to the severity and duration of active delirium itself. It is highly prevalent across treatment settings, occurring in one-fifth of hospitalised patients (1) and in up to half of older inpatients (2). Despite its significance, case identification remains poor with approximately two-thirds of cases in inpatients missed or misdiagnosed as depression, dementia and other neuropsychiatric syndromes (202). Underdetection intensifies the poor prognosis associated with delirium, such that patients who are detected late have higher mortality rates (18, 19, 77), whereas early intervention and prevention can attenuate these outcomes and lessen the long-term burden of delirium (6, 7).

A characteristic feature of delirium is acuity of onset, with symptoms frequently appearing over hours to days. Indeed, this contextual feature is a core criterion for diagnosis and emphasised in prevailing diagnostic systems. An additional consideration to this paradigm is the concept of a prodromal phase, in which some patients can experience a variety of symptoms prior to full delirium onset. Although this concept has been mooted for decades, there remains a lack of clarity about the exact nature, incidence and course of these early features. This is because few studies investigating the delirium prodrome have been conducted, and many of these reports have not had the prodrome as a primary focus and hence vary greatly in methodology, populations studied and assessments used.

Lipowski provided some of the most comprehensive descriptions of delirium upon which many modern concepts of the syndrome are founded (44, 154). This work posited that delirium is frequently preceded by a myriad of features including reduced clarity of thought processes, emotional lability, sleep-wake cycle disturbance and a spectrum of perceptual abnormalities. Moreover, it was further asserted that this prodrome tended to occur when delirium was primarily caused by an underlying medical illness, whereas delirium due to trauma or surgery, being more acute in onset, lacked a prodromal phase. The concept that the prodromal phase can consist of delirium features, both cognitive and non-cognitive, as well as somatic emotional symptoms, is echoed in some of the subsequent literature in various study populations (155-161, 165, 167), see table 1 and 2 (Chapter 2). Sirois described headaches and general uneasiness as delirium approached in a study of

100 consecutive liaison psychiatry referrals (167). Matsushima and coworkers found prodromal changes of background slowing on EEG (theta/alpha ratio), sleep-wake cycle disturbance, anxiety and hyperactivity in a small sample (n= 6) of coronary care unit patients developing DSM-III-R delirium compared to controls (165). Osse and colleagues demonstrated that early changes in activity levels (measured using an actigraphic device) are associated with development of delirium in older post-operative cardiotomy patients (166). Levkoff and colleagues found that almost 70% of older inpatients studied experienced a prodromal phase, consisting of varied cognitive and non-cognitive features of delirium (159), and studies in bone marrow transplant patients have shown cognitive decline in patients with imminent delirium (157, 158). Hip surgery patients are the most frequently studied group, although the three studies in this population have methodological differences (155, 156, 161). Duppils and Wikblad observed patients for behavioural changes and found that although some post-operative changes, particularly anxiety, were common in patients with and without delirium, urgent calls for assistance, disorientation, psychomotor restlessness and inattention were more prevalent in those with impending delirium, compared to controls (161). Using the Revised Delirium Rating Scale (DRS-R98), De Jonghe and co-workers identifed that memory impairment, disorientation and formal thought disorder independently predicted delirium in a similar hip fracture cohort and that as delirium approached, DRS-R98 scores increased (155). This latter finding was replicated recently using the Korean version of the DRS-R98, in which pre-delirious post-operative hip surgery patients were found to have significant increases in an array of delirium features in the days before delirium developed, compared to those without impending delirium (156).

Using delirium specific instruments to detect a prodromal state can help to ascertain the relevance of subsyndromal delirium as a precursor to full-blown delirium. Subsyndromal delirium (SSD) is a state in which a patient expresses certain features of delirium without meeting the threshold for full formal diagnosis. It can occur either as a transitional state from no delirium to delirium and vice versa (70) or it can occur in isolation (240). It is phenotypically more related to delirium than no delirium (75) and has prognostic significance such that those with SSD have been found to experience adverse outcomes at rates intermediate between delirium and no delirium, independent of confounders (241). Interestingly, one study in post-cardiotomy patients has found that progression from SSD to full-syndromal delirium (FSD) was reduced with low-dose risperidone (73) suggesting that not only can SSD occur as a prodromal state but that intervention at this early stage may have huge benefits for delirium prevention. Although SSD presentation may contribute to the prodromal phase in some patients, the exact nature of the delirium prodrome is not yet fully understood and is postulated to include a constellation of other non-delirium specific symptoms which vary greatly in nature and range from cognitive disturbances to affective, behavioural and somatic symptoms. Providing clarity as to the characteristics and course of this prodrome may promote strategies to prevent progression to a full-blown episode by facilitating appropriate and prompt intervention during a clinically identifiable stage of delirium vulnerability. The aim of this study was to identify features that indicate imminent delirium in older medical inpatients without prevalent delirium upon admission.

7.2. METHODS

7.2.1. SETTING AND PARTICIPANTS

A prospective observational cohort study was conducted in Cork University Hospital and the Mercy University Hospital (Cork city, Ireland) from October 2011 to August 2013. Medical patients of ≥70 years of age admitted through the emergency department were screened for study eligibility within a maximum of 36 hours from admission. Patients who refused, who were gravely ill or dying, or who were admitted directly to the intensive care unit (ICU) were excluded from screening assessment. Following this assessment, patients with prevalent delirium on admission; and those in whom formal delirium assessment was unfeasible due to severe communication difficulties (e.g. severe dysphasia, advanced non-communicative dementia) or coma were excluded from further study. Demographic data pertaining to all those approached was collected. Eligible patients were then invited to participate in the prospective study and informed consent was sought. Consenting participants underwent daily assessment for at least seven days or until discharged. Patients without delirium who were discharged within three days of admission were excluded from the study. This was because in those discharged early, we considered it impossible to confidently outrule incident delirium in the seven days following admission.

7.2.2. ASSESSMENTS

7.2.2.1. Delirium

Delirium assessments were performed by a trained delirium assessor (NO'R) using the Revised Delirium Rating Scale, a 16-item scale including 13 severity items (rated from 0 to 3) and 3 diagnostic items (rated from 0 to 2 or 3), giving a total possible score range of 0 to 46. This diagnostically precise instrument evaluates symptom severity over the previous 24-hour period and hence can be used to characterise delirium phenomenology. Additionally, it has high inter-rater reliability, validity, sensitivity and specificity for differentiating delirium from other neuropsychiatric conditions including dementia and depression (90, 205). In this study, in keeping with guidelines for its use (173), delirium was diagnosed if the DRS-R98 severity score was ≥15 and / or if the total score was ≥18.

7.2.2.2. Prodromal Checklist

In order to characterise the behavioural aspects of the delirium prodrome, a novel checklist of potential prodromal features was created based on suggested features from the existing literature. This prodromal checklist included 34 features, categorised into five separate domains (see figure 10 and appendix A). Each item was scored from 0 to 2 (0 = not present; 1 = possibly or somewhat present; 2 = definitely present). This checklist was used to examine for the emergence of possible prodromal features on a daily basis. At admission, a close relative / carer was also interviewed using the Prodromal Checklist to ascertain if any features were present in the days leading up to admission. It was completed using all available information:

interview with the relevant nursing staff (and with family member / carer on day 1), direct observation of the patient during assessment, as well as information taken from the nursing notes.

7.2.2.3.Baseline assessments

Demographic data (age, sex) and information relating to social history (including marital status; place of residence; alcohol and smoking history; and educational attainment) was collected. Comorbidity burden was measured using the Modified Cumulative Illness Rating Scale (M-CIRS) and pre-admission regular and 'as required' (PRN, pro re nata) medication history was documented for the week prior to admission. A list of deliriogenic medications (see table 9, Chapter 5) was derived from the existing literature and the NICE guidance (5, 218) and used to identify if a patient was on an at-risk medication prior to admission. Functional status was evaluated using the Modified Barthel Index (BI), nutritional status was measured using the Mini-Nutritional Assessment – Short Form (MNA-SF) and screening for sensory impairment was performed using simple bedside assessments of hearing and sight. Patients were also screened for depression using the ABCDS (AB Clinician Depression Screen), a modified version of the Geriatric Depression Scale (see Chapter 2 and appendix A for more detail on these instruments).

7.2.2.4. Assessment of previous cognitive status

For all patients, the medical case notes were reviewed for a diagnosis of pre-existing cognitive impairment or dementia made by a suitably trained physician. This was confirmed by the use of the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) to assess pre-admission cognitive impairment and decline. This 16 item scale was scored by a caregiver or close relative and a mean item cut-off score of ≥3.5 was used to diagnose dementia (193). Consensus discussion (with ST and DM) was used to apply diagnosis in borderline cases. In the absence of an IQCODE-SF / collateral history / previous diagnosis, patients were considered not to have dementia if they scored ≥ 27 / 30 on the SMMSE, as a previous study (192) has shown that only 2% of hospitalised older people with an MMSE ≥27/30 have dementia. In those with lower SMMSE scores without collateral history, premorbid cognition was determined as "unknown" (n = 2).

7.2.3. ETHICAL PROCEDURES

The nature and purpose of the study was discussed in detail with participants and written information was supplied. However it was anticipated that many participants would not be capable of giving informed written consent due to cognitive impairment at study entry. Therefore, in keeping with former studies, informed consent was obtained from patients capable of providing it, and assent to participation was sought from those who were incompetent to consent (based on informal assessment during the consent process), as well as support from a nearest relative or carer. Formal ethical approval was granted by the Clinical Research Ethics

Committee of the Cork Teaching Hospitals. Due to the non-invasive nature of the study, ethics committee approval was granted to augment patient assent with proxy consent from next of kin where possible, or a responsible caregiver, in accordance with the Helsinki Guidelines for Medical Research involving human subjects (207).

7.2.4. STATISTICAL ANALYSES

Demographic data were expressed as means ± SD or medians and IQR, depending on the distribution of the data. Comparisons of groups (delirium, no delirium) were made using a χ^2 or Fisher Exact test for differences in proportions, a t-test for differences in means or Mann Whitney U non-parametric tests for differences in mean ranks. Associations between prodromal features and incident delirium were assessed using a Cox proportional hazards model. Incident delirium was defined as a DRS-R98 severity score of ≥15 and / or total score of ≥18. Models were adjusted for age, sex, comorbidity, functional status and cognitive status (see Chapter 5 for univariate and multivariable logistic regression models) and log likelihood was used to assess model fit. Confidence intervals of 95% were utilised and are reported in the results. The proportional hazards assumptions were checked using an extended Cox model with time-dependent covariates. Basic descriptives were performed using SPSS version 20 and recurrent event survival analyses using Stata version 11.

7.3. RESULTS

A total of 555 patients were approached over the study period and 529 were assessed (figure 9, Chapter 5). Prevalent delirium on admission was detected in 184 patients (34.8%), while 23 patients were not amenable to full delirium assessment on day 1 due to factors such as coma, stupor, or other communication problems. Thus, 322 patients were included in the prospective study, however many were discharged within 3 days (n=88), 36 withdrew, five underwent surgical procedures and two became too unwell to participate and hence were excluded from the analysis, leaving 191 patients with at least four consecutive days of assessment included in the final analysis. The median age of the included patients was 80 (IQR 10), 52.9% (n=101) were male and only eight patients (4.2%) were admitted from nursing homes (see table 10, Chapter 5) for a report of the baseline characteristics of the cohort, separated into groups based on incident delirium status). Multivariable logistic regression (see Chapter 5, table 12) identified M-CIRS, BI and pre-morbid dementia as independent predictors of incident delirium in this cohort.

Cox proportional hazards models were used to identify prodromal features that predicted delirium onset. Initially we investigated the prodromal items as a three-point scale as illustrated earlier (0 = not present; 1 = possibly or somewhat present; 2 = definitely present), however no features emerged as significantly predictive. Hence, the scale was collapsed into a two-point scale: 0=not present; 1= possibly or definitely present. The first model included all 34 prodromal items along with the independent baseline predictors from the multivariable logistic regression (M-CIRS,

BI and pre-morbid dementia), as well as age and sex. A step-wise approach was used to identify the most parsimonious model (table 19), removing non-significant variables at each step and monitoring for changes in model fit using the likelihood ratio. The variables did not vary significantly across time and hence proportional hazards assumptions were not violated. The features which were most predictive of impending delirium up to a week before delirium development were increasing confusion or 'fogginess' (HR 2.28, 95% CI 1.4-3.72); being easily distractible or going 'off-track' (HR 1.89, 95% CI 1.11-3.21); needing prompting for usual tasks (HR 1.86, 95% CI 1.1-3.14); seeming tired in the morning (HR 1.77, 95% CI 1.12-2.81); drowsiness during the day (HR 1.74, 95%CI 1.12-2.71); being 'fidgety', restless or wandering (HR 1.72, 95%CI 1.08-2.75); and irritability (HR 1.72, 95% CI 1.06-2.78).

7.4. Discussion

This is the first study designed primarily to characterise prodromal features in older medical inpatients with imminent delirium. Our novel prodromal checklist was developed by identifying all possible prodromal behavioural features from the existing literature on the subject and by concentrating these features into five specific domains. Our data shows that incident delirium in older medical inpatients is preceded by a behavioural prodrome characterised by seven features from this checklist (irritability; being easily distractible or going 'off-track; increasing confusion or 'fogginess'; needing prompting for usual tasks; seeming tired in the morning; drowsiness during the day; being 'fidgety', restless or wandering). Hence, our findings depict a prodromal state which closely resembles that which Lipowski

described anecdotally based on observations made throughout his career: "*one may often distinguish a prodromal stage during which the patient tends to have some difficulty in concentrating and thinking clearly; feels restless and anxious; and may complain of irritability, fatigue, malaise, hypersensitivity to lights and sounds, drowsiness, insomnia, vivid dreams and nightmares, and even transient illusions and hallucinations."*(154)

Moreover, our findings resonate well with those of other prodromal studies. Firstly, we found irritability to be predictive of imminent delirium. Duppils and colleagues found that signs of irritation / aggression / suspiciousness was slightly more common in patients with impending delirium (24%) compared with controls (12%) (161). In a study of Bone Marrow Transplant (BMT) patients, Fann and co-workers found using the 30-item Profile of Mood States that negative emotions such as tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and confusion-bewilderment subscale scores began an upward trajectory from approximately five days prior to onset of a delirium episode, peaking at day three to five post-delirium onset (157). Secondly, we found that patients with impending delirium were significantly more likely to be considered easily distractable or to be going 'off-track', an informal description of inattention. This characteristic has emerged as a prodromal feature in many studies and case studies. De Jonghe and colleagues found that poor concentration measured by the digit span was common in the prodromal phase, occurring in 67.3% of delirious patients two days before delirium onset and in 81.8% of patients on the day before delirium occurred (155). In Levkoff and colleagues'

cohort of older hospitalised patients, 25.4% had either inattention or distractability in the delirium prodrome (159), and in two studies of BMT patients, decreasing attention span was demonstrated in the prodromal period before delirium onset compared to controls (157, 158). Crammer, in his self-report of a delirium experience, recounts an apparent decline in his awareness of the environment at least 24 hours prior to delirium onset (162). Disruption in the sleep-wake cycle has been identified as a feature of the delirium prodrome. In Levkoff's cohort of older medical inpatients, approximately one-quarter of prodromal patients experienced circadian disruption, including difficulty getting to sleep at night, being awake at night and sleepy during the day, similar to our findings (159). Again, our findings of hyperactive features in the prodromal phase compares well to the findings of Levkoff and co-workers, where 54% of patients who went on to develop delirium had notable psychomotor change, predominantly hyperactivity, in the preceding days. Increased psychomotor activity has also been described in prodromal hip fracture (156, 161) and in coronary care patients (165).

By including 'increasing confusion or fogginess', we were attempting to capture not just an obvious change in cognitive state but also the vagueness or disengagement that is commonly perceived but difficult to specify in patients with delirium or impending delirium. Carers or other untrained observers sometimes remark that the patient is 'not themselves', which may refer to this vague state. Although other studies have objectively demonstrated cognitive decline in various domains prior to delirium onset (156-158), no other study has alluded to this subtle manifestation of

brain dysfunction as a potential component of the prodromal phase. The item 'needing prompting for usual tasks' was intended to detect the poor motivation particularly associated with hypoactive delirium but also sometimes evident in hyperactive presentations, however again, this item has not previously been specifically investigated. None of the somatic features or general complaints in domain A of the prodromal checklist were significantly associated with delirium emergence in this cohort. This may be explained in part by the high comorbidity of the cohort overall (mean M-CIRS 20.56 ± 6.025), such that patients with and without delirium experienced these features or it may be that the items were too non-specific to rate on a daily basis. Interestingly, none of the items from domain E (speech / talk disturbance) were endorsed as significantly predictive of impending delirium, although previous studies have demonstrated disruptions in this domain during the delirium prodrome (155, 156), using versions of the DRS-R98 to detect these changes. Of note, Duppils and Wikblad, using similar observational methods to us, did not find an increase in incoherent speech in the pre-delirium stage (161).

Hence, our results indicate a specific prodromal profile in older medical inpatients, however it remains unclear as to how these pre-delirium features relate to the phenomenology of the ensuing delirium episode. It is possible that the features we have outlined are attenuated delirium symptoms which increase in expression as delirium unfolds. Being 'fidgety', restless or wandering may be a precursor to motor agitation, as may irritability which could equally signal the onset of affective lability. Increasing confusion or 'fogginess' may relate to any of the cognitive features or

indeed abnormalities of language, thought process, perception or delusions. Being easily distractible or going 'off-track' as well as needing prompting for usual tasks may indicate a descent into more severe levels of inattention, whereas morning tiredness and daytime drowsiness may herald the onset of significant disturbances in sleep-wake cycle. Conversely, it may be that the prodromal symptoms evolve in a distinct way to those that eventually appear when delirium emerges. Another consideration is whether prodromal features differ depending on the underlying aetiology or treatment setting. If this were the case, delirium and prodromal screening may need to be tailored to specific patient groups. Future studies of delirium prodrome should explore these issues further.

The strengths of this study include the prospective study design incorporating robust daily assessments for delirium by a trained and experienced delirium assessor. This together with daily documentation of individual symptoms from all available sources of information allowed us to carefully characterise the prodromal features of impending delirium in this large sample of older hospitalised medical patients. Another strength was the relatively large sample of patients with incident delirium and a comparison group of non-delirious patients. Most previous studies of prodromal features included less than 50 cases of delirium, and as low as ten cases in Matsushima's study of coronary care patients. The exceptions include Levkoff and colleagues who reported on 91 cases of delirium in 325 older general medical and surgical inpatients and de Jonghe and co-workers who studied 101 hip fracture patients, of which 66 became delirious and were included in the analysis. Other

studies of hip fracture patients included fewer delirium cases: in Duppils and Wikblad's study, 32 of 103 patients developed delirium and in Lee and co-workers' Korean cohort, 18 of 65 became delirious. In Fann and colleagues' study of BMT patients, 45 of 90 participants developed delirium, while Beglinger and coworkers reported delirium in 19 of 54 patients. We studied 61 cases of delirium and 130 controls which compares well with previous studies of this phenomenon. Analyses were adjusted for the significant baseline predictors of delirium in this cohort (i.e. pre-morbid dementia, comorbidity and functional status), thus allowing us to deduce that the identified features were aspects of the prodrome rather than reflective of other impairments.

Despite the methodological strengths, this study does have some important limitations. Firstly, the sample was non-consecutive, as with a single delirium assessor, it would have been unfeasible to assess consecutive patients in the longitudinal fashion required for the study's robustness. Secondly, although the prodromal checklist has face validity given its broad coverage of potential prodromal symptoms, the validity or reliability of the caregiver and nursing reports used to score the items has not been estimated. Of the 191 patients included in the analysis, 61 (31.9%) developed incident delirium. This is not reflective of a true incidence rate however, as many initially included patients were excluded from analysis for various reasons, including discharge within 3 days (n=88) and withdrawal (often with up to five assessments already performed, n=36). If the denominator includes these patients (n=315), the incidence of delirium in this cohort is approximately 19.4%,

which concurs with the existing literature on the subject. A systematic review of delirium epidemiology in medical inpatients (197) describes incidence rates varying between 3% and 29%, depending on the frequency of assessment. In the studies which report lower incidence rates (i.e. 3% to 11%), the frequency of assessment is either unclear or prompted by clinical need, or in one study, performed every 48 hours, whereas the majority of studies reporting higher incidence rates (12%-29%), utilised at least daily delirium assessment.

Delirium is challenging to detect, and diagnosis not only depends on face-to-face interview and observation, but also on the detail and accuracy of the collateral history made available to the assessor. It is thus possible that in some cases the prodromal phase was actually representative of a missed early diagnosis of delirium. Equally, more frequent delirium assessments may have perhaps identified symptoms and fluctuations more accurately. However, given the withdrawal rate of 11.2% (36 / 322), most commonly due to the duration and cognitive content of the assessment, performing more frequent assessments is unlikely to have been feasible. Furthermore, the delirium assessor was thorough in searching for evidence of delirium by interviewing at least one nursing staff member for each patient on a daily basis and by frequently checking the medical and nursing notes for documentation of delirium or a proxy term (e.g. confusion, agitation, withdrawal). Hence, we believe that delirium was diagnosed as early as was clinically possible within the confines of the study and that the features described in our results are indeed characteristics of the delirium prodrome.

Despite the study limitations, our results have illuminated clinically identifiable characteristics which herald the onset of delirium. Recognition of such harbingers of delirium in older medical inpatients may facilitate earlier detection and prompt intervention, and hence being alert to the prodromal features of delirium in this vulnerable inpatient group is important. It is well-recognised that in older medical patients admitted acutely, a thorough collateral history from a close family member or caregiver should be taken, particularly if there is evidence of impaired cognition, in order to identify the context of this impairment and establish whether it is due to prevalent full- or subsyndromal delirium, or a more chronic progressive decline. We propose that this collateral history should also include the seven prodromal features identified in this study to progress our efforts at delirium detection towards identifying those who are en route to developing the condition over the ensuing days. Following admission, monitoring for these features should also be undertaken on a daily basis by staff members (see figure 11 for a suggested approach). It is clear from the existing evidence that delirium prevention has the most significant impact on reducing the burden of delirium in the long-term (7), however it is yet to be ascertained if utilising delirium intervention strategies in the prodromal phase can actually prevent delirium or improve the prognosis. One study in post-cardiotomy patients indicates that antipsychotic prophylaxis in prodromal SSD may reduce the incidence of delirium (73), although results from a recent study in medical and surgical ICU patients disputes this (242). Furthermore, the effect of intervention in this stage on long-term patient outcomes has not yet been studied. Hence, further studies of this nature are required to definitively answer if these early changes present an opportunity for meaningful pharmaco-prophylaxis.

In summary, our study highlights that delirium in older medical inpatients is significantly associated with a variety of prodromal features which predict its onset and are clinically identifiable. Actively seeking out evidence of these features is likely to improve delirium identification rates and may lead to targeted preventive strategies which in turn can improve long-term prognosis.

Figure 10: Prodromal Checklist

(0 = not present; 1 = possibly or somewhat present; 2 = definitely present)

Prodromal Checklist			
A. General complaints. In the last 24 hours, have you noticed any changes in the patient's general wellbeing? 1. Appetite 2. Pattern of pain / discomfort 3. Frequency of requests for analgesia 4. Frequency of help seeking OR calling for attention 5. Other non-specific changes (e.g. general malaise, 'not themselves') 6. Does the patient have nocturnal worsening of symptoms? **B. Affect / emotional changes.** In the last 24 hours, have you noticed any changes in the patient's mood? 1. Tearfulness / sadness 2. Irritable / grumpy 3. Fear 4. Excess anxiety or worry 5. Inappropriate elation or euphoria 6. Excess remorse or guilt **C. Demeanour or cognitive changes** In the last 24 hours, have you noticed any changes in the patient's ….. 1. Awareness of surroundings or situation? 2. Being apathetic or disinterested? 3. Being easily distractible or going 'off-track'? 4. Level of confusion or 'fogginess'? 5. Needing prompting / encouragement to do usual tasks?	**0/1/2**	**D. Sleep/ activity changes** In the last 24 hours, have you noticed any changes in the patient's sleep / activity? 1. Poor sleep pattern at night (max 2) 1-3 hours awake (1) >3 hours awake (2) Nightmares (1) Difficulty getting to sleep (>30 minutes) (1) Seems to be tired in the morning (1) 2. Drowsiness during the day some of the time (1) a lot of the time (2) 3. Being 'fidgety', restless or wandering 4. Being combative or resisting care 5. Being less active than usual / expected 6. Slower movements 7. Does the patient SHIFT suddenly from low to high activity or vice versa? Over minutes (2) Over hours (1) 8. Does the patient SHIFT suddenly from wakefulness to drowsiness or vice versa Over minutes (2) Over hours (1) **E. Speech/ Talk disturbance** In the last 24 hours, have you noticed any changes in the patient's conversation? 1. Ability to find the right words or name things properly? 2. Understanding you 3. Holding a conversation 4. Saying odd things that don't make sense 5. Rambling off the point 6. Saying very little or nothing, lack of spontaneous speech	**0/1/2**

Table 19: Cox Proportional Hazards model. Prodromal features significantly associated with impending delirium

Most parsimonious model, Log likelihood -425.744., HR = Hazard ratio; SE = Standard error, CI = Confidence interval.

The final model excluded Modified Cumulative Illness Rating Scale as the best model fit was achieved without it.

Variable	HR	95% CI (HR)	SE	p value
Premorbid Dementia	1.96	(1.25-3.07)	0.448	**0.003**
Barthel Index Score (inverted)	1.08	(1.04-1.12)	0.023	**<0.001**
Increased confusion / 'fogginess'	2.28	(1.4-3.72)	0.568	**0.001**
Distractibility	1.89	(1.11-3.21)	0.511	**0.018**
Needing prompting for usual tasks	1.86	(1.1-3.14)	0.497	**0.021**
Tired in the morning	1.77	(1.12-2.81)	0.417	**0.015**
Drowsy during the day	1.74	(1.12-2.71)	0.392	**0.014**
Restlessness	1.72	(1.08-2.75)	0.412	**0.023**
Irritability	1.72	(1.06-2.78)	0.421	**0.027**

Figure 11: A suggested approach towards monitoring for prodromal features

[+] It is important to monitor regularly for evidence of delirium, but here I describe only monitoring for prodromal features

Collateral History on admission:							
1. Has X been more confused lately or do their thoughts seem a bit 'foggier'?	Yes / no						
2. Has X been more easily distracted recently or seem to go 'off track' when interacting with you?	Yes / no						
3. Has X needed more prompting or encouragement to do things that he / she would usually do?	Yes / no						
4. Has X seemed more tired than usual in the morning recently?	Yes / no						
5. Has X been drowsy at points during the day recently?	Yes / no						
6. Has X been more 'fidgety', restless or been wandering recently?	Yes / no						
7. Has X been more irritable or grumpy than usual recently?	Yes / no						
Positive answers to any of the above should alert you to the possibility of prevalent or emerging delirium and the patient should be reviewed by an appropriately qualified doctor							
Monitoring on the ward[+]							
Has the patient developed any of the following in the last 24 hours:	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. Thoughts appear 'foggy' or 'confused'							
2. Easily distractable or goes 'off-track' when interacting							
3. Needs more prompting or encouragement than usual for ADLs / eating / drinking / other tasks							
4. More tired in the morning than before							
5. Drowsy at times during the day							
6. Fidgeting, restless or wandering on the ward							
7. Increased irritability or grumpiness							
Positive answers to any of the above should alert you to the possibility of prevalent or emerging delirium and the patient should be reviewed by an appropriately qualified doctor.							

8. Delirium is Preceded by a Cognitive Prodrome in Older Medical Inpatients

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8.1. Introduction

Delirium is a serious acute neuropsychiatric syndrome which occurs commonly across the hospital setting (1), especially in older inpatients (2). It is independently associated with multiple adverse consequences, such as functional and cognitive decline, institutionalisation and mortality (3), outcomes which are exacerbated by late or missed diagnosis. Gonzalez and colleagues found an 11% increase in mortality with every additional 48 hours of delirium in a cohort of acutely unwell older adults, (18) and Kakuma and co-workers (19) reported a significant increase in six-month mortality in older patients discharged from the ED with undetected delirium, compared to those in whom a diagnosis of delirium had been made. Despite this, case identification remains low in clinical settings, with as many as 75% of cases unrecognised in the emergency department (ED) (23) and up to two-thirds missed or misdiagnosed on the wards (202).

Delirium presents with a constellation of symptoms which vary from patient to patient and fluctuate over the course of the day. Hence, making an accurate diagnosis requires training, experience, and time as well as a detailed collateral history from an informant. In order to improve detection, it is now generally recognised that a two-stage process should be employed: routine screening for core delirium features using a quick, simple test, with subsequent expert formal assessment in those who screen positive. As yet, there is no consensus as to which screening method is best, although there is some evidence to suggest that tests of attention may be useful (105, 108). Although the benefits of early detection should not be underestimated, it is important to highlight that as with most clinical conditions, prevention of delirium is prognostically better than cure, with multifaceted prevention programmes impacting most successfully on the long-term burden of delirium. These programmes, by recognising delirium-proneness, and by utilising a systemised approach to risk factor modification, have been shown to reduce delirium incidence by over one-third (7, 243, 244) and also to attenuate delirium-related mortality (243).

One of the core features for delirium diagnosis using any of the available diagnostic systems is acuity of onset, with symptoms typically developing over hours to days. There is growing evidence to suggest, however, that delirium can be preceded by a prodromal phase, which heralds its onset (10). This area has been under-researched to date, the small number of studies varying greatly both in primary study objectives and in methodology, including study population, measurements used and frequency

of assessment. Nonetheless, results from these studies (described below and in Chapter 2) indicate that the prodromal phase may comprise of some features of the delirium cluster, both cognitive and non-cognitive, as well as other somatic or emotional symptoms. The cognitive aspects of the prodrome vary from one study to the next, however the most commonly described features include impairments in attention and working memory, orientation, short-term memory and visuospatial function. Nonetheless, very few studies have used objective measures to characterise emerging cognitive deficits in the prodromal phase.

The most detailed study to date of the cognitive characteristics of the delirium prodrome was conducted by Beglinger and colleagues in bone marrow transplant (BMT) patients (158). Participants were assessed at a pre-transplantation visit with a 90-minute screening battery that included the Modified MMSE (3MS); Trail-Making Tests Parts A and B (TMT A, TMT B); the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); the Wechsler Abbreviated Scale of Intelligence (WASI); and a visual analogue scale of thinking clarity. Subsequently, while inpatients, delirium assessments were undertaken twice weekly for up to four weeks post-transplant or until discharge. At these points, a shorter cognitive test battery was used including TMT A, TMT B, 3MS and the List Learning, Coding, Fluency, List Recall, and List Recognition Subsets of the RBANS. The study included 19 BMT patients who developed incident delirium, 33 BMT patients who remained delirium-free, as well as ten healthy control patients. Although there were no group differences at baseline, the groups began to diverge in the post-transplant period. In

general, the post-transplant patients showed some decline in cognition in comparison to healthy controls, but this was most pronounced in those who would go on to develop delirium. In these pre-delirious patients, initially a significant decline in List Learning and List Recall was noted, followed by a considerable deterioration in TMT B, List Recall and Coding from the second-last visit to the last visit before delirium diagnosis. All cognitive domains deteriorated further in this group once delirium occurred, then varied over the subsequent ten days, yet did not return to their normative average during the course of the study. This suggests that the delirium prodrome in BMT patients is characterised by acquired deficits in attention, memory, visuomotor processing speed and learning. However, given the infrequent testing in this study, it is possible that some other prodromal features were overlooked. Another study in BMT patients found that prodromal cognitive impairments such as disorientation, memory decline and poor performance on the digit span, began several days prior to delirium onset and continued on an increasing trajectory for 7-10 days before resolving (157). De Jonghe and co-workers used the Revised Delirium Rating Scale (DRS-R98), Mini-Mental State Examination (MMSE) and the digit span daily to assess hip fracture patients for delirium development and found that the frequently observed cognitive symptoms before delirium onset were disorientation, difficulty concentrating and short and long-term memory impairment (155). Other studies have also explored the delirium prodrome by utilising delirium severity scales, however they did not report the results of the specific cognitive tests used to score individual items. Levkoff and colleagues, using the Delirium Symptom Interview (DSI) on a daily basis, found that disorientation and, to a lesser extent, inattention / distractability occurred relatively commonly prior to delirium onset in

older hospitalised patients (159). Using the Korean version of the DRS-R98, Lee and co-workers found that impairments in orientation, long and short-term memory and visuospatial function began to emerge up to four days before delirium diagnosis in a cohort of hip fracture patients. Prodromal disorientation was similarly noted in Duppils and Wikblad's cohort of hip fracture patients (161) using subjective ratings of behavioural change.

Thus, although it is likely that the delirium prodrome includes new deterioration in attention, orientation, memory and visuospatial function as well as other cognitive domains, it remains unclear as to how best to measure these prodromal features or indeed detect patients who are particularly vulnerable to delirium development over the ensuing days. Given that prevention, early identification and prompt, appropriate management of delirium is key to minimising the associated unfavourable outcomes, it is intuitive that the earlier patients are detected, the greater the opportunity for meaningful impact. Understanding how best to identify patients during this pre-delirium phase may help to facilitate the development of targeted prevention and intervention strategies. Hence, the aim of this study was to identify cognitive tests which can be used to detect the prodrome to delirium in older medical inpatients.

8.2. METHODS

8.2.1. SETTING AND PARTICIPANTS

This was a prospective observational cohort study conducted in two hospitals in Cork city, Ireland (Cork University Hospital and Mercy University Hospital) between October 2011 and August 2013. The study's procedures are described in detail in Chapter 3. In brief, patients ≥70 years of age admitted medically without prevalent delirium on initial screening were eligible for inclusion. Patients who refused, who were terminally unwell, or admitted to ICU, and those with severe communication difficulties or coma were also excluded. Informed consent was sought from eligible patients and those who consented underwent daily delirium assessment for at least seven days or until discharge. If patients were discharged early without delirium (≤ 3 days of admission), we were unable to confidently outrule an emerging delirium post-discharge, and so these patients were excluded from the analysis.

8.2.2. ASSESSMENTS

8.2.2.1. Delirium

A trained delirium assessor (NO'R) performed all delirium assessments using the Revised Delirium Rating Scale (DRS-R98). This is a 16-item diagnostically precise scale comprising 13 severity items (rated from 0 to 3) and 3 diagnostic items (rated from 0 to 2 or 3), giving a cumulative score range of 0 to 46. It has been shown to have high inter-rater reliability, validity, sensitivity and specificity for discriminating delirium from other neuropsychiatric diagnoses (90, 205) It can also be used to evaluate

symptom severity over the previous 24-hour period and hence can be used to describe delirium phenomenology as it evolves. In this study, delirium was diagnosed using a cut-off of ≥15 on the severity scale and / or ≥18 using the total score, in keeping with the guidelines for its use (173).

8.2.2.2. Cognitive testing

Included patients underwent daily cognitive tests in addition to delirium assessment. Because previous studies have indicated that the prodrome to delirium includes impairments in attention, orientation, short-term memory and visuospatial function, we focused on these domains, and employed tests that would be short and quick so that they would remain acceptable to the participants on a daily basis.

Six-item Cognitive Impairment Test (6-CIT)

The 6-CIT was our primary test as it encompasses three of the four target domains: orientation (to year, month and time of day), attention (twenty to one; months of the year backwards - MOTYB) and short-term recall (a five-item name and address), see figure 12 and appendix A. The 6-CIT was originally developed by Katzman and colleagues (113) as a screening test for dementia by abridging Blessed's Mental Status Test (114) and is also known as the Six-item Orientation-Memory-Concentration Test, the Short Orientation-Memory-Concentration Test and the Short Blessed Test. It is scored out of twenty-eight with higher scores indicating greater degree of impairment. It has a broad spectrum of use, including dementia screening

in primary care (115); cognitive screening in the acute setting (116); in Alzheimer's research (117, 118); and in large population-based studies (119). To date, there have been no published studies of its diagnostic accuracy in screening for delirium, however it is quick, requires minimal training and has been shown to be acceptable by nursing staff when used as a cognitive screening test (127). In this study, alternate forms of the 5-item name and address were used so that a patient was never given the same item to recall twice, see appendix A.

Attention tests

Inattention is the cardinal feature of delirium and the most prominent cognitive feature to emerge from studies of the prodrome, however it is unclear as to how attention should best be assessed (245). A recent review by Tieges et al (108) concluded that although attention tests show potential in delirium screening, there is limited evidence as to which test is most suitable. A previous study published by our group showed that MOTYB was sensitive in screening for delirium in older inpatients; however in younger cohorts or in those with pre-existing dementia, it required supplementation with other tests (105). As aforementioned, the MOTYB is a component of the 6-CIT. In the 6-CIT, MOTYB is scored based on the number of errors, so that no errors scores 0; 1 error scores 2; and 2 or more errors scores 4. For consistency with our previous work (105), we additionally scored MOTYB separately using a dichotomous scoring method: patients recited the months of the year backwards starting with December, getting back as far as July without error in order to pass (MOTYB-July). Counting backwards from twenty to one (20-1) is another

element of the 6-CIT which measures attention. It is scored similarly to the 6-CIT scoring of MOTYB. It is generally considered less cognitively challenging than MOTYB, but has not previously been studied specifically for delirium screening.

In addition to MOTYB and counting backwards from 20 to 1, we assessed attention using the Spatial Span Forwards (SSF), which is a visual measure of attention span based on the digit span forwards (111). Performance on the SSF has been shown to differentiate delirium from dementia (110, 246). The test is performed using an A5-sized section of white card depicting eight red squares (measuring 1.5cm^2 each) configured three / two / three over three rows. Pre-set sequences are tapped out for the patients to replicate, beginning with a sequence of two squares up to a maximum sequence of seven. Generally, subjects who are unable to accurately repeat a sequence of five squares are considered to have failed the test.

Visuospatial Function

Because visuospatial function is not represented in the 6-CIT, we also performed a verbal test of visuospatial ability during longitudinal assessments. Patients were asked a series of five questions (Environmental Visuospatial Questions, EVSQ) on a daily basis (see figure 12 and appendix A) and were then scored according to the number of correct answers, with higher scores indicating less impairment. The questions were varied from day to day to attempt to allow for learning effect. We also included the clock-drawing test (CDT) and interlocking pentagons (IPT) in our

assessment, however, many patients were not keen to perform this on a daily basis. Approximately one-third of all assessments had missing data for the CDT and / or IPT, and hence we do not report these results here.

8.2.2.3. Baseline data

Information pertaining to demographics and social history (including marital status; place of residence; alcohol and smoking history; and educational attainment) was gathered; the Modified Cumulative Illness Rating Scale (M-CIRS) was used to measure burden of comorbidity; and medication history was recorded. Functional status (Modified Barthel Index, BI) and nutritional status (Mini-Nutritional Assessment - Short Form, MNA-SF) were assessed and simple bedside screening for sensory impairment was performed. The ABCDS (AB Clinician Depression Screen), a modified version of the Geriatric Depression Scale, was used to screen for depression.

8.2.2.4. Assessment of previous cognitive status

Although all patients underwent SMMSE (Standardised Mini Mental State Examination) testing at baseline, this test was not used to diagnose pre-existing dementia. Poor performance on cognitive tests in this setting can be due to delirium, sub-syndromal delirium or acute illness, and hence non-specific in the detection of premorbid dementia. Instead, each patient's medical chart was reviewed for documentation of prior cognitive impairment or dementia by an appropriately

trained clinician. Subsequently, diagnosis was confirmed by using the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF), a 16-item scale scored by a caregiver or close relative which has been validated as a screening test for dementia. We used a mean item cut-off score of ≥3.5 to diagnose dementia (193). In borderline cases, consensus discussion (ST, DM) using all available information was used to establish dementia status. Where collateral history / IQCODE-SF / previous diagnosis were unavailable, patients were deemed not to have dementia if they scored ≥27 / 30 on SMMSE as precedented in other studies (192), however in those with SMMSE scores < 27 / 30, premorbid cognition was uncertain in the absence of collateral history (n=2).

8.2.3. ETHICAL PROCEDURES

The study objectives and procedures were explained verbally and in writing to all patients. However due to cognitive impairment at study entry, it was presumed that many subjects were not capable of giving informed written consent. Therefore, as in former similar studies, informed consent was taken from competent patients and assent to participation was sought from those who were incapacitated, as well as approval from a nearest relative or carer. Formal ethical approval was granted by Cork Research Ethics Committee and due to the non-invasive nature of the study, ethics committee approval was granted to supplement patient assent with proxy consent from next of kin (where possible) or a responsible caregiver, as above, in accordance with the Helsinki Guidelines for Medical Research involving human subjects (207).

8.2.4. STATISTICAL ANALYSES

A Cox proportional hazards model was used to assess the associations between prodromal cognitive features and the development of incident delirium, defined as above. From previous analysis (Chapter 5, table 12), we know that in this cohort significant independent baseline predictors of incident delirium were comorbidity, functional status and pre-existing dementia and hence, all models were adjusted for these predictor variables, as well as age and sex. Log likelihood was used to assess model fit. Confidence intervals of 95% were employed and are reported in the results. All longitudinal analyses were performed using Stata version 11.

8.3. RESULTS

A total of 191 patients were included in the analysis. The median age of the cohort was 80 (IQR 10), just over half (52.9%, n=101) were male and eight patients (4.2%) were admitted from nursing homes (see Chapter 5, figure 9 for a detailed description of flow of patients through the study and Chapter 5, table 10 for a report of baseline characteristics). Longitudinal analyses were performed using Stata version 11. We used Cox proportional hazards models (using Breslow method for ties), firstly to ascertain which cognitive tests predicted emergent delirium, and then to further examine the individual items in each test.

8.3.1. Prediction of Impending Delirium by Cognitive Tests

Our initial model included the 6-CIT, MOTYB-July, SSF and EVSQ as well as sex, age, and the independent clinical predictors of incident delirium in the cohort, namely dementia status, Barthel Index (BI) and Modified Cumulative Illness Rating Scale (M-CIRS). The latter three were included in the initial model as potential confounding variables. On evaluating the proportional hazards assumption using time dependent covariates, we found that MOTYB-July, SSF and 6-CIT varied with time and hence we proceeded with our analysis using an extended Cox model. Of note, during our assumptions evaluation, we also found that M-CIRS varied with time. As this is a baseline feature and was only measured once, we opted to exclude it from the model. Subsequently, a step-wise approach was used to achieve the most parsimonious model, removing the most non-significant variable at each step and monitoring for changes in model fit using the AIC (Akaike Information Criterion). The final model is illustrated in table 20. Significant cognitive predictors of impending delirium within a week of admission were impairments on the 6-CIT, (Hazard Ratio, HR 1.03 per one unit increase (= disimprovement) in score, 95% CI 1.01-1.05, p=0.002); MOTYB-July, (HR 0.71 for passing the test, 95% CI 0.55-0.90, p= 0.006) and EVSQ (HR 0.68 for one unit increase (= improvement) in score, 95% CI 0.48-0.97, p=0.035). SSF remained in the final model, however was non-significant.

8.3.2. Prediction of Impending Delirium by Cognitive Impairment at Domain Level

In the second analysis, we looked at the respective domains of the 6-CIT, as well as the other individual tests to investigate which cognitive domains in particular became impaired in the delirium prodrome. Our initial model included all items on the 6-CIT, SSF score and EVSQ score. Of note, because in previous studies we have used the MOTYB-July method of scoring MOTYB (i.e. ability to get to July without error) we included this method, rather than the method employed in the 6-CIT (number of errors). Additionally, as before, we included the other important variables (sex, age, dementia, functional status and comorbidity), see table 21. An extended Cox model was used as some of the covariates violated the Cox assumption of proportionality. We used robust estimation to allow for autocorrelations between assessments, and a similar approach as in our first analysis to arrive at the most parsimonious model, see table 22. This shows that the items from our assessments which predicted the onset of incident delirium within a week of admission were:

- Orientation to month (HR 0.78 for a correct answer, 95% CI 0.63-0.97, p=0.024);
- SSF score (HR 0.93 for each unit increase (= improvement) in score, 95% CI 0.87-0.98, p=0.015);
- MOTYB-July (HR 0.68 for a correct answer, 95% CI 0.54-0.86, p=0.001);
- 20-1 (HR 1.14 for each unit increase (= disimprovement) in score, 95% CI 1.05-1.24, p= 0.002);

- Recall of 5-item address (HR 1.08 for each unit increase (= disimprovement) in score, 95% CI 1.01-1.16, p=0.017);
- EVSQ score (HR 0.65 for each unit increase (= improvement) in score, 95% CI 0.48-0.9, p=0.009).

To summarise, orientation, attention, short-term memory and visuospatial function are disturbed in the prodrome to delirium.

8.4. Discussion

This study of 191 older medical inpatients aimed to characterise the cognitive aspects of the delirium prodrome. We performed daily assessments for delirium, as well as a battery of carefully selected short cognitive tests to investigate for evidence of a cognitive prodrome to delirium. These tests assessed cognitive domains that were *a priori* hypothesised to be disrupted during the delirium prodrome, based on the existing literature, i.e. attention, orientation, short-term memory and visuospatial function. Our data is consistent with this hypothesis, in that impairments in these domains predicted onset of delirium in our cohort.

Our findings compare well with those of previous studies of the delirium prodrome. Beglinger and colleagues found that patients with impending delirium began to perform more poorly on almost all assessments up to two visits before delirium onset, namely TMT A and B, List Recall, and Coding, highlighting that there was evidence of impairments in attention, working memory, psychomotor speed and

scanning in the prodromal phase (158). Our study highlighted that deficits in attention tests such as MOTYB, 20-1 and SSF were notable during the prodrome. The SSF, a visual version of the digit span forwards, assesses attention span but also requires intact working memory for visual material. The results of Beglinger and colleagues are reflective of the view that, although attention is the most markedly disturbed domain in delirium, multifactorial cognitive dysfunction is also central to presentation. Interestingly, the authors noted a practice effect on all tests for the healthy controls. Although the delirium patients did not reach their pre-study normative average values during the study time, all BMT patients, delirious and non-delirious, had improving performance of immediate and delayed recall over time, suggesting that this was the most recoverable domain in this cohort. Fann and co-workers also found that several prodromal features started to emerge prior to delirium onset in BMT patients, namely attention; perceptual disturbance; cognition; and evidence of fluctuations (157). The authors suggested that clinicians should not rely on more easily recognisable delirium features symptoms, such as agitation, psychosis or disorientation as it is the more subtle features, for example impaired attention and working memory, which occur first and more often and may be more useful in screening. De Jonghe and colleagues reported very similar findings to ours in their cohort of hip fracture patients (155). They found that cognitive features occurred significantly more frequently in the prodromal phase than in control patients. Disorientation and long-term memory impairment occurred as early as three days prior to full delirium onset, with short-term memory and inattention occurring two days pre-delirium. Other features which occurred in this prodrome in older hip fracture patients included incoherence of speech and an underlying

somatic illness. Franco and co-workers found in a cohort of older medical inpatients that MMSE score on admission predicted risk for delirium development by showing that for each unit decline on the MMSE on admission, the odds for delirium increased by 0.164 (247). There are well-recognised issues in using a cognitive test in the acute setting to ascertain pre-morbid dementia status, due to the potential for confounding by delirium, subsyndromal delirium and acute illness. Nonetheless, this MMSE score was considered by the authors to be reflective of pre-existing cognitive impairment for two reasons. Firstly, prevalent delirium on admission was outruled using the Columbian version of the CAM, although given the highly variable diagnostic accuracy of the CAM (105), it is possible that some prevalent cases and some subsyndromal patients were missed using this method. Secondly, the features of the baseline MMSE which subsequently most significantly distinguished the delirium vulnerable from the control group were orientation, delayed recall, comprehension, writing and visuoconstructional ability. Mean score on attention / calculation did not differ significantly between the two groups. Given the predominance of attentional disturbance in delirium and most likely its prodrome, these results support their view that the impairments on the baseline MMSE were less likely to be reflective of prevalent delirium.

In our study, we used assessments which were chosen based on findings from previous studies of the delirium prodrome, and hence concentrated on measuring attention, orientation, short-term memory and visuospatial ability. These domains are four of the most frequently affected domains in delirium (42) and so it makes

sense that they would also be impaired in the prodromal phase. We chose the 6-CIT because it encompasses three of our four proposed prodromal features. It has been found to correlate well with the MMSE (r^2=- 0.82to -0.926) (115, 116, 120-123), but is shorter in duration, taking only 2 to 3 minutes to perform. It is less culturally biased (124), and less affected by level of education than the MMSE (122). The 6-CIT has other advantages over other tests in that it doesn't require any equipment and it lacks the potential for interpretive error that other tests such as interlocking pentagons and clock-drawing may have (122). As it is a completely verbal test, it can also be used in the visually impaired (125). Studies have shown high acceptability among nursing staff (127), and that scoring accuracy is higher than for the MMSE (126). It is easily translatable into other languages (122) and importantly, where serial testing is required, no significant learning effect has been demonstrated (123). As is the case with other cognitive tests, such as the MMSE (129), scores on the 6-CIT are influenced by a patient's age (123), so this must be considered when using the test in practice.

Given the predominance of inattention over deficits in other domains during a delirium episode, we elected to measure attention using multiple methods. The 6-CIT incorporates two tests of attention, namely the MOTYB and 20-1, however the scoring of the MOTYB as part of the 6-CIT is not consistent with previous work from our group. Hence, we also scored it using a second method for consistency (see figure 12). Additionally, we included the SSF as a third attention test. This test was chosen for two major reasons. Firstly, studies have indicated it to be sensitive in

delirium detection, and in distinguishing delirium from dementia (110, 246). Secondly, because it is non-verbal it may be used in patients with expressive dysphasia or other communication difficulties. Visuospatial function is not assessed using the 6-CIT, so we measured this separately using a series of questions designed to evaluate a patient's perception of their immediate surroundings (see figure 12). This test was scored out of five and questions were varied on a daily basis, taking into account a patient's visual status (not performed if blind; limited to large items at beside if impaired). We also used the clock-drawing test and interlocking pentagons, but many patients were unwilling to perform these tests every day, mainly due to the effort required to use pen and paper. Hence, although ideally we would have included these commonly used and validated tests in our analysis, we could not due to the large amount of missing longitudinal data (>one-third of assessments). Excluding these tests allowed us to include a greater number of participants in our final analysis.

Our first analysis showed that the 6-CIT, together with MOTYB-July and EVSQ were significantly predictive of impending delirium. In our second analysis, concentrating on the individual cognitive domains from the 6-CIT, as well as the SSF and EVSQ, our best model showed that elements of all four tested domains were predictive of delirium onset. Orientation to month was a significant predictor of impending delirium, whereas orientation to year or time of day were not predictive on multivariable analysis. Most studies of delirium or prodrome in which disorientation is described do not specify which exact element of time is most affected. One study

of cognitive impairment conducted by O'Keeffe and co-workers in 262 hospitalised older adults, fifteen of whom had delirium (248), found that all delirious patients were disorientated to year and day of the month, fourteen were disorientated to time of day, and twelve misidentified the month or day of the week. Although disorientation is well-recognised in delirium, it is important to note that it has been shown to be the least frequently occurring cognitive feature, absent in almost one-quarter of patients and of only mild severity in almost one-half (42), and hence larger studies would be required to thoroughly explore the nature of disorientation in delirium. Additionally, it is also possible that disorientation is an impairment that evolves somewhat from prodrome to full-syndromal delirium and hence prodromal disorientation may vary slightly from that which is found in the later delirious condition. Better descriptions of disorientation in prodromal studies would allow this to be assessed further.

This study has many strengths. Firstly, delirium assessments were performed daily by an experienced clinician trained in delirium diagnosis. Secondly, most other studies of delirium prodrome included less than fifty delirium cases and so the comparatively large number of delirium cases (n=61) in our study is another strength of this work. Only 36 patients withdrew out of the 322 initially included, which shows that the cognitive tests used were largely acceptable to the patient cohort. Were we more strict about including objective pen-and-paper tests of visuospatial ability, we are likely to have had a much higher withdrawal rate. Dementia is one of the top differential diagnoses when assessing for delirium, and patients with

dementia are likely to have impairments on all of the cognitive tests we used to identify the delirium prodrome. However, we identified pre-morbid dementia using very robust methods and adjusted for its presence in the analysis. Thus, we are confident that our results are reflective of the delirium prodrome and not premorbid dementia.

One of our study's limitations is that for feasibility, given that delirium assessments were performed by a sole researcher, the sample was non-consecutive. Secondly, only a short battery of tests were performed daily. Again this was in order to ensure that the daily assessments were acceptable to participants. Additionally, we aimed to use tests that could be translated easily into clinical practice and so simplicity and short duration were important test characteristics. In studies such as this, capturing the onset and fluctuations of delirium is challenging unless assessments are performed very frequently. Once again, this must be balanced against study feasibility and what will be considered acceptable by the study cohort. We felt that the best balance would be achieved by daily assessment. Although our methodology and analysis attempted to capture a delirium prodrome occurring during the first week of admission, the majority of delirium cases transitioned into delirium on day 2 (n=30), and so for these cases we were only able to capture a very short prodrome, highlighting the importance of prompt assessment. In this study, the vast majority of patients were assessed within 24 hours of presentation to the emergency department, and the rest assessed well within 36 hours. Early review is vital in future studies of delirium prodrome as delay may lead to either missed prodromal features

or potentially a missed case of incident delirium having transitioned from a prodromal state.

This exploratory study illustrates that delirium onset can be predicted by impairments in attention, orientation, short-term memory and visuospatial function independent of underlying dementia, and indicates that the 6-CIT may be a useful test to identify those who are particularly vulnerable to developing delirium over the ensuing days. Although we cannot propose a 6-CIT cut-off that heralds the prodromal state, our results suggest that monitoring patients daily for a decline in performance on the 6-CIT, or one of the other short domain-specific tests, may facilitate very early detection of the pre-delirious patient. Whether or not intervention in this prodromal period can impact on delirium incidence has yet to be studied, however given that earlier detection and prompt intervention can improve outcomes, being alert to changes in the prodromal period may impact greatly on detection rates, and hence facilitate earlier appropriate treatment.

Figure 12: The Six-item Cognitive Impairment Test and other tests used in the study of cognitive prodrome

A.	**The Six-item Cognitive Impairment Test (6-CIT)**	**Scoring**
	1. What year is it?	Score 4 if incorrect
	2. What month is it?	Score 3 if incorrect
	Repeat after me: "John / Smith / 42 / High Street / Bedford." I want you to try to remember that name and address. I will ask you about it later.	(not scored)
	3. About what time is it?	Score 3 if more than 1 hour wrong
	4. Count backwards from 20 down to 1	Score 2 if one error Score 4 if two or more errors
	5. Say the months of the year in reverse order, starting with December	Score 2 if one error Score 4 if two or more errors
	6. What was that name and address you repeated after me earlier?	Score 2 for each error Maximum score 10 for 5 errors
		Total score = ____/ 28
B.	**The Months of the Year Backwards (MOTYB-July)**	Subject must get back as far as July without error in order to pass the test.
C.	**Spatial Span Forwards (SSF, see appendix A)**	Subject must repeat sequences of squares of increasing difficulty tapped out by the examiner. Correctly repeating a sequence of 5 squares is generally considered the criteria to pass the test.
D.	**Environmental Visuospatial Questions (EVSQ)**	
	1. Where is the toilet? 2. Where is the nurses' station? 3. Where is the way out? 4. Which is bigger, ……* or …….*? 5. Which is closer to you, the window or the door? 6. Which of my hands is closer to you? 7. Which is taller, ….. *or ……*? 8. Which is closer to you, ……* or …….*?	Five of these questions were asked daily and the subject was given a mark for each correct answer. The test was scored out of five. *Objects in room or on bedside table are used here

Table 20: Extended Cox model showing the cognitive tests which predicted incident delirium in the cohort

Most parsimonious model showing hazard estimations, n=191. Breslow method for ties. Log pseudolikelihood= -175.58. AIC 359.16

Cognitive Test	HR	95% CI (HR)	sig.
EVSQ score (per unit increase)	0.68	(0.48-0.97)	**0.035**
6-CIT total score (per unit increase)	1.03	(1.01-1.05)	**0.002**
MOTYB-July (passing the test)	0.71	(0.55-0.90)	**0.006**
SSF score (per unit increase)	0.94	(0.87-1.01)	0.076

EVSQ = Environmental Visuospatial Questions Test (higher score means better cognition); 6-CIT = Six-item Cognitive Impairment Test (higher score means worse cognition); MOTYB-July = Months of the Year Backwards scored so that a pass is getting back as far as July without error; SSF = Spatial Span Forwards (higher score means better cognition); CI = confidence interval; HR = Hazard Ratio

Table 21: Covariates included in the initial Cox model investigating the individual cognitive items which predicted delirium onset in the cohort

Domain	**Test item**
Orientation	1. What year is it? 2. What month is it? 3. What time of day is it (to nearest hour?)
Short-term Recall	The patient is given a 5-item name and address and asked to recall it after approximately 1-2 minutes
Attention	1. MOTYB-July 2. 20-1 3. SSF
Visuospatial	Environmental Visuospatial Questions score (marked out of 5)
Baseline Predictor	**Measure**
Sex	
Age	
Premorbid dementia status	IQCODE-SF ± SMMSE ± Expert opinion: combined into final Yes/No status
Functional status on admission	Barthel Index
Comorbidity burden	Modified Cumulative Illness Rating Scale

MOTYB-July = Months of the Year Backwards scored so that a pass is getting back as far as July without error. 20-1 = counting backwards from twenty down to one, scored such that one error scores two points; two or more errors scores four points; SSF = Spatial Span Forwards; IQCODE-SF = Informant Questionnaire on Cognitive Decline in the Elderly – Short Form; SMMSE = Standardised Mini-Mental State Examination

Table 22: Extended Cox model showing the cognitive items which predicted incident delirium in the cohort

Most parsimonious model showing hazard estimations, n=191. AIC 365.88. Breslow method for ties. Log pseudolikelihood= -176.94

Test	HR	95% CI (HR)	sig.
Orientation to month	0.78	(0.63-0.97)	**0.024**
SSF score	0.93	(0.87-0.98)	**0.015**
MOTYB-July	0.68	(0.54-0.86)	**0.001**
20-1	1.14	(1.05-1.24)	**0.002**
5-item address recall	1.08	(1.01-1.16)	**0.017**
EVSQ score	0.65	(0.48-0.9)	**0.009**

Orientation to month: Answers the question 'What month is it?' correctly. HR is for correct answer.
SSF = Spatial Span Forwards, HR per unit increase. Higher score means better cognition, maximum =7.
MOTYB-July = Months of the Year Backwards scored so that a pass is getting back as far as July without error. HR is for passing the test.
20-1. HR per unit increase in errors (0= no errors; 1 = only one error; 2 = at least two errors)*
5-item address recall. HR per unit increase in errors, maximum = 5 for greatest number of errors*
EVSQ = Environmental Visuospatial Questions Test, HR per unit increase. Higher score means better cognition, maximum = 5.
HR = Hazard Ratio; CI= Confidence Interval
* For this analysis both 20-1 and 5-item recall was scored slightly differently than the scoring method used in the 6-CIT. In the 6-CIT each level of error scores 2 marks, whereas in this analysis each level of error only gained one mark. This was so that the scores would be weighted similarly to the SSF and the EVSQ.

9. DELIRIUM PHENOMENOLOGY OCCURS IN THE DELIRIUM PRODROME

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9.1. INTRODUCTION

Delirium is a complex neuropsychiatric syndrome which occurs in the setting of acute illness or injury. It is highly prevalent across treatment settings, occurring in one-fifth of hospitalised patients (1) and with higher frequency in older inpatients (2) and other vulnerable groups (12, 13). Delirium independently impacts adversely upon patient outcomes (3), yet it remains widely undetected or mistakenly labelled as dementia or depression (202). Unfortunately, although preventative strategies and early intervention can mitigate against the short- and long-term burden of delirium (6, 7), under-recognition exacerbates poor prognosis such that those who remain undiagnosed or are detected late have higher risk of mortality (18, 19, 77). One study found that for each additional 48 hours that delirium went undiagnosed, patient mortality rose by 11% (18). Hence, strategies that facilitate earlier delirium detection are crucial to improving care.

Although delirium is characteristically acute in onset, often occurring over hours or days, it is now well-recognised that some patients experience a prodromal phase (41). One of the earliest mentions of this pre-delirium stage can be found in Lipowski's 1990 seminal work entitled *'Delirium: Acute Confusional States'* (154), in which it is postulated that delirium is commonly preceded by a multitude of features including diminished clarity of thought processes, emotional lability, sleep-wake cycle disruption and a range of perceptual abnormalities. Latterly, there have been few studies exploring the features of the delirium prodrome and these have differed in methodology, populations studied and assessments used (see tables 1 and 2 in Chapter 2). Thus, the symptom profile and course of these prodromal features has yet to be fully appreciated, and like delirium itself, the prodrome can manifest a variety of phenomenological features. Some are recognised as part of the delirium spectrum, both cognitive and non-cognitive features (155), leading many to consider the prodromal phase to be conceptually akin to that of sub-syndromal delirium (155). The fact that many non-delirium elements occur in the pre-delirium phase also, for example somatic (167), behavioural (161) or emotional (157) features, disputes this categorisation. Nonetheless, identifying and defining the non-delirium elements of the prodromal phase is challenging, as these features are often less concrete than delirium features and are not defined in any related diagnostic classification systems. Examples of these features include general uneasiness (167); urgent calls for assistance (161); anxiety (164); dysphoria (169) and pain at varying sites (157, 165), but again, they vary from study to study for the reasons outlined above. Because delirium features have strongly anchored definitions and those trained in delirium assessment are confident and experienced in identifying these

features, the study of delirium symptoms in the prodromal phase is considered more accessible, and hence many prodromal studies have used delirium phenomenological instruments to explore the features of the prodromal phase.

The first such report from Levkoff and colleagues (159) used the Delirium Symptom Interview (DSI), a structured interview based on DSM-III, to evaluate delirium features in 325 older medical and surgical patients, including those with dementia. A prodromal phase was identified in almost 70% of patients with imminent delirium, the mean duration being 2.7 days. Multiple DSI symptoms occurred in the prodrome, the most frequent being disorientation; speech abnormalities; sleep pattern disruption; changes in psychomotor activity; perceptual disturbances; difficulties with concentration; and fluctuating behaviour. Although the comparative frequencies of these symptoms in non-delirious patients were not reported, both disorientation and fluctuating behaviour at baseline significantly increased the odds of delirium development. In a prospective study of 90 bone marrow transplant (BMT) patients, Fann and colleagues performed factor analysis of delirium symptoms by combining items from the Delirium Rating Scale (DRS) and the Memorial Delirium Assessment Scale (MDAS) (157) and somewhat similar to other phenomenological work (43), a three-factor structure to delirium episodes was identified: psychosis-behaviour; cognition; and mood-consciousness. Features from the former two factors preceded delirium onset by up to nine days, and in particular changes in attention, perception, cognition and fluctuations rose precipitously from about four days before delirium diagnosis. Assessments were conducted thrice weekly and,

again in this study, the presence or absence of features in non-delirious patients is not discussed. In another study of BMT patients, Beglinger and co-workers characterised the neuropsychological performance of 19 delirium patients before, during and after the episode compared to controls (33 post-transplant and 10 healthy normal patients) (158). In the pre-delirium phase, performance in measures of attention; learning; psychomotor speed; and scanning began to decline up to one week prior to delirium onset indicating prodromal cognitive impairment. Additionally, investigators found that MDAS scores and Revised delirium Rating Scale (DRS-R98) severity and total scores were trending upwards in the visits before delirium was diagnosed. De Jonghe and colleagues studied the onset of DRS-R98 features in older hip fracture patients at risk of delirium (155). The presence of incoherence; disorientation; poor concentration; and short- and long-term memory impairments significantly predicted impending delirium on logistic regression. There was also an increase in prevalence of perceptual abnormalities, fluctuations and acute onset of symptoms in the pre-delirious patients. Because this study was nested within a study of the treatment effect of haloperidol versus placebo, it is possible that results may have been confounded. However, in the trial no effect was found for treatment condition on delirium incidence nor on total DRS-R98 scores prior to delirium development. The most recent study to use a phenomenological tool to identify prodromal features was conducted by Lee and colleagues (156). This study of 65 hip surgery patients, 18 of whom developed delirium post-operatively, used the Korean version of the DRS-R98 (K-DRS-R98) to identify features which predict delirium onset and found that in the days prior to delirium development those with impending delirium scored significantly higher on several K-DRS-R98 items than

those who remained delirium-free. From three to four days prior to delirium emergence, abnormalities in sleep-wake cycle; thought process; orientation; long-term memory; and lability of affect were observed and in the two days immediately before diagnosis, patients had more notable perceptual abnormalities; visuospatial dysfunction; delusions; motor agitation; and short-term memory impairment. They also noted that the K-DRS-R98 scores increased incrementally as delirium approached, whereas in controls K-DRS-R98 scores remained the same.

Other studies have sought to identify delirium features in the prodromal period by utilising different methods. Duppils and Wikblad used a subjective observational approach to identify if behavioural changes were more prevalent in those developing delirium than those who were not and found that as well as an increase in attention-seeking behaviour, there was a suggestion (although no formal evaluation was made), that certain delirium features occurred more frequently in the delirium destined group prior to diagnosis, namely increased psychomotor activity; reduced attention; and perceptual disturbances. In a study of long-term care patients, Voyer and co-workers used the Confusion Assessment Method (CAM) and an abridged version of the Mini-Mental State Examination (MMSE) on a weekly basis to identify that evidence of perceptual disturbances; disorganised thinking; and worsening registration was significantly associated with progression to delirium (160). Providing clarity as to the characteristics and course of this prodrome, both delirium and associated elements, may suggest strategies to prevent progression to full delirium, by facilitating appropriate and prompt intervention during a clinically identifiable

stage of delirium vulnerability. In previous chapters, we have discussed the behavioural and cognitive features of the delirium prodrome, many of which are not defined elements of the delirium syndrome. In this report, we aim to characterise the delirium-specific features that herald delirium onset.

9.2. METHODS

9.2.1. SETTING AND PARTICIPANTS

This was a prospective observational cohort study conducted in two acute general hospitals in Cork city, Ireland (Cork University Hospital and the Mercy University Hospital) between October 2011 and August 2013. The study protocol and procedures are described in Chapter 3. In brief, patients of ≥70 years of age admitted medically through the emergency department were screened for study eligibility within 36 hours of admission (and usually within 24 hours). Patients with prevalent delirium on admission; those with severe communication problems limiting assessment, those who refused; and those who were comatose, gravely ill or dying were excluded. Eligible and consenting participants were assessed daily for delirium development for the next seven days or until discharged. Those discharged without delirium within three days of admission were excluded due to inability to confidently outrule incident delirium development post-discharge. Information relating to medical history, social history and previous history of depression was collected and patients were assessed for functional status, nutrition and sensory impairment (see Chapters 3 and 5 for details).

9.2.2. ASSESSMENTS

9.2.2.1. Delirium

Delirium assessments were performed on a daily basis by a trained delirium assessor (NO'R) using the Revised Delirium Rating Scale. This is a 16-item scale including 13 severity items (rated from 0 to 3) and 3 diagnostic items (rated from 0 to 2 or 3), which together give a total possible score range of 0 to 46. This diagnostically precise instrument can be used to describe delirium phenomenology by evaluating breadth and severity of symptoms over the previous 24-hour period. It has high inter-rater reliability, validity, sensitivity and specificity for the diagnosis of delirium and in distinguishing it from other neuropsychiatric conditions including dementia and depression (90, 204, 205). In accordance with guidelines for its use (173), in this study delirium was diagnosed if the DRS-R98 severity score was ≥15 and / or if the total score was ≥18.

9.2.2.2. Assessment of previous cognitive status

A close relative or caregiver was interviewed using the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF), and a mean cut-off score of ≥3.5 was used to diagnose dementia (193). Additionally, the medical notes were reviewed for documentation of a prior diagnosis of dementia by a suitably trained physician. Borderline cases were discussed and consensus opinion was used to apply diagnosis. In those with no available collateral history and no documented dementia diagnosis, a score of ≥ 27 / 30 on the SMMSE was considered normal. We were unable to definitively ascertain premorbid cognitive status in those with lower

SMMSE scores and no informant history, and hence in these patients premorbid cognition was determined as “unknown” (n=2).

9.2.3. ETHICAL PROCEDURES

Formal ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The details of ethical procedures are discussed in Chapter 3. In summary, informed consent was sought from those capable, however it was expected that many would not be competent to give informed consent and, hence, due to the non-invasive nature of the study, approval was granted to augment patient assent with proxy consent from next of kin or a responsible caregiver, in accordance with the Helsinki Guidelines for Medical Research involving human subjects (207).

9.2.4. STATISTICAL ANALYSES

Demographic data were expressed as means ± SD or medians and IQR, depending on the distribution of the data. Comparisons of groups (delirium, no delirium) were made using a χ^2 or Fisher Exact test for differences in proportions, a t-test for differences in means or Mann Whitney U non-parametric tests for differences in mean ranks. Associations between prodromal DRS-R98 items and incident delirium were analysed using Cox proportional hazards models. The proportional hazards assumptions were tested using an extended Cox model with time-dependent covariates. Delirium was defined as a DRS-R98 severity score of ≥15 or a total score

of ≥18. Models were adjusted for comorbidity, functional status and cognitive status, as these were found to be independent predictors of incident delirium on multivariable logistic regression (Chapter 5). Sex and age were also included in the survival models. The AIC (Akaike Information Criterion) and log likelihood were used to assess model fit. Confidence intervals of 95% were utilised and are reported in the results. Recurrent event survival analyses were performed using Stata version 11.

9.3. RESULTS

A total of 555 patients were approached over the study period, and following exclusions according to the study protocol, 191 patients were included in the analysis (see Chapter 5, figure 9 for flow of patients through the study). The median age of the cohort was 80 (IQR 10), 52.9% (n=101) were male and 32 patients had pre-morbid dementia (see Chapter 5, table 10 for more detail on baseline characteristics). Cox proportional hazards models (using Breslow method for ties) were used to identify DRS-R98 features that predicted delirium onset. The first model included DRS-R98 items 1 to 15, as well as the independent baseline predictors of incident delirium from multivariable logistic regression analysis, namely M-CIRS (Modified Cumulative Illness Rating Scale), BI (Barthel Index) and pre-morbid dementia. We excluded DRS-R98 item 16 (physical disorder) from the analysis, as it simply scores the extent to which a physical condition is considered to account for symptoms and hence this item does not relate to delirium phenomenology. A step-wise approach was used to arrive at the final model (see table 23). At each step, non-significant variables were removed and changes in model fit were assessed by

monitoring the log pseudolikelihood and the AIC (Akaike Information Criterion). On assessing the proportional hazards assumption using time dependent covariates, we found that DRS-R98 items 2 (perceptual disturbances and hallucinations); 4 (lability of affect); 10 (attention); 14 (temporal onset of symptoms); and 15 (fluctuation of symptom severity) varied with time and, hence, we proceeded using an extended Cox model. Features which were most predictive of emerging delirium in the first week of admission were DRS-R98 items 1 (sleep-wake cycle disturbance, HR 1.48, 95% CI 1.08-2.04, p=0.016); 2 (perceptual disturbances and hallucinations, HR 1.1, 95% CI 1.03-1.17, p=0.006); 4 (lability of affect, HR 1.14, 95% CI 1.05-1.24, p=0.002); 10 (attention, HR 1.32, 95% CI 1.23-1.42, p<0.001); 11 (short-term memory, HR 1.45, 95% CI 1.18-1.78, p<0.001); 14 (temporal onset of symptoms, HR 1.34, 95% CI 1.22-1.47, p<0.001); and 15 (fluctuation of symptom severity, HR 1.27, 95% CI 1.09-1.48, p=0.002).

9.4. Discussion

This study aimed to identify the delirium-specific features which predict the development of incident delirium in older medical inpatients, by assessing participants on a daily basis using the DRS-R98, a tool which is diagnostically precise and also characterises delirium phenomenology in detail. We found using recurrent event survival analysis, correcting for other factors that predicted delirium (co-morbidity, function and pre-morbid dementia) that abnormalities in sleep-wake cycle; perception; attention; and short-term memory; as well as presence of affective lability; acute onset and increasing severity of symptom fluctuations were

all significantly predictive of delirium development in this cohort during the first week of admission.

Our findings are generally consistent with results from existing studies in this area. The most consistent prodromal delirium feature across all the studies is inattention or poor concentration, followed by perceptual abnormalities; presence of fluctuations; memory impairment; and sleep-wake cycle disruption, all of which were identified in our study. Given that inattention is a cardinal feature of delirium, it is unsurprising that it should also feature prominently in the prodromal period. Another central feature for delirium diagnosis is evidence of fluctuation of symptom type and severity, and it is also interesting to note that this undulating clinical course predates the diagnosis of delirium in many patients. Abnormalities in sleep-wake cycle are also highly prevalent in delirium, occurring in 97% of delirium cases (42), however perceptual disturbances are evident in only approximately half, so their significance in the delirium prodrome across studies is an interesting observation. It may be that delirious patients who have disturbances in perception are more likely to have transitioned through a prodromal phase during the onset of delirium, however this needs further investigation.

Although our study findings echo much of the existing literature, there are some features which have been shown in other studies to be reasonably prevalent in the prodromal phase that we did not find to be predictive of delirium development. Our

findings portray that lability of affect predicts delirium onset. The only other study to significantly identify this feature was the study of Korean hip surgery patients by Lee and colleagues (156), although in the report of Fann and co-workers (157), there appeared to be a very slight increase in lability up to five days before delirium onset. There was no evidence of prodromal affective lability in the study conducted by de Jonghe and colleagues (155), and other prodromal studies did not investigate for this feature. It is unclear why findings related to this feature are divergent, and cannot be explained by study population given that the results from both hip surgery cohorts differ. Other studies report on deficits in orientation; long-term memory and visuospatial ability in the prodromal period (155-157, 159), whereas this analysis did not produce these results. In a previous chapter, we reported more comprehensively on the cognitive elements of the delirium prodrome. We used serial bedside cognitive assessments (see Chapter 8) to ascertain the domains involved, and found that incident delirium could be predicted by impairments in orientation to month; attention; short-term memory and visuospatial function, similar to existing studies as above. In this analysis of DRS-R98 items, we found that only impairments in attention and short-term memory were significantly indicative of imminent delirium. It is likely that the bedside cognitive assessment tools were able to detect more subtle changes than the scores on the DRS-R98 items.

Given the consistency with which delirium features have been shown in the pre-delirium phase, despite the sparsity of studies and diversity between methodologies, it could be considered that this phase is purely a manifestation of subsyndromal

delirium (SSD) which then evolves into the full-blown syndrome. Although there is no definite consensus as to the exact definition of SSD, it is widely accepted that the concept refers to the presence of delirium features in a patient who does not meet diagnostic criteria for full-blown delirium. SSD is often considered a natural point on the road between no delirium and delirium, however the temporal relationship between SSD and full-syndromal delirium is not fully understood and whether or not the SSD point can be bypassed during an episode is not clear. It has been postulated that SSD may occur as a precursor to delirium in the setting of a subacute delirium onset, or that it ensues as a delirium episode resolves gradually, or it may arise independently of any full-syndromal event, although it remains unclear if SSD in each these situations differs phenomenologically or with respect to other factors, such as aetiology. It is apparent that SSD is not simply a phenomenological state, but that it has significant clinical impact, in that it independently leads to outcomes intermediate between no delirium and delirium and so occupies a continuum both in clinical presentation and in long-term prognosis (249). Despite the notion that SSD can precede delirium, it is important to remember that the concept of delirium prodrome encapsulates many other features than those recognised as part of the delirium spectrum, as described in previous chapters, and hence although the prodromal period can include SSD, it should not be its sole defining characteristic.

Strengths of this study include the prospective daily measurement of delirium phenomenology using a well-validated delirium rating instrument by a trained, experienced researcher, as well as the relatively large sample of delirious patients

with a larger comparative control sample of delirium-vulnerable patients. This study was conducted in a cohort of older medically hospitalised patients who are at particular at risk for delirium, and so caution should be exercised before generalising results to other patient groups. The vast majority of prodromal studies, with the exception of those conducted in BMT patients (157, 158) and in coronary care (165), also studied patients of older age with median ages in the 80's across studies, undoubtedly in order to ensure sufficient power to detect a significant effect. Nonetheless, despite the variety of treatment settings involved in existing studies, results are generally consistent, even including those in younger populations, and our findings resonate well.

In conclusion, delirium in older hospitalised patients can be predicted by the occurrence of less intense delirium phenomenology, particularly the presence of inattention; perceptual disturbances; presence of fluctuations; memory impairment; and sleep-wake cycle disruption. Being vigilant to the presence of these features in older patients not meeting full criteria for diagnosis may supplement other risk assessment and screening methods in the early identification of the delirium-vulnerable, and hence facilitate more timely and appropriate management. Future studies investigating the relationship between prodromal features and delirium phenomenology and other factors such as aetiology; risk factors; clinical course and outcomes are needed to promote further understanding of the clinical significance of the delirium prodrome.

Table 23: Extended Cox model showing the DRS-R98 features which predict impending delirium

Most parsimonious model showing hazard estimations, Breslow method for ties. Log pseudolikelihood= -187.57, AIC 393.13; M-CIRS= Modified Cumulative Illness Rating Scales; DRS-R98= Revised Delirium Rating Scale; HR = Hazard ratio; CI= Confidence interval; SE = Standard error

	HR	95% CI (HR)	SE	sig.
Premorbid dementia	0.93	0.61-1.42	0.2	0.745
M-CIRS	1.06	1.02-1.09	0.02	0.001
DRS-R98 item 1: Sleep-wake cycle disturbance	1.48	1.08-2.04	0.24	0.016
DRS-R98 item 2: Perceptual disturbances and hallucinations	1.1	1.03-1.17	0.04	0.006
DRS-R98 item 4: Lability of affect	1.14	1.05-1.24	0.05	0.002
DRS-R98 item 10: Attention	1.32	1.23-1.42	0.05	<0.001
DRS-R98 item 11: Short-term memory	1.45	1.18-1.78	0.15	<0.001
DRS-R98 item 14: Temporal onset of symptoms	1.34	1.22-1.47	0.06	<0.001
DRS-R98 item 15: Fluctuation of symptom severity	1.27	1.09-1.48	0.1	0.002

10. Motor Profile of Incident Delirium in Older Medical Inpatients: Frequency; Stability; and Predictors

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10.1. Introduction

Delirium as a clinical entity has been recognised since ancient times, although up until 1980 when its definition became standardised in DSM III (250), acute and subacute cognitive disturbances were known by a disparate array of terms reflecting differences in aetiology and clinical setting, rather than describing distinct syndromes. This unitary concept of delirium has facilitated a greater awareness of its significance and has helped to advance research over the past few decades, yet the protean nature of delirium lends itself to subclassification (38). The varying symptom profile and severity that occurs from patient to patient and within the same individual in the form of fluctuations encourages efforts to identify delirium subgroups and hence search for differing pathogenesis, aetiology, treatment response and prognosis between these groups.

Although multiple characteristics have been utilised to subclassify delirium, motor activity profile is the most studied and the most practicable method (38). Because motor change occurs with such frequency in delirium, it is considered a core element of delirium phenomenology and although some motor features, particularly hypoactivity, are subtle to the untrained eye, motor activity disturbance is readily observable when it is actively sought out. Furthermore, in recent years the approach towards defining and assigning motor subtypes in delirium has advanced. The Delirium Motor Subtype Scale (DMSS) is a 13-item instrument derived from analysis of features used in previous subtyping methods. Unlike former approaches, it has undergone meticulous validation and correlates highly with accelerometry measures of motion (48). In addition, the DMSS shows relative specificity for delirium, and has predictive validity with respect to delirium prognosis (47). Recently it has been further reduced by latent class analysis to a four-item version, the DMSS-4, allowing for speedier assessment without losing subtyping accuracy (49), and a study in older medical inpatients found that the DMSS-4 has high concordance with the DMSS and good inter-rater reliability (50).

The incidence and outcomes of the individual delirium subtypes has varied widely across studies, likely due to inconsistent methodologies and referral bias within study samples (38). Furthermore, most studies have been cross-sectional in methodology, which is inherently limited in its capacity to capture the dynamic and fluctuating nature of delirium. Longitudinal work in the palliative care setting has found that subtypes are most commonly stable across time with the most prevalent

subtype being hypoactive (11, 51). Conversely, in a longitudinal study of hip fracture patients, approximately 87% of patients had a variable motor profile throughout the delirium episode (52). It is possible that hip fracture patients follow a different course to other patient cohorts. For example, it is now generally accepted that in most settings hypoactive delirium carries the worst prognosis, whereas Marcantonio and colleagues found that amongst hip fracture patients with delirium, it was those with hypoactive motor profile (albeit using categories based on the Memorial Delirium Assessment Scale, MDAS) who experienced the best outcomes, independent of delirium severity and other confounders (53).

Longitudinal studies in palliative care patients have found that motor activity profile is more closely related to delirium phenomenology than to aetiology or medication exposure (54). The subtypes can differ with respect to the non-cognitive features of delirium, but they do not differ in relation to the spectrum and severity of cognitive impairment (38, 54), except that in patients without a motor subtype, cognitive impairment is less pronounced than in those presenting with a motoric subtype. This former 'no subtype' group have less phenomenologically intense delirium than the other subtypes and often have rating scores in the subsyndromal range on the DRS-R98 (54). Although there are few studies investigating how motor subtypes relate to various risk factors for delirium, some work suggests that increasing age and premorbid cognitive impairment may be more common in those with hypoactive presentation (55, 56).

To date, studies in older medical inpatients with delirium have all been cross-sectional in nature and results have been widely conflicting. Liptzin and Levkoff (1992) found that 52% of 125 older medical inpatients with incident delirium had a mixed profile, whereas only 19% were hypoactive, and that motor subtype did not relate to sex, age, place of residence or presence of comorbid dementia (57). Subsequently, O'Keeffe and Lavan found that mixed subtype predominated in 94 acute geriatric medicine patients with delirium, but that those with hypoactive profile had higher illness severity and longer length of stay (58). A more recent cross-sectional study of older medical inpatients primarily designed to identify MMSE (Mini-Mental State Examination) items on admission that predict the occurrence of incident delirium, used DRS-R98 motor items to apply motor profile and found that the most common subtype in patients with incident delirium was hypoactive (38%) (59). Furthermore, a study investigating the occurrence of delirium in older patients in the emergency department found that 92% of cases were hypoactive, based on the Richmond Agitation Sedation Scale, and worryingly more than three quarters of cases were missed by emergency physicians (23). It is difficult to draw any conclusions about the discordant results of these studies, due to their cross-sectional nature and also because of the very different subtyping methods employed. Longitudinal data, using a validated instrument, is required to more accurately investigate the motor profile in this patient group.

Hence, the aim of this study is (i) to explore the course and stability of motor subtypes in older medical inpatients, (ii) to identify how motor subtypes relate to

baseline risk factors such as demographics, functional ability, presence of pre-morbid dementia and comorbidity, and (iii) to identify how motor profile relates longitudinally to cognitive performance in this cohort.

10.2. METHODS

10.2.1. SETTING AND PARTICIPANTS

This study was part of a larger prospective observational cohort study of incident delirium conducted in two acute general hospitals in Cork city, Ireland (Cork University Hospital and the Mercy University Hospital). Details of the study protocol and procedures are outlined in chapter 3. In summary, over a two-year period from 2011 to 2013, patients of ≥70 years of age without prevalent delirium on admission and who were admitted medically through the Emergency Department (ED) were eligible for study inclusion. Delirium status on admission was ascertained by the study's principal investigator (NO'R). Those eligible for study inclusion were then assessed daily for delirium development for the next seven days or until discharged. Participants who had not developed delirium and were discharged within three days of admission were excluded because delirium development post-discharge could not confidently be ruled out in these patients. Patients who developed incident delirium (cases) and who remained admitted continued to undergo daily assessment as tolerated until assessment day fourteen, followed by weekly assessment for up to six weeks. Patients who did not develop delirium in the first week (controls) and who remained inpatients beyond this, continued to undergo weekly assessments for delirium after the first seven days of participation. Hence there were up to 18

potential assessment points for delirium cases (days 1 to 14 and weeks 3 to 6), and up to 12 potential assessment points for non-delirious controls (days 1 to 7 and weeks 2 to 6).

10.2.2. ASSESSMENTS

10.2.2.1. Delirium Rating Scale- Revised '98

Delirium assessments were performed on a daily basis by a trained delirium rater (NO'R) using the Revised Delirium Rating Scale (DRS-R98). This is a 16-item scale comprising 13 severity items (rated from 0 to 3) and 3 diagnostic items (rated from 0 to 2 or 3), which collectively give a total possible score range of 0 to 46. It is a diagnostically precise instrument which can differentiate delirium from other neuropsychiatric conditions, such as dementia and depression (90, 204, 205). It can be used to rate symptoms over the previous 24-hour period. In this study, in keeping with recommendations for its use, delirium was diagnosed if the severity score was ≥15 and / or if the total score was ≥18 (173). The DRS-R98 has been used to identify a three factor structure to delirium phenomenology: cognitive; circadian; and higher order thinking (42, 43). Because we were interested in exploring the longitudinal relationship between motor profile and cognition, a cognitive subscale of the DRS-R98 was calculated for each assessment by adding the scores of each of the cognitive items of the scale, i.e. items 9 to 13 (item 9- orientation; item 10- attention; item 11- short-term memory; item 12- long-term memory; item 13 visuospatial ability).

10.2.2.2. Delirium Motor Subtyping Scale – 4 (DMSS-4)

The DMSS-4 (see appendix A) can be used by any healthcare professional with an understanding of delirium presentation, and is used to assign one of four motor classifications. Hypoactive subtype requires at least one hypoactive feature present and no hyperactive features. Conversely, hyperactive subtype requires that the patient has at least one hyperactive feature and no hypoactive features. Patients with one or more features from each group are classed as mixed subtype, while those with no feature from either group are deemed no subtype. In this study, the DMSS-4 was rated by questioning the nursing staff along with observations made (by NO'R) during patient interview. The DMSS-4 was applied to all patients on a daily basis irrespective of their delirium status.

10.2.2.3. Application of longitudinal motor subtypes for delirium cases

In patients who developed delirium, a longitudinal motor profile was applied to each patient by examining motor subtype expression primarily for each day with delirium. In some cases, motor profile during days of no delirium was taken into account if we considered the score in question to reflect a fluctuation within a delirium episode. Over the course of a delirium episode, participants were classified as having either a relatively stable, consistent motor profile throughout, or a variable pattern to motor subtype classification. Hence there were five possible longitudinal subtypes, four stable and one variable: hypoactive subtype throughout; hyperactive subtype throughout; mixed subtype thoughout; no subtype throughout; and variable profile. Borderline cases were decided by consensus discussion with DM.

10.2.2.4. Assessment of previous cognitive status

Prior cognitive status was determined primarily using the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF), an instrument which uses structured informant history to detect dementia. It is particularly useful in the acute setting where cognitive tests are less specific for dementia (191). In this study, as in similar populations, a mean score of ≥3.5 was considered consistent with premorbid dementia (193). In addition to the IQCODE-SF, the medical notes were examined for a prior diagnosis of dementia made by a suitably trained physician. Borderline cases were discussed with ST and DM and, in these cases, diagnosis was reached by consensus opinion. In those with no available informant report and no documented dementia diagnosis, the baseline SMMSE (Standardised Mini Mental State Examination) was examined and a score of ≥27 /30 was considered normal, in keeping with similar studies (181). In those with lower SMMSE scores, in the absence of collateral history, we were unable to apply dementia diagnosis and, thus, prior cognitive status was deemed “unknown” in these patients (n=2).

10.2.2.5. Baseline data

Other baseline variables were collected including demographic data (age, sex); medical history; and functional status. Comorbidity burden was measured using the Modified Cumulative Illness Rating Scale (M-CIRS) and baseline functional status was assessed using the Modified Barthel Index (BI) on admission.

10.2.3. OUTCOMES

Data pertaining to in-hospital mortality and discharge destination were collected using the hospital electronic system. Patients and General Practitioners were contacted at six months post study entry to ascertain six-month outcomes (mortality; place of residence).

10.2.4. ETHICAL PROCEDURES

Ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The principles and procedures of the study were discussed with all patients but it was anticipated that many participants would have cognitive impairment at study entry and hence would not be capable of giving informed written consent. Thus, although informed written consent was sought from those who were competent to give it, due to the non-invasive nature of the study, ethical approval was also granted to enhance patient assent with proxy consent from next of kin or a responsible caregiver in those cases where capacity was questioned. These methods are in keeping with the Helsinki Guidelines for Medical Research involving human subjects (207).

10.2.5. STATISTICAL ANALYSIS

Statistical analyses were conducted using the SPSS-20.0 package. Demographic data were expressed as means ± SD or medians and IQR, depending on the distribution of the data. Comparisons of groups (1. stable vs. variable profile; 2. comparisons

between all five longitudinal patterns) were made using a χ^2 test for differences in proportions and a t-test, Mann Whitney U-test or ANOVA for differences in means. Logistic regression analysis was used to ascertain if motor subtypes were predictive of composite adverse outcomes of (i) death during hospitalisation or new admission to nursing home following the index admission, and (ii) death or institutionalisation at six months.

The Generalised Estimating Equation (GEE) method was utilised to analyse longitudinal data for the relationship over time between the four individual motor subtypes and independent variables (delirium event; DRS-R98 severity score; cognitive subscale of the DRS-R98; baseline functional status; premorbid cognitive status; comorbidity burden; sex; and age). Four separate binary comparisons were conducted, contrasting each motor category against the others: 1) no subtype vs. any subtype; 2) hypoactive vs. the other three profiles; 3) hyperactive vs. the other three profiles; and 4) mixed vs. the other three profiles. The GEE method allows for the fact that within subject observations are correlated and estimates the population average across time (expressed as coefficients). The estimated coefficients depict the relationship between the independent predictors and motor subtype status at each time point, rather than comparing motor profile groups based on longitudinal course. This allowed each available score for every included patient to be incorporated in the analysis, taking into account the correlation between scores for each respective participant.

10.3. RESULTS

In total, 555 patients were approached and, following study protocol exclusions, 191 participants were included in the longitudinal analysis, 61 of whom developed incident delirium (see Chapter 5, figure 9 for flow of patients through the study). The median age of the cohort was 80 (IQR 10), just over half (n=101) were male and 32 (16.9%) had pre-morbid dementia. Table 24 illustrates clinical and demographic information for the overall group, as well as for subgroups based on delirium status and on longitudinal motor subtype. The median number of assessments per patient was seven for both control patients and for those with incident delirium (range = 2 to 14 for cases; 2 to 9 for controls). In total, there were 1,219 contemporaneous DRS-R98 and DMSS-4 assessments conducted, and in 61 cases of delirium there were 113 delirium days with motor profile ascertained. Stability of motor subtype was significantly more predominant than variability (stable subtype n=45, 73.8%; variable subtype n=16, 26.2%; $p<0.001$). Sex, age, dementia status, BI, M-CIRS, and length of stay in days were entered into a GEE model to explore for independent predictors of stability of motor subtype (table 26). The only significant predictor of stability was BI (β =0.166; 95% CI 0.082-0.25; Wald Chi-Square 15.086; QIC 464.91; $p<0.001$). The most common subtype per delirium day was hypoactive subtype (66.4%, n= 75 / 113) and this subtype was also more common when longitudinal subtypes were applied (62.3%, n= 38 / 61), see table 25.

Including all 191 patients (1,219 assessments), GEE was used to identify variables related to DMSS motor subtype. The independent variables included in the initial

model were sex; age; dementia status; delirium status; BI; M-CIRS; and the cognitive subscale of DRS-R98. The latter variable was introduced to assess how the motor subtypes related to cognitive state over time. Because DRS-R98 severity score was not significant in any of the preliminary models, we did not include it in the analysis nor consider modifying the score to exclude motor items as has been done in previous studies (54). Four analyses are presented in table 26, highlighting the factors which differentiate each subtype from the other three. Neither age nor dementia were related to any of the subtypes. Both hyperactive and hypoactive subtypes were significantly associated with higher degrees of baseline functional dependence (BI) and comorbidity (M-CIRS), whereas mixed subtype and no subtype related to lower degree of impairment on these scales. Both hyperactive and hypoactive subtypes were significantly associated with greater levels of impairment on the cognitive subscale of the DRS-R98. There was no association on logistic regression analysis between the five different longitudinal subtypes and adverse outcomes during the index admission or at six months, nor was there an association when the longitudinal subtypes were considered as a binary variable, stable vs. variable profiles.

10.4. Discussion

This is the first longitudinal study of motor activity profile in older medical inpatients, with results indicating that the majority of incident delirium cases maintain a stable motor course throughout the episode, and are primarily hypoactive in presentation. Although results from cross-sectional studies in older patients are divergent, the

preponderance of hypoactive subtype found in our data resonates with the findings of other recent work conducted in the emergency department, where over 90% of delirious older patients presented with hypoactive profile (23). We found that the only predictor of motor profile stability was level of functional independence on admission, with lower levels of independence predicting a stable course over a variable one. Importantly, table 24 illustrates that this finding is not simply due to an association between hypoactivity and poor function. A previous report from this study indicates that one of the most significant independent predictors of incident delirium in this cohort was functional impairment on admission. In addition, this work highlights that this baseline feature also predicts the stability of delirium throughout the episode, compounding the significance of functional impairment as a baseline measure for delirium risk stratification.

Despite the dynamic nature of delirium and its multifactorial aetiology, the vast majority of research investigating the prevalence of and differences between delirium motor subtypes with respect to, for example, phenomenology, aetiology, detection rates and outcomes have used cross-sectional methodology. In order to better understand how factors interplay with the various motor subtypes, longitudinal observational studies are required. To date, longitudinal studies have only been conducted in two clinical settings, palliative care and in hip fracture patients (11, 52, 54). Findings from these studies have been conflicting in relation to stability of motor profile, predominant subtype, as well as the differences between the subtypes with respect to outcomes. The only common finding between all

longitudinal studies (including ours) is that motor subtypes were not distinguished by age or presence of pre-morbid dementia. Other than this, our results resonate with different findings from these previous studies, and also contrast in certain ways. Firstly, the study of palliative care patients found that they adhered to a principally stable course, the primary motor subtype being hypoactive (11), comparable to our findings, whereas Slor and colleagues found that hip fracture patients followed a more variable pattern with hyperactive subtype being the most prevalent of the stable profiles (52). This disparity between our study and that of Slor and colleagues is interesting given that these studies were similar with respect to median age (>80 years) and the use of daily delirium and motor assessment. In the study of palliative care patients, the median age was slightly younger at 70 years and assessments were conducted twice weekly. In relation to motor subtyping methods, we employed a version of the DMSS, similar to the study in palliative care patients, and in contrast to that in hip fracture patients in which the motor items from the DRS-R98 were utilised for this purpose. Of note, a separate report from the same Dutch study found high correlation between the DRS-R98 method and the more rigorously validated DMSS in delirious patients, with the correlation between DRS-R98 categories and their corresponding subgroups on the DMSS ranging from 69-100% (251).

Hence, our study is somewhat closer in methodology to that of Slor and colleagues, which indicates different delirium trajectories between hip fracture patients and older medical inpatients. It is conceivable, yet not proven, that delirium due to hip

fracture and other trauma follows a contrasting course to that caused by medical illness, substance intoxication or withdrawal. In 1990, Lipowski postulated that these respective deliria differ in relation to the occurrence of prodromal features (154), and so if this were true, it supports the theory that post-delirium trajectories in these distinct groups may also diverge. Studies of delirium prodrome have not investigated differences in prevalence of prodromal features between these groups, however one study in hip fracture patients identified a prodromal period in over 80% of patients, disputing Lipowski's proposal. Nonetheless, in terms of outcomes, our findings are similar to that of Slor and colleagues. Our study of older medical inpatients found no difference in a combined adverse outcome of death or institutionalisation on discharge and at six months between the motor subtypes, whereas in palliative care patients, Meagher and co-workers found that hypoactivity was independently associated with increased mortality at 30 days.

Our results also suggest that there may be important clinical differences between the subtypes in this population, particularly in relation to cognitive impairment. This depicts another very important difference between our findings and that of Meagher and colleagues in palliative care patients. In our cohort, the motor subtypes differed with respect to the cognitive subscale of the DRS-R98, such that purely hyperactive and hypoactive profiles were more impaired than mixed subtype and no subtype. In contrast, Meagher and colleagues found that cognitive subscale remained comparative across motor subtypes (54). Antecedent cross-sectional studies herald similar findings, indicating that motor subtypes do not differ with respect to the

degree of cognitive impairment nor the domains involved, although as these studies involved mainly patients referred to a psychiatry consultation-liaison team, referral bias may have impacted upon results (252-254). This difference in findings may signify that cognitive features of delirium occurring in different treatment settings or patient groups can vary and have a different relationship to motor activity profile.

This study has many strengths. Firstly, delirium diagnosis was ascertained by a trained experienced researcher using a well-validated diagnostically precise instrument. Secondly, participants were assessed on a daily basis, the instruments employed being used to rate features over the previous 24 hours, giving a richness of detail to the data, which may be lost when the interval between assessments is greater than one day. Furthermore, motor profile was determined using the intensively evaluated DMSS-4, which is now the most widely accepted method for motor subtyping in delirium. A limitation of our study is that because it was part of a larger study of delirium prodrome, patients with prevalent delirium were excluded and, hence, these data only reflect the longitudinal motor subtype characteristics in patients with incident delirium. It is possible that delirium occurring in older patients on admission may follow a different course to that which emerges during hospitalisation. On cross-sectional analysis of the prevalent delirium patients in this study, hypoactive subtype predominated with 67.4% of patients meeting hypoactive criteria on the DMSS-4, and the study by Han and co-workers also indicates that hypoactivity prevails as the dominant motor subtype in this group (23). However, we do not know if the course remains stable or varies throughout the episode. Another

limitation is that given the low representation of any subtype other than hypoactive, either from day-to-day assessment or as a longitudinal profile, it is possible that the study is underpowered to detect differences between the subtypes with respect to baseline variables and the cognitive subscale of the DRS-R98. Larger studies with greater numbers of patients, specifically with stable mixed and hyperactive motor profiles, are required to further examine the relationship between the subtypes and other factors. In particular, we must confirm how subtypes relate to impaired cognition in this clinical setting. If this relationship does indeed differ between patient groups, it may provide very important information to guide future work linking aetiology and neuropathophysiology.

In conclusion, we found that older medical inpatients with incident delirium follow a stable and predominantly hypoactive course during admission. This underlines the importance of fostering a greater awareness and understanding of the features and significance of hypoactivity in our hospitals, where hyperactivity and its associated challenges gain the most attention. Functional impairment on admission is not only a harbinger of delirium in this population, but also influences its course and thus should act as a prompt for us to urgently employ delirium prevention strategies at the earliest possible opportunity of contact with at risk patients.

Table 24: Demographics and clinical characteristics of the overall group and as subgroups based on incident delirium status and longitudinal motor subtype

M-CIRS= Modified Cumulative Illness Rating Scale; ns = non-significant; sd = standard deviation. * comparisons between the five longitudinal categories (Chi-square for proportions; ANOVA with Bonferroni correction for continuous variables). □comparisons between stable and variable profiles (Chi-square for proportions; independent sample t-test for continuous variables, except ❖Mann-Whitney U-test)

	Whole group n=191	Controls n=130	Delirium cases n=61	sig.	Delirium cases							
					Stable profile total n=45	Stable profile - divided by subtype				Variable profile n=16	sig.*	sig.□
						Hypoactive throughout n=38	Hyperactive throughout n=2	Mixed throughout n=2	No subtype throughout n=3			
Age (mean, sd)	80.1 (5.9)	79.4 (5.5)	81.4 (6.3)	0.03	81.4 (6.6)	81.3 (7.1)	83 (5.7)	81 (0)	82.7 (1.5)	81.4 (5.4)	ns	ns
Sex, male (n, %)	101 (52.9)	70 (53.8)	31 (50.8)	ns	21 (46.7)	17	0	2	2	10 (62.5)	ns	ns
Co-morbid dementia (n, %)	32/189 (16.9)	14/129 (10.8)	18/60 (30)	0.001	12 (27.3)	8	2	0	2	6 (37.5)	ns	ns
Barthel Index, inverted (mean, sd)	6.5 (4.9)	5.08 (4.3)	9.4 (4.8)	<0.001	10.2 (4.9)	10.9 (4.8)	4.5 (6.4)	10.0 (1.4)	6.3 (3.2)	7.2 (4)	ns	0.02❖
M-CIRS (mean, sd)	20.8 (5.9)	19.3 (5.4)	23.9 (5.9)	<0.001	24.4 (5.8)	24.7 (5.7)	17.5 (3.5)	29 (7.1)	22.3 (6.8)	22.6 (5.9)	ns	ns

Table 25: Frequency of motor subtypes in patients with delirium

*Comparison between stable and variable profiles using chi-square statistic

Longitudinal profile **n=61**	**n (%)**	**sig.**
Stable subtype	45 (73.8)	p<0.001*
• **Hypoactive throughout**	38 (62.3)	
• **Hyperactive throughout**	2 (3.3)	
• **Mixed Subtype throughout**	2 (3.3)	
• **No subtype throughout**	3 (4.9)	
Variable subtype	16 (26.2)	

Of 113 delirium days, 75 were hypoactive; 7 were hyperactive; 15 were mixed subtype and 16 were no subtype

Table 26: Four GEE models exploring the relationship between motor subtype and other variables.

GEE = Generalised Estimating Equation. Variables include demographics (sex, age); presence of pre-morbid dementia; baseline functional ability (BI, Modified Barthel Index, inverted so that higher scores indicate greater degrees of impairment); comorbidity burden (M-CIRS, Modified Cumulative Illness Rating Scale); delirium event; DRS-R98 (Revised Delirium Rating Scale) severity score; score on the cognitive subscale of the DRS-R98. All 191 patients included. Only significant variables are shown.

Parameter	β	S.E.	95% C.I.	Wald χ^2	d.f.	sig.
No subtype vs. the other 3 categories						
Inverted BI score	-0.1	0.02	-0.13 to -0.07	41.17	1	<0.001
M-CIRS total score	-0.04	0.01	-0.06 to -0.01	7.1	1	0.008
Male sex	0.34	0.16	0.03 to 0.65	4.63	1	0.031
Delirium event						
- no	0.46	0.2	0.06 to 0.86	5.14	1	0.023
- yes	0					
Cognitive subscale score	-0.1	0.03	-0.16 to -0.03	8.27	1	0.004
Hyperactive subtype vs. the other three categories						
Inverted BI score	0.1	0.02	0.07 to 0.13	40.15	1	<0.001
M-CIRS total score	0.04	0.01	0.01 to 0.06	7.76	1	0.005
Male sex	-0.34	0.15	-0.63 to -0.04	4.99	1	0.026
Delirium event						
- no	-0.45	0.2	-0.85 to -0.06	5.04	1	0.025
- yes	0					
Cognitive subscale score	0.1	0.03	0.03 to 0.16	9.17	1	0.002
Mixed subtype vs. the other three categories						
Inverted BI score	-0.09	0.02	-0.13 to -0.04	14.45	1	<0.001
M-CIRS total score	-0.05	0.02	-0.09 to -0.02	10.21	1	0.001
Delirium event						
- no	-2.33	0.38	-3.08 to -1.58	37.4	1	<0.001
- yes	0					
Cognitive subscale score	-0.22	0.05	-0.33 to -0.12	17.9	1	<0.001
Hypoactive subtype vs. the other three categories						
Inverted BI score	0.12	0.02	0.09 to 0.16	42.66	1	<0.001
M-CIRS total score	0.04	0.01	0.01 to 0.07	8.88	1	0.003
Cognitive subscale score	0.1	0.04	0.03 to 0.17	7.66	1	0.006

11. Motor Profiling can Differentiate Older Medical Patients with Subsyndromal Delirium from those with No Delirium

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11.1. Introduction

Delirium is a serious neuropsychiatric condition which is ubiquitous across healthcare settings and independently linked to a variety of adverse events including prolonged length of hospital stay, loss of independence, and mortality (3). Full-syndromal delirium (FSD) is present when a patient meets pre-defined criteria using a robust diagnostic classification system, however in addition to FSD, a delirium spectrum exists such that subsyndromal delirium (SSD) describes a state characterised by the presence of certain delirium features without fully meeting FSD thresholds. The context in which SSD develops is not fully understood, however it is posited that SSD can exist as a transitional state between no delirium and FSD or vice versa, and some work has indicated that antipsychotic prophylaxis during SSD can reduce progression to FSD in the post-operative period (73). It is also recognised that SSD may occur in isolation without ever traversing full-syndromal thresholds (75).

Although SSD is a more moderate presentation than FSD, it has prognostic significance in that outcomes have repeatedly been shown to be intermediate between those of patients with no delirium and those with FSD (53, 62, 65, 69, 74).

As well as FSD, SSD is prevalent across the acute hospital, occurring in 7-50% of inpatients, depending on the ward setting and the diagnostic criteria used (76). Clarity in relation to SSD definition and diagnosis has in general been lacking, with methods varying greatly from study to study. Some authors have used categorical definitions based on the presence of core delirium or CAM features and others have applied pre-defined cut-offs on dimensional diagnostic instruments (76). Recently, a phenotype of SSD has been conceptualised using analysis of pooled multi-cultural data. This study found that SSD is closer in phenotype to delirium than non-delirium and that some core delirium phenomenological features occur in SSD, however with milder severity than in FSD (75). Laterally, results from our research group has found that certain core diagnostic features (including impairments in higher order thinking and cognition, particularly attention) were the key differentiating features between SSD and FSD, and SSD and no delirium (76). Furthermore, in this cross-sectional study, SSD patients with inattention had higher ratings on the DRS-R98 severity and total scales than those without, and also scored higher on items related to higher order thinking; cognition (including attention); motor agitation; and contextual items such as acuity of onset and severity of fluctuations. These findings support a more anchored definition of the concept and presentation of SSD to facilitate diagnosis in the clinical and research setting. This definition recognises that although other

delirium features can vary between patients with SSD (as they do in FSD), certain core criteria are necessary for SSD diagnosis to be made, namely impaired attention span; and an acute or subacute onset of symptoms. These important features are central to the diagnosis and philosophy of full-syndromal delirium and so their being fundamental to the definition of a milder delirium spectrum disorder is intuitive (76).

Hence, SSD is conceptually akin to FSD, albeit less phenomenologically intense, presenting with milder manifestations of core delirium features that do not reach FSD diagnostic criteria. Despite this, to date there has been no study exploring the relationship between SSD and motor disturbance. Abnormal motor behaviour is now recognised as core to delirium presentation (38), with subgroups based on motor profile being used as the primary method for delirium subclassification. One longitudinal study of the stability of motor subtypes in delirious palliative care patients identified that those presenting with no motor subtype were likely to have lower DRS-R98 scores more consistent with SSD than FSD, even when motor items on the DRS-R98 were excluded from the analysis (11). Franco and colleagues found in a large pooled sample that any abnormal motor behaviour was significantly more prevalent in patients with SSD or FSD than those without either, however did not differentiate between SSD and FSD nor specifically examine the prevalence of motor subtypes in the sample (255). Given that motor features are often the most visible and observable features of delirium, understanding their relevance in SSD may help to facilitate the development of feasible methods for detecting SSD. Hence, the aim of this study was to examine the prevalence of motor disturbance in SSD compared

to FSD, measured using validated motor subtyping methods, and which motor subtypes predominate. We were also interested in examining if the motor profile of SSD remains stable across episodes or whether the profile varies from day to day. Additionally, we aimed to identify non-motor phenomenological differences between SSD and FSD or no delirium in older medical inpatients.

11.2. METHODS

11.2.1. SETTING AND PARTICIPANTS

This prospective observational cohort study of incident delirium was conducted in Cork University Hospital and the Mercy University Hospital, two acute general hospitals in Cork city, Ireland, between October 2011 and August 2013. Patients of seventy years and older who were admitted medically through the Emergency Department (ED) were eligible for inclusion. Further details of the study protocol and exclusion criteria are detailed in Chapter 3.

Older medical patients underwent assessment for prevalent delirium by the principal investigator (NO'R), within a maximum of 36 hours of presentation to the ED. Those without delirium on admission were then considered for inclusion in a prospective study of incident delirium, in which delirium assessment was conducted daily for the next seven days or until discharged. Those discharged free of delirium within three days of admission were ultimately excluded as in these patients delirium development post-discharge could not be outruled with certainty. Participants who

developed incident delirium (cases) continued to undergo daily assessment as tolerated until assessment day fourteen or until discharge or death. Thereafter, cases underwent weekly assessment for up to six weeks. Those who did not develop delirium during the first seven days of assessment (controls), continued to undergo weekly delirium assessment for a maximum of six weeks or until discharge or death.

11.2.2. ASSESSMENTS

11.2.2.1. Delirium Rating Scale- Revised '98

Daily delirium assessments were conducted by a trained rater (NO'R) using the Revised Delirium Rating Scale (DRS-R98), a widely used, well-validated, specific and sensitive tool for diagnosing delirium. It comprises 16 items which rate 13 severity features (from 0 to 3) and three diagnostic features (from 0 to 2 or 3), using phenomenological descriptive anchors for scoring each item. It is used to measure symptoms over the previous 24 hours, with the total possible score ranging from 0 to 46, higher scores indicating greater breadth and intensity of symptoms. The DRS-R98 is a precise diagnostic instrument which can distinguish delirium from other neuropsychiatric conditions, for example dementia and depression (90, 204, 205), making it an ideal tool for assessing phenomenology. In this study, consistent with guidelines for its use, FSD was diagnosed if the DRS-R98 severity score was ≥15 and / or if the total score was ≥18 (173). The DRS-R98 can also be used to identify subsyndromal delirium (SSD), although definitions differ from study to study. In this study, in keeping with methods previously proposed by our research group (249), we considered SSD present if the DRS-R98 total score was between 6 and 17 (inclusive);

and a score of at least 1 was reached on each of items 10 (attention) and 14 (temporal onset of symptoms).

11.2.2.2. Delirium Motor Subtyping Scale – 4 (DMSS-4)

The Delirium Motor Subtype Scale (DMSS) is a data-derived scale (47) which shows good specificity for delirium and correlates well with objective measures of motion (48). The 13-item scale was condensed to four items by latent class analysis, in order to facilitate use in busy treatment settings. This more concise version, the DMSS-4, has good concordance with the DMSS and similarly classifies patients into one of four motor subgroups based on the presence or absence of four key features: hypoactive; hyperactive; mixed and no subtype (see appendix A) (49). The DMSS-4 can be used by any healthcare professional with an understanding of delirium and in this study it was scored by questioning relevant nursing staff, supplemented by observations made (by NO'R) during patient interview. Each patient was assessed daily using the DMSS-4 regardless of delirium status.

11.2.2.3. Application of longitudinal motor subtypes for FSD and SSD patients

A longitudinal motor profile was applied to each patient who developed FSD or SSD by studying the motor subtype expression for each relevant day. In FSD patients, this was based primarily on presentation during days with delirium, however days with SSD were sometimes considered if they were felt to reflect a fluctuation within a delirium episode. Similarly, in SSD patients, longitudinal subtype was assigned based

on motor presentation during days with SSD. Using this method, participants were classified as having either a relatively stable motor profile throughout, or a variable motor pattern, giving five potential longitudinal subtypes, four stable and one variable: hypoactive subtype throughout; hyperactive subtype throughout; mixed subtype thoughout; no subtype throughout; and variable profile. Borderline cases were assigned longitudinal subtype following consensus discussion with DM.

11.2.2.4. Assessment of previous cognitive status

Premorbid cognitive status was established primarily using the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF), which utilises structured care-giver interview to detect cognitive change over the preceding ten years. It is especially useful in the acute setting, when cognitive baseline is often unknown and where cognitive tests are poorly specific for dementia (191). In this study, as in comparable populations, we used a mean score of ≥3.5 to detect premorbid dementia (193). The medical charts were also examined for a prior diagnosis of dementia made by a suitably trained physician. Borderline cases were decided by consensus discussion with ST and DM. In those without an available informant for the IQCODE-SF and no documented dementia diagnosis, a score of ≥27 /30 on baseline SMMSE (Standardised Mini Mental State Examination) was considered normal, consistent with similar studies (181). In patients with lower SMMSE scores, without formal diagnosis or IQCODE-SF, prior cognitive status was considered “unknown” (n=2).

11.2.2.5. Baseline data

Baseline data were also recorded including demographics (age, sex); comorbidity; and functional status, see Chapter 3 for more detail. The Modified Cumulative Illness Rating Scale (M-CIRS) was used to evaluate burden of comorbidity, and baseline functional status was measured using the Modified Barthel Index (BI) on admission.

11.2.3. ETHICAL PROCEDURES

Formal ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. Study aims and procedures were explained to each patient, however due to the nature of the study it was anticipated that many participants would be incapable of giving informed consent. Hence, in these cases, ethical approval was granted to augment patient assent with proxy consent from next-of-kin or responsible caregiver, consistent with the Helsinki Guidelines for Medical Research involving human subjects (207).

11.2.4. STATISTICAL ANALYSIS

Data were analysed using SPSS version 20. Demographic data and rating scale data are listed as means ± SD, for the whole group and for subgroups based on delirium status: FSD; SSD; No Delirium (ND). Differences in proportions were estimated using a χ^2 test. Continuous variables including age; M-CIRS; BI and DRS-R98 scores (total scores; severity scores; and individual item scores) were compared between the groups using one-way ANOVA, followed by pairwise comparisons. DRS-R98 item 16 was not included in this analysis as in all cases of FSD this was scored as 2 and so

became a constant. All other items on the DRS-R98 were used to make comparisons between the groups, although there was a pre-defined difference between SSD and ND for items 10 (attention) and 14 (temporal onset of symptoms) as scoring at least 1 on each of these items was a pre-requisite for membership of the SSD category.

11.3. RESULTS

Following exclusions according to the study protocol, 191 patients were included in the analysis. Sixty-one participants developed incident full-syndromal delirium, 41 experienced a defined period of subsyndromal delirium but never developed full syndromal delirium and 89 patients remained completely free of either subsyndromal or full-syndromal delirium throughout the study period (see figure 13 for flow of patients through the study). The median age of participants was 80 years (IQR 10) and 52.9% (n=101) were male (see table 27 for clinical and demographic information relating to the overall group and for subgroups based on delirium status).

There were 1,219 delirium assessments conducted with corresponding assessments of motor profile. Hypoactive subtype was the most common subtype overall and was particularly prevalent when delirium or SSD was present, whereas in patients with no delirium, no subtype predominated, see table 28 for details. Classifying SSD patients according to longitudinal subtype, we found that the majority of SSD patients demonstrated a stable course (n= 32, 78%, $p<0.001$), and the predominant

stable profile was hypoactivity (n = 19 / 41, 46.3%). No SSD patients were found to have a stable hyperactive or mixed course throughout.

Given our methods for applying delirium status, mean scores on the DRS-R98 were inevitably lower in patients with no delirium than SSD and in SSD than in FSD. However, the applied (dimensional) definition of delirium did not emphasise any particular items and as such we examined for differences between the groups in mean scores for individual items on the DRS-R98 using ANOVA with Bonferroni correction. Results are shown in table 29 and illustrated graphically in figure 14. Every DRS-R98 item from 1 to 15 was significantly higher in FSD than in ND, $p<0.001$. FSD was significantly different to SSD for all items except items 1 (sleep-wake cycle abnormalities); 3 (delusions); 4 (lability of affect); and 8 (motor retardation); whereas SSD was significantly different from no delirium for items 3 (delusions); 6 (thought process abnormalities); 8 (motor retardation); 10 (attention); 11 (short-term memory) and the contextual items.

11.4. Discussion

The results of our study highlight the predominance of hypoactive full-syndromal delirium relative to other motoric presentations. In addition, for the first time we report that hypoactive subtype is the primary motor profile in SSD. Existing studies have found that SSD is phenomenologically more similar to FSD than to ND, manifesting with milder expression of core delirium features. Although no studies

have specifically explored the relevance of motor profile to SSD presentation, one large study identified that motor retardation measured on the DRS-R98 was one of the factors differentiating SSD from ND (75) and another study found that any abnormal motor behaviour was significantly more common in those with FSD or SSD than ND (255). Now we find, using validated motor profiling methods, that almost two-thirds of SSD assessments meet motor subtype criteria (predominantly hypoactive) and although the prevalence of motor subtype presentations in SSD is less than that in FSD, it remains significantly higher than that in no delirium, which presents most commonly with no subtype. This finding, given how central motor disturbance is to FSD presentation, further consolidates the association between SSD and FSD, and differentiates them from those without a delirium spectrum disorder. The only other study to refer to motor subtypes in relation to SSD found that DSM-IV diagnosed delirium patients presenting with no motor subtype were more likely to have DRS-R98 scores in the SSD range, however this study was aimed at describing the frequency and stability of motor subtypes in patients with delirium and hence did not *a priori* include patients without FSD (i.e. those with either no delirium or pre-defined SSD), the observation in relation to SSD being made *post-hoc*. In this study when longitudinal subtypes were applied, stable patterns of motor expression were more common in FSD than variable patterns. Our findings suggest that this is also the case in SSD, the most common stable motor pattern being hypoactive. Interestingly, none of our cohort with SSD presented with either stable hyperactive or stable mixed profiles, and those who manifested either of these motor presentations during the SSD course followed a variable profile. It is important to note that some experts consider the DRS-R98 to be somewhat biased towards

diagnosing delirium in the setting of hyperactive presentations and hence it is possible that those presenting with hyperactivity or mixed profiles were more likely to reach full-syndromal thresholds than remain in the SSD range. Nonetheless, because of the predominance of hypoactivity in this cohort, this potential bias towards hyperactivity is unlikely to have had significant impact on the results.

We also explored phenomenological differences between FSD, SSD and ND using mean scores on various items of the DRS-R98. We found that older medical FSD patients scored significantly higher on many DRS-R98 items than SSD patients, namely perceptual abnormalities; language; thought process abnormalities; motor agitation (but not retardation); all cognitive items (including attention) and all contextual items, although the pattern of symptoms is almost parallel (see figure 14) between the two conditions. These results are comparable to those from a point prevalence study conducted by our group, in which FSD was differentiated from SSD by language and thinking; all cognitive items; and diagnostic items (76). In a much larger analysis of pooled multicultural data, features which distinguished FSD from SSD similarly included perceptual disturbance and acuity of onset, however additionally, delusions and affective lability delineated the groups. In this study, again the pattern of symptoms appeared very similar in FSD and SSD participants (75), although of course FSD patients had higher mean severity of all items.

What is more important clinically given the prognostic implications of having any delirium spectrum disorder is the ability to differentiate those with SSD from those with ND. In our study, we found that these groups diverged in relation to delusions; thought process abnormalities; motor retardation; attention; short-term memory; acuity of onset; and severity of fluctuations (although scoring at least one on each of attention and acuity of onset items was a pre-requisite for SSD diagnosis). Once again, these results resonate well with our previous work in which disorganised thinking; inattention; and both short- and long-term memory differentiated the two groups (76). Furthermore, for the comparison between SSD and ND, Trzepacz and colleagues similarly identified that delusions; motor retardation; temporal onset; as well as all cognitive items differentiated SSD from ND, however this analysis found that sleep-wake cycle abnormalities; perceptual disturbance; and affective lability were additionally discriminating. Importantly, this study found that sleep-wake cycle disruption; motor retardation; and all cognitive items differentiated SSD from ND but not from FSD. In our study, the only features to significantly delineate SSD from ND (and not FSD) were delusions and motor retardation, the latter of which echoes our findings in relation to motor subtyping. Hence, our results suggest that although hypoactivity is common to SSD and FSD and distinguishes them from ND, motor agitation may be one of the factors that separates the two delirium spectrum disorders, bearing in mind the hypothesis mentioned above in relation to DRS-R98 defined delirium and hyperactive presentations.

This is the first study exploring the presentation of motor subtypes in SSD and its strengths include the relatively high numbers of patients with SSD, the prospective nature of the study incorporating daily assessments, as well as the use of a standardised and well-validated delirium assessment instrument by a trained and experienced delirium researcher. Furthermore, motor profile was applied using the most intensively evaluated and widely used motor subtyping method, the DMSS-4. We defined SSD using a method developed following detailed review of the existing literature supplemented by data gathered by our research group, and hence it is the most up-to-date and accurate method currently available (76). Although this study was conducted only in older medical inpatients, thus limiting its generalisability, there are significant elements which resonate well with the existing SSD literature. Firstly, our results highlight the fact that SSD is an intermediate state between ND and FSD. In table 27 we can see that mean age; prevalence of comorbid dementia; and levels of functional impairment and comorbidity are lowest in patients with no delirium, and highest in those with FSD, with levels in SSD being between these levels, although not all of these comparisons reach statistical significance. In particular, escalating rates of comorbid dementia with increasing delirium syndromal status (from ND to SSD to FSD) has been demonstrated in a previous study, using both categorical and dimensional approaches to SSD definition (76). Secondly, as described above, our findings in relation to the phenomenological differences between SSD, FSD and ND are largely consistent with prior work and any dissimilarities may be accounted for by variations in study populations and methodology.

In summary, this study has identified that SSD in older medical inpatients presents primarily with a stable hypoactive motor subtype, whereas those patients without any delirium spectrum disorder most commonly express no motor subtype. This characteristic is one of a series of core elements that not only differentiates SSD from ND, but further aligns SSD conceptually with FSD. The fact that hypoactivity as defined by the DMSS-4 can delineate SSD and FSD from ND is an important clinical finding which may help us to more accurately detect patients on the delirium spectrum early on and hence promote speedier intervention.

Figure 13: Flow of patients through the study of subsyndromal delirium

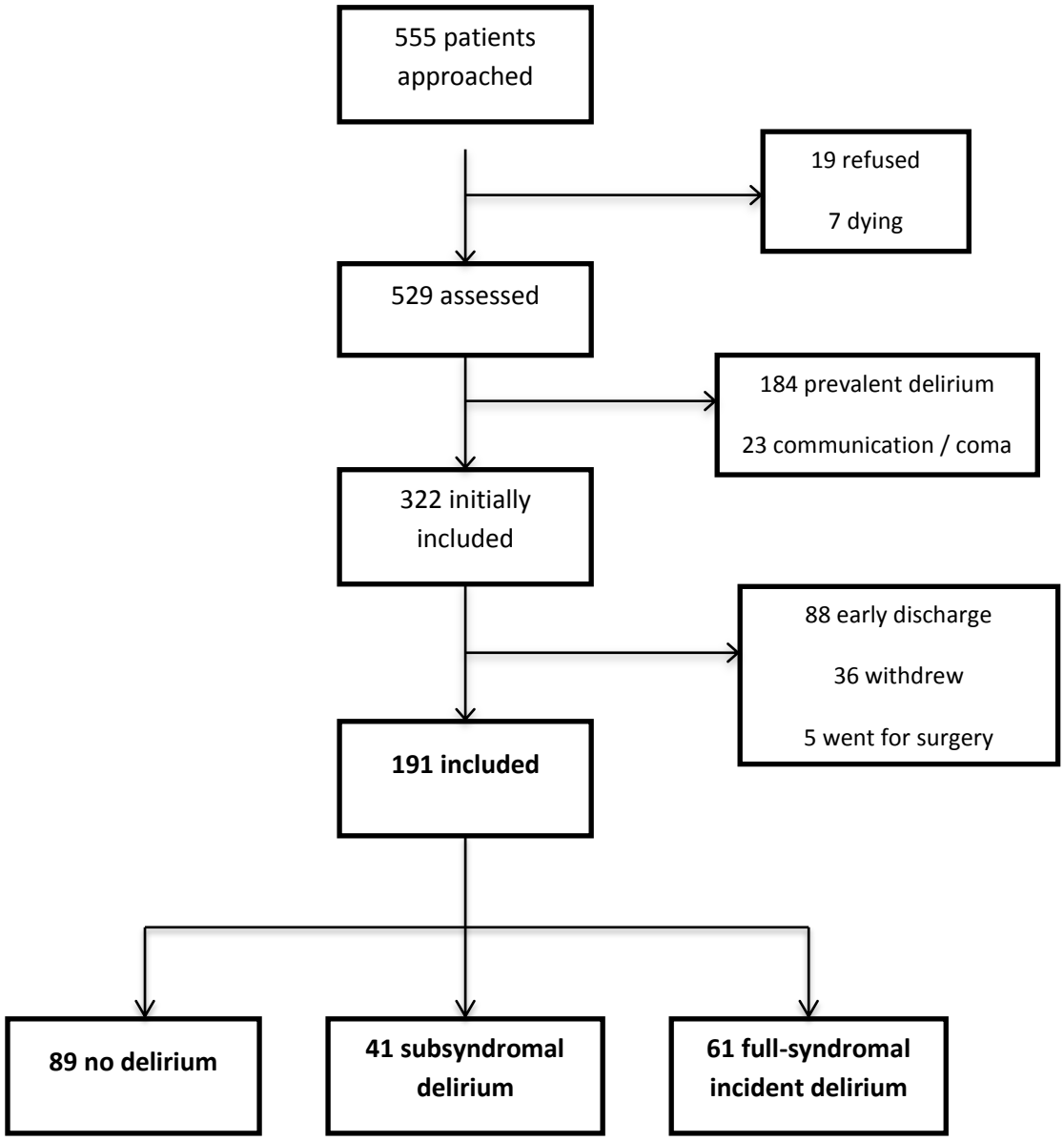


Table 27: Demographics and clinical characteristics of the overall group and as subgroups based on delirium status

a. Using ANOVA with Bonferroni correction, mean age of FSD > ND at p= 0.02, other comparisons ns
b. Using ANOVA with Bonferroni correction, mean iBI of i) FSD > SSD at p= 0.008; ii) FSD > ND at p<0.001; iii) SSD > ND at 0.012
c. Using ANOVA with Bonferroni correction, mean M-CIRS of i) FSD > SSD at p= 0.004; ii) FSD > ND at p<0.001; iii) SSD>ND ns

ND = no delirium; SSD= Subsyndromal delirium; FSD= full-syndromal delirium; iBI = Inverted Barthel Index; M-CIRS= Modified Cumulative Illness Rating Scale; ns = non-significant; sd standard deviation; * = Chi-square tests

	Whole group **n=191**	**No delirium** **n=89**	**Subsyndromal delirium** **n=41**	**Full-syndromal delirium** **n=61**	**sig.**
Age mean (sd)	80.05 (5.9)	78.8 (5.4)	80.7 (5.8)	81.4 (6.3)	(a)
Sex, male n (%)	101 (52.9)	49 (55)	21 (51.2)	31 (50.8)	ns*
Co-morbid dementia n (%)	32/189 (16.9)	4/89 (4.5)	10/40 (25)	18/60 (30)	<0.001*
Barthel Index, inverted mean (sd)	6.5 (4.9)	4.3 (4.1)	6.7 (4.4)	9.4 (4.8)	<0.05 (b)
M-CIRS mean (sd)	20.8 (5.9)	18.8 (5.1)	20.3 (6.0)	23.9 (5.9)	(c)

Table 28: Prevalence of motor subtype by assessment: no delirium, subsyndromal delirium and full-syndromal delirium

Chi-square p <0.001

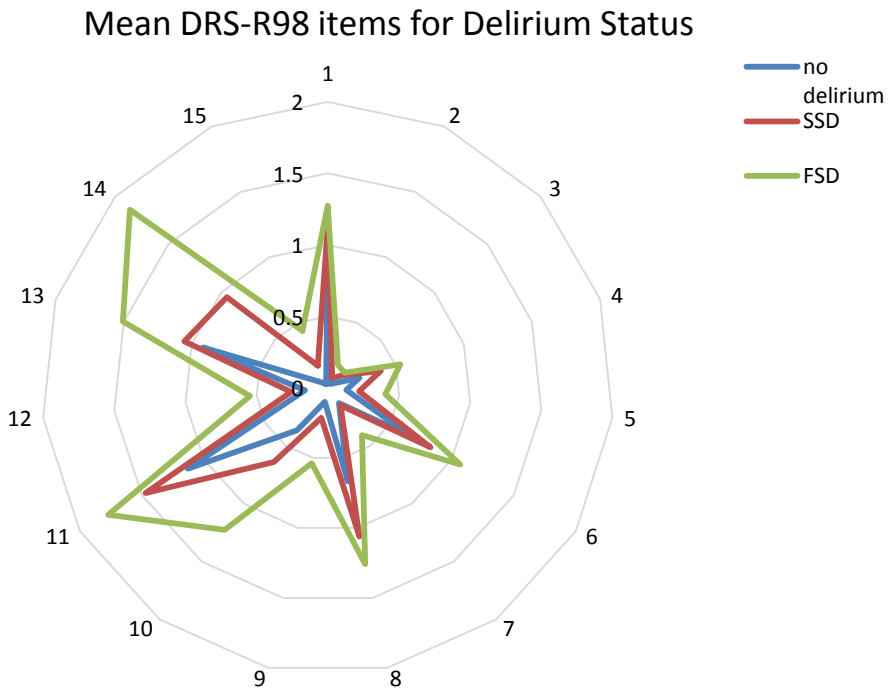
	Whole group n=1,219	**No delirium n=829**	**Subsyndromal delirium n=277**	**Full-syndromal delirium n=113**
Hyperactive n (%)	29 (2.4)	20 (2.4)	2 (0.7)	7 (6.2)
Hypoactive n (%)	538 (44.1)	292 (35.2)	171 (61.7)	75 (66.4)
Mixed subtype n (%)	27 (2.2)	6 (0.7)	6 (2.2)	15 (13.3)
No subtype n (%)	625 (51.3)	511 (61.6)	98 (35.4)	15 (14.2)

Table 29: DRS-R98 items and scale scores (means +/- SD) for each assessment, ANOVA with pairwise comparisons using Bonferroni correction.

a) FSD > ND significant; b) FSD > SSD significant; c) SSD > ND significant (* $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$; $^{+}$not applicable). ND = No delirium; SSD = subsyndromal delirium; FSD = full syndromal delirium

DRS-R98 item	No delirium	Subsyndromal delirium	Full-syndromal delirium	sig.
1. Sleep-wake cycle disturbance	1.01 ± 0.63	1.26 ± 0.67	1.67 ± 0.62	a***
2. Perceptual disturbances and hallucinations	0.04 ± 0.26	0.9 ± 0.44	0.51 ± 0.97	a***; b*
3. Delusions	0.05 ± 0.21	0.14 ± 0.36	0.44 ± 0.73	a***; c*
4. Lability of affect	0.26 ± 0.49	0.46 ± 0.57	0.89 ± 0.75	a***
5. Language	0.16 ± 0.37	0.3 ± 0.48	0.68 ± 0.54	a***; b**
6. Thought process abnormalities	0.75 ± 0.48	0.91 ± 0.42	1.42 ± 0.55	a***; b***; c*
7. Motor agitation	0.15 ± 0.37	0.22 ± 0.44	0.78 ± 0.89	a***; b***
8. Motor retardation	0.81 ± 0.64	1.3 ± 0.67	1.56 ± 0.82	a***; c***
9. Orientation	0.14 ± 0.39	0.36 ± 0.56	0.96 ± 0.84	a***; b***
10. Attention	0.38 ± 0.61	1.29 ± 0.53	1.74 ± 0.85	a***; b***; c^{+}
11. Short-term memory	1.24 ± 0.88	1.63 ± 0.87	2.14 ± 0.86	a***; b*; c**
12. Long-term memory	0.21 ± 0.47	0.4 ± 0.61	0.82 ± 0.85	a***; b**
13. Visuospatial ability	1.03 ± 0.69	1.28 ± 0.7	1.82 ± 0.73	a***; b***
14. Temporal onset of symptoms	0.34 ± 0.82	1.9 ± 0.77	2.5 ± 0.52	a***; b***; c^{+}
15. Fluctuation in symptom severity	0.07 ± 0.27	0.28 ± 0.45	0.95 ± 0.51	a***; b***; c***
DRS-R98 Severity score	6.25 ± 2.65	9.63 ± 2.1	15.42 ± 2.76	a***; b***; c***
DRS-R98 Total score	7.71 ± 3.12	13.19 ± 2.5	20.85 ± 2.81	a***; b***; c***

Figure 14: Radar graph illustrating the key phenomenological differences between no delirium, subsyndromal delirium and full-syndromal delirium



12. DISCUSSION

This thesis aimed to contribute to the current evidence by characterising delirium and its prodrome in older medical inpatients and by identifying methods to detect delirium early. This chapter firstly highlights the main findings of this thesis. Secondly, the strengths and limitations of this work are outlined. Thirdly, the potential clinical impact of this thesis is discussed and suggestions in relation to delirium screening and early detection are made. Fourthly, areas for future research are proposed and lastly, I conclude this thesis with a brief summary.

12.1 MAIN STUDY FINDINGS

12.1.1. THE PRODROMAL FEATURES OF DELIRIUM

This thesis is the first work designed primarily to characterise the delirium prodrome in older medical inpatients, and explored this concept in relation to behavioural features, cognitive features and delirium phenomenological features. Behavioural features were longitudinally assessed using a newly developed Prodromal Checklist, based on the existing literature (Chapter 7). I found that seven behavioural features were significantly predictive of delirium development independent of confounding variables (premorbid dementia; comorbidity burden; and functional impairment). These features were: irritability; being easily distractible or going 'off-track; increasing confusion or 'fogginess'; needing prompting for usual tasks; seeming tired

in the morning; drowsiness during the day; and being 'fidgety', restless or wandering. Many of these features have been identified by other studies (see Chapter 7) as occurring in the delirium prodrome, however it remains unclear as to how they relate to delirium phenomenology as it unfolds. Chapter 8 reports findings relating to the study of cognitive prodrome. I assessed participants on a daily basis using a series of cognitive tests and found that impairments in attention, orientation, short-term memory and visuospatial function were significantly indicative of impending delirium, independent of dementia and other confounders (Chapter 8). Again these features resonate well with other studies of the cognitive aspect of the delirium prodrome in other populations. In order to examine the delirium phenomenological features (including cognitive features) which occur in the prodromal phase, I used the Revised Delirium Rating Scale (DRS-R98) to assess patients daily and found that sleep-wake cycle abnormalities; perceptual disturbances; affective lability; inattention; short-term memory impairment; acuity of onset; and increasing severity of symptom fluctuations were all significantly predictive of delirium development in this cohort (Chapter 9). The findings outlined in these three chapters indicate that older medical inpatients with delirium may present with a variety of prodromal features including behavioural features; cognitive features; non-cognitive neuropsychiatric features; and emotional / affective features.

12.1.2. Early Identification of Delirium and those at Risk of Delirium

This thesis explored the utility of several screening approaches in the detection of delirium. Firstly, a selection of cognitive tests were assessed in relation to their diagnostic accuracy in identifying prevalent delirium in older medical inpatients within 36 hours of admission (Chapter 4). I found that the 6-CIT was the most robust test in detecting delirium in this acutely unwell cohort with an AUC of 0.876 (95% CI 0.84-0.91) and, in particular, I found using discriminant analysis that the 6-CIT has the potential to differentiate between patients with cognitive impairment due to delirium from those with cognitive impairment caused by dementia without delirium, correctly classifying 78.1% of the original grouped cases (Wilk's Lambda = 0.748, F=62.15, df1:1, df2:1, df3:184, p<0.001). This finding is especially important due to the challenges of distinguishing between these two diagnoses in clinical practice, a process which requires detailed collateral history, often unavailable in the acute setting. Promoting the use of the 6-CIT as a delirium screening approach may, hence, facilitate speedier identification of those with delirium, a medical emergency, and distinguish them from those with dementia (without delirium) early on in admission.

Secondly, I assessed if the screening approach recommended by the NICE guidance was useful in detecting delirium (Chapter 6). This approach advises monitoring for delirium indicators in four major domains, namely changes in cognitive function; perception; physical function; and social behavior. I developed a questionnaire based on the wording of the guidance and a blinded and independent group of researchers

then used this questionnaire to survey relevant nursing staff. Although the questionnaire had low Kappa agreement with the delirium diagnostic methods used (CAM and DRS-R98), I proceeded to assess the diagnostic accuracy of the questionnaire in detecting delirium (according to NICE guidance that any positive response indicates a positive screen) and unfortunately the sensitivity was too low for the questionnaire to be considered a useful screening test (64.3-66.7%). When I explored if the individual domains were able to discriminate those with delirium from no delirium, the only domain in this questionnaire to have any utility for this purpose was the cognitive domain (correctly classifying 77.1-82.9% of participants). Although this approach was highly delirium specific (85-93%), sensitivity was far too low (25-42%) for clinical use.

Thirdly, I evaluated which baseline factors were associated with the development of incident delirium. The NICE guidance recommends that daily delirium screening is undertaken in those at risk of delirium, namely those of 65 years and older; those with cognitive impairment; those with a current hip fracture; and those with severe illness at risk of decompensation. However, in a busy acute hospital implementation of this highly inclusive risk stratification method would be challenging. I collected data pertaining to known delirium risk factors (from the NICE guidance and the existing literature) and using multivariable analysis, found that premorbid dementia; higher comorbidity burden and greater functional impairment were all independently associated with incident delirium development. This information may

help to streamline risk stratification, prevention and detection strategies to those who are most vulnerable to delirium development.

12.1.3. Motor Profile and Phenomenology

To date, the motor subtype of delirium in older medical inpatients has only been described in cross-sectional samples, the results of which have been inconsistent. Given the dynamic nature of delirium, a longitudinal assessment of motor subtypes is necessary to accurately define how they relate to other factors, such as aetiology, risk factors and non-motor phenomenology. I examined longitudinal motor subtypes in patients with delirium in this cohort and found that they were predominantly stable, the most prevalent subtype being hypoactive subtype (62.3%). As well as being independently associated with incident delirium, functional impairment was also independently associated with having a stable motor profile, whereas neither age nor premorbid cognitive status had a significant relationship with stability or motor subtype. Unlike work in the palliative care population (54), this study found that in older medical patients, motor subtypes differed in relation to cognitive phenomenology (measured by the cognitive subscale of the DRS-R98), such that hypoactive and hyperactive subtypes had more cognitive impairment than those with mixed subtype or no subtype.

In addition to finding that hypoactive motor profile is the primary subtype in FSD, when subtypes were applied to those with SSD (Chapter 11) for the first time in this

thesis, I found that almost two-thirds of SSD patients fitted criteria for hypoactive subtype, whereas those with no delirium most commonly had no motor subtype. This finding consolidates that of other studies which found that SSD is phenomenologically closer to FSD than to no delirium, providing further evidence for delirium as a spectrum disorder. Additionally, in Chapter 11, I identified features which distinguished SSD from FSD and from no delirium, the latter comparison being clinically most important given the prognostic implications of having any delirium spectrum disorder. In this cohort of patients, the delirium features which were significantly more severe in SSD than in no delirium were delusions; thought process abnormalities; motor retardation; attention; short-term memory; acuity of onset; and severity of fluctuations, which compares well with the existing literature on this subject.

12.2 Strengths and Limitations

12.2.1. Prospective study

Strengths of the primary longitudinal study include the prospective study design (Chapters 5; 7; 8; 9; 10; and 11), allowing the features of prodromal delirium and incident delirium to be characterised; and the early inclusion into the study, daily assessment of subjects, the use of a well-validated sensitive instrument for the detection of delirium, such that incident delirium is unlikely to have been missed, and the use of the DMSS-4, now the most well-validated and widely used motor subtyping method, to apply motor subtypes. Furthermore, the fact that I have undergone intensive training in delirium assessment and had significant delirium

experience in both research and in a clinical capacity prior to commencement of this study is another study strength. Daily assessments for delirium phenomenology, prodromal features, cognition, and motor subtyping allowed me to carefully characterise FSD, SSD and the delirium prodrome in this cohort of older medical inpatients. This study was conducted in a cohort of older medically hospitalised patients who are at particular risk for delirium, and so caution should be exercised before generalising results to other patient groups, especially as the study sample was not consecutive. Even so, the prevalence and incidence rates found are broadly similar to those previously reported (197) and the low number of exclusion criteria meant that our cohort is likely to be representative of a "real life" inpatient population. Furthermore, my findings in relation to prodromal features are generally consistent with those of previous studies, including those in younger populations. Only 36 patients of the 322 initially included withdrew from the prospective study, highlighting the acceptability of the testing processes we used, particularly salient when considering repeated cognitive testing (Chapter 8) which patients often find tiring and cumbersome. Another study strength is the relatively large sample of patients with incident delirium (n=61), in comparison to other studies of delirium prodrome (see table 1). Chapter 11 reports on the motor subtype and phenomenology of participants with SSD, and again, the high number of subjects with SSD compares well to other similar studies. Another strength of this thesis is that I used the most up-to-date and accurate method to define SSD, an approach recently reported by our research group.

I collected data pertaining to easily identifiable and clinically relevant baseline risk factors and using multivariable logistic regression, I identified the baseline predictors of delirium in this cohort (i.e. pre-morbid dementia, comorbidity and functional status). Dementia is one of the top differential diagnoses when assessing for delirium, and patients with dementia are likely to have impairments on all of the cognitive tests we used to identify the delirium prodrome. However, we identified pre-morbid dementia using very robust methods (see Chapter 3, section 3.3.5.1.) and adjusted for its presence in the analysis. Thus, we are confident that our results are reflective of the delirium prodrome and not premorbid dementia.

Importantly, concerning the prospective assessment of prodromal features, both the Prodromal Checklist (completed by nursing staff) and the DRS-R98 assessments were conducted contemporaneously, and although the information acquired from the nursing staff to complete the Prodromal Checklist was not used to inform DRS-R98 scoring, there is a potential for bias. Furthermore, this novel checklist has not been tested for validity or reliability in the assessment of prodromal features. In relation to the study of cognitive prodrome, some of the cognitive tests used contributed to the scoring of the cognitive items on the DRS-R98 (see appendix B), so it is unsurprising that some of the results from Chapters 8 and 9 are similar. Both chapters indicate that changes in attention and short-term memory occur in the delirium prodrome, however prodromal changes in orientation and visuospatial function too subtle to be detected using the DRS-R98 were identified using the 6-CIT and the novel EVSQ test (developed in order to make assessment of visuospatial

function more palatable in ill older adults). Interestingly, the findings in Chapter 9 also reflect some of the findings in Chapter 7, specifically 'tiredness in the morning' and 'drowsiness during the day', identified using the prodromal checklist, mirrors prodromal sleep-wake cycle abnormalities detected using the DRS-R98. The symptom of 'irritability' recognised using the prodromal checklist may be a component of the affective lability identified in the prodrome using the DRS-R98. A limitation in the study of cognitive prodrome (Chapter 8) is that although we collected data on the CDT and IPT, due to reluctance on the part of participants to perform these tests on a daily basis, there were too much missing data (>1/3 of assessments), to include these tests in the longitudinal analysis.

A limitation in the studies of motor subtyping (Chapters 10 and 11) is that because the prospective study excluded patients with prevalent delirium on admission, I only have longitudinal data pertaining to the subtypes of patients with incident delirium. Cross-sectional analysis of motor subtypes in the study participants with prevalent delirium also shows a preponderance of hypoactive subtype (67.4%), however we do not know if prevalent delirium in older medical inpatients follows a stable course so we cannot make assumptions about the longitudinal subtype in this group. Another potential limitation is that so few participants had any stable subtype other than hypoactivity which may mean that the study was underpowered to differentiate the subtypes in relation to other factors, such as risk factors and cognitive performance.

12.2.2. CROSS-SECTIONAL STUDIES

12.2.2.1. Screening for prevalent delirium

In relation to the study of screening instruments in the detection of prevalent delirium (Chapter 4), strengths again include the diagnosis of delirium by a trained rater using a well-validated tool, and additionally, the evaluation of six cognitive tests for diagnostic accuracy. Furthermore, the high number of participants (470 in total, 184 with delirium) is a study strength, but because the sample was not consecutive, the diagnostic accuracy calculations conducted in this analysis must be interpreted with caution, despite the fact that prevalence rates resonate with the existing literature on the subject (197). Also, I as a sole researcher conducted all cognitive tests and delirium tests contemporaneously and delirium diagnosis was applied afterwards. Ideally, the cognitive assessments would be conducted by an independent and blinded researcher to minimise bias. Premorbid dementia was diagnosed using highly acceptable methods for studies such as this, however data pertaining to premorbid cognitive ability was not available for all included patients, which meant that on discriminant analysis of separate neurocognitive groups, we could not attempt to differentiate between those with comorbid delirium and dementia and those with delirium without dementia.

12.2.2.2. Utility of the NICE-based questionnaire

One strength of this study is that it is, as far as I am aware, the first attempt to investigate the clinical utility of the NICE recommendations in relation to delirium screening. A novel questionnaire was developed and trained researchers used this

questionnaire to survey relevant nursing staff, independent of my delirium assessments. A study limitation is the small convenience sample of delirium cases included, which may affect the study's validity and generalisability.

12.3. Clinical Implications and Suggestions for Clinical Practice

12.3.1. Delirium Screening

As is discussed at multiple points throughout this thesis, delirium is highly prevalent but is underdetected at alarming rates. Formal diagnosis is challenging and requires experience and expertise. It is now recognised and advocated by the NICE guidelines that delirium diagnosis should be undertaken in two steps: firstly, a quick, sensitive rule-out screening method should be used; and secondly, formal assessment by an expert should then be performed in those who screen positive at stage one. Although multiple screening methods have been proposed, there is no consensus as to which is most suitable. The NICE guidance recommends monitoring for a series of delirium indicators in those at risk of delirium, but in Chapter 6 the clinical utility of an operationalised version of these guidelines is tested and found not to be sensitive enough for clinical use in this capacity. In Chapter 4, I report the findings of a cross-sectional study which assessed the diagnostic accuracy of a number of different cognitive screening methods in a cohort of older medical inpatients and found that for the most robust test was the 6-CIT. Using a cut-off of 8 / 9, the sensitivity was 89.9% (95% CI 83.8-93.9) and NPV was 91.2% (95% CI 85.8-94.7), indicating that this test may be useful at step one in screening. The 6-CIT has many other qualities which make it suitable as a screening test (see Chapter 2, section 2.5.3.3.2. and Chapter 8,

section 8.4), including its brevity, high acceptability among staff and patients, and minimal training requirements. Additionally, results reported in Chapter 4 suggest that this using this instrument may facilitate differentiation between different neurocognitive groups on admission. Hence, I suggest considering this tool as a first-line screening approach for delirium in the clinical setting.

12.3.2. Monitoring for Prodromal Features

The main aim of this thesis was to characterise the delirium prodrome in older medical inpatients, and three chapters (Chapters 7, 8, and 9) report the findings in relation to this aim. In this study, multiple behavioural, cognitive and delirium features were found to occur in the delirium prodrome (outlined above) and I suggest that monitoring for prodromal features in those at risk of delirium may facilitate early detection of those with imminent delirium. Firstly, when an older patient is admitted, it is good practice that a thorough collateral history should be taken, especially if there is any question of cognitive impairment, in order to establish the context of this impairment and to confirm other important medical details. At this point, I propose that this collateral history should also include the seven behavioural features identified in Chapter 7 in order to help ascertain if the patient may have impending delirium. This may help to focus our delirium prevention and intervention strategies to those who are most at risk. Following admission, staff members should also consider monitoring for these features on a daily basis (see Chapter 7 figure 11 for a suggested approach).

In the above section (12.3.1.), I suggested the use of the 6-CIT as a screening method for delirium. Additionally, Chapter 8 reports that this tool may be useful in detecting the cognitive decline that occurs in the delirium prodrome. Hence, I suggest using the 6-CIT as a daily monitoring tool for delirium and its prodrome. Any increase (worsening) in a patient's score should prompt further assessment. Following this, if the patient does not meet full criteria for delirium in the setting of cognitive decline, it could well be that the patient is either in the prodromal phase of delirium or they may meet criteria for SSD. If the patient is in the prodromal phase, this should alert staff to engage even more actively with delirium prevention techniques and hopefully attenuate the duration and severity of the episode when it occurs. If the patient has SSD, this may too be prodromal in nature and herald the onset of FSD in the ensuing days. Even if SSD does not traverse into FSD, this is still important to identify as SSD has prognostic implications of its own which must be taken seriously.

12.3.3. Foster a Greater Awareness of Hypoactivity

Chapters 10 and 11 discuss in detail the motor subtypes of FSD and SSD in this cohort of older medical inpatients. By far the most prevalent subtype in both FSD and SSD was hypoactive subtype, and when we individually examined FSD, SSD and 'no delirium' assessments, we found that hypoactive subtype occurred about half as frequently in no delirium (35.2%) than in FSD (66.4%) or SSD (61.7%), $p<0.001$. This indicates that hypoactivity measured using the DMSS-4 is significantly more common in delirium spectrum diagnoses than no delirium. Unfortunately, the misperception that delirium presents primarily with hyperactivity still prevails across clinical

settings and the hypoactive subtype remains the least detected form of delirium, despite the fact that it incurs the most severe adverse outcomes. Therefore, I consider it important that delirium education programmes with particular focus on the identification of hypoactivity and its significance are developed for all clinical staff disciplines. Improved awareness and understanding of the hypoactivity associated with delirium may further facilitate delirium detection in the clinical setting.

12.4. Future Research

The most clinically important question in relation to the concept of the delirium prodrome is whether or not intervening swiftly in the prodromal period can reduce delirium incidence and hence the associated adverse sequelae. In order to answer this question, we must first be able to confidently diagnose the delirium prodrome. We must also understand which patients are more likely to traverse through a prodromal period en route to delirium diagnosis. For example, is the prodrome and its duration related to delirium aetiology, risk factors, phenomenology and course? Following on from this, we then must design and conduct randomised trials to assess the impact of an intervention in the prodromal period. This study is the first study designed specifically to capture the delirium prodrome in an older medical inpatient cohort and the findings are important. However, further studies are required to validate these findings both in a similar population and in other patient groups and clinical settings and subsequently, diagnostic criteria for the prodromal period must be developed and validated, before we progress to interventional trials.

This study identified for the first time that SSD in older medical inpatients has a motor profile, which is predominantly hypoactive. Further research is required to investigate if this is the case in other patient cohorts. We also identified features which differentiate SSD from FSD and 'no delirium', the latter comparison being most clinically important, as outlined in Chapter 11. SSD occurs in many settings. It can occur as part of the prodromal phase or in the recovery period after delirium and it can also occur in isolation, without ever reaching diagnostic thresholds for FSD. Future work should investigate if SSD differs phenomenologically in each of these settings and if other factors, such as aetiology, relate to these individual settings.

Another finding from this work is that the 6-CIT may be a useful screening instrument in the detection of prevalent delirium on admission. More importantly, our results suggest that the 6-CIT may be able to differentiate between those with delirium and those with dementia without delirium on admission. This finding needs further investigation with larger populations, more defined neurocognitive groups and a greater number of researchers to ensure that the 6-CIT is conducted independently of the delirium assessments and reduce the potential for bias.

12.5. CONCLUSION

Delirium is highly prevalent and serious, being associated with poor outcomes. Despite the fact that prompt diagnosis may improve these outcomes, delirium

remains underdetected. This thesis describes factors which may assist with early detection of delirium in older medical inpatients, including screening approaches for prevalent delirium; the identification of baseline predictors of incident delirium; the description of prodromal features in three domains; and the predominance of hypoactive motor subtype in both SSD and FSD. These findings should inform future efforts in developing delirium detection and prevention strategies, as well as staff education programmes. Future research is required particularly to ascertain if intervention in the prodromal period impacts on delirium incidence and outcomes.

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APPENDICES

A. Assessment tools used

B. Details on how delirium instruments were scored in this study

C. Data recording files

D. Ethical considerations

E. Published material

Appendices

A. Assessment Tools Used

- Confusion Assessment Method
- Revised Delirium Rating Scale
- Delirium Motor Subtype Scale – 4
- Six-item Cognitive Impairment Test
- Spatial Span Forwards Card
- Spatial Span Forwards Instructions for Use
- Clock Drawing Test
- Clock Drawing Test Scoring Template
- Interlocking Pentagons Test
- Environmental Visuospatial Questions Test
- Standardised Mini Mental State Examination
- Barthel Index
- Mini Nutritional Assessment- Short Form
- AB Clinician Depression Screen
- Geriatric Depression Scale (Short Form)
- The Modified Cumulative Illness Rating Scale
- Prodromal Checklist
- The Informant Questionnaire on Cognitive Decline in The Elderly- Short Form
- Excerpt from the NICE guidelines CG103
- Delirium Etiology Checklist

CAM SCORING SHEET

Positive ☐ **Negative** ☐

(1a OR 1b) AND 2 AND (3 OR 4) [CAM sensitive]

Item 1

(a) **Acute onset** Y O N O [acute on chronic O] _____

(b) **Fluctuation** Y O N O

Item 2

Inattention Y O N O _____

Months Forwards

J F MH A MY JE JY A S O N D

_____

Months Backwards

D N O S A JY JE MY A MH F J

_____

Item 3

Disorganised Thinking Y O N O _____

Proverb (cloud / meat / stitch / blood / vessels / actions / book / chickens / leopard / cat)

Questions (stone / leaf / wellingtons / elephants / hammer / fish / flour / bird / bigger / fork)

Details:

_____

Item 4

Consciousness

Alert Y O N O Other _____

(hyperalert or vigilant/ lethargic but readily rousable/ stuporose or comatose)

REVISED DELIRIUM RATING SCALE (DRS-R-98)

The following is an excerpt from the DRS-R98 Administration Manual. A copy of this was used as a scoring sheet for each DRS-R98 assessment.

Trzepacz PT MJ, Kean J, Abell M, Meagher DJ. . The Delirium Rating Scale- Revised- 98 (DRS-R98) Administration Manual. A guide to increase understanding of how to solicit delirium symptoms to administer the DRS-R98. Indianapolis, IN, USA: Paula Trzepacz ®; 2009.

This is a revision of the Delirium Rating Scale (Trzepacz et al. 1988). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

DRS-R-98 SEVERITY SCALE

1. Sleep-wake cycle disturbance

Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0. Not present

1. Mild sleep continuity disturbance at night or occasional drowsiness during the day

2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)

3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. Perceptual disturbances and hallucinations

Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and ''complex'' if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0. Not present

1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)

2. Illusions present

3. Hallucinations present

3. Delusions

Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

0. Not present

1. Mildly suspicious, hypervigilant, or preoccupied

2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible

3. Delusional

4. Lability of affect

Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0. Not present

1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control

2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others

3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language

Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0. Normal language

1. Mild impairment including word-finding difficulty or problems with naming or fluency

2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)

3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities

Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0. Normal thought processes

1. Tangential or circumstantial

2. Associations loosely connected occasionally, but largely comprehensible

3. Associations loosely connected most of the time

7. Motor agitation

Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0. No restlessness or agitation

1. Mild restlessness of gross motor movements or mild fidgetiness

2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.

3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation

Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0. No slowness of voluntary movements

1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.

2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care

3. Severe motor retardation with few spontaneous movements.

9. Orientation

Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn't know one's own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0. Oriented to person, place and time

1. Disoriented to time (e.g., by more than 2 days or wrong month or wrong year) or to place (e.g., name of building, city, state), but not both

2. Disoriented to time and place

3. Disoriented to person

10. Attention

Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (e.g., verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, e.g., digit span.

0. Alert and attentive

1. Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses

2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task

3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment

11. Short-term memory

Defined as recall of information (e.g., 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0. Short-term memory intact

1. Recalls 2/3 items; may be able to recall third item after category cueing

2. Recalls 1/3 items; may be able to recall other items after category cueing

3. Recalls 0/3 items

12. Long-term memory

Can be assessed formally or through interviewing for recall of past personal (e.g., past medical history or information or experiences that can be corroborated from another source) or general information that is culturally relevant. When formally tested, use a verbal and/or visual modality for 3 items that are adequately registered and recalled after at least 5 minutes. The patient should not be allowed to rehearse during the delay period during formal testing. Make allowances for patients with less than 8 years of education or who are mentally retarded regarding general information questions. Rating of the severity of deficits may involve a

judgment about all the ways long-term memory is assessed, including recent and/or remote long-term memory ability informally tested during the interview as well as any formal testing of recent long-term memory using 3 items.

0. No significant long-term memory deficits

1. Recalls 2/3 items and/or has minor difficulty recalling details of other long-term information

2. Recalls 1/3 items and/or has moderate difficulty recalling other long-term information

3. Recalls 0/3 items and/or has severe difficulty recalling other long-term information

13. Visuospatial ability

Assess informally and formally. Consider patient's difficulty navigating one's way around living areas or environment (e.g., getting lost). Test formally by drawing or copying a design, by arranging puzzle pieces, or by drawing a map and identifying major cities, etc. Take into account any visual impairments that may affect performance.

0. No impairment

1. Mild impairment such that overall design and most details or pieces are correct; and/or little difficulty navigating in his/her surroundings

2. Moderate impairment with distorted appreciation of overall design and/or several errors of details or pieces; and/or needing repeated redirection to keep from getting lost in a newer environment despite, trouble locating familiar objects in immediate environment

3. Severe impairment on formal testing; and/or repeated wandering or getting lost in environment

DRS-R-98 OPTIONAL DIAGNOSTIC ITEMS

These three items can be used to assist in the differentiation of delirium from other disorders for diagnostic and research purposes. They are added to the severity score for the total scale score, but are NOT included in the severity score.

14. Temporal onset of symptoms

Rate the acuteness of onset of the initial symptoms of the disorder or episode being currently assessed, not their total duration. Distinguish the onset of symptoms attributable to delirium when it occurs concurrently with a different preexisting psychiatric disorder. For example, if a patient with major depression is rated during a delirium episode due to an overdose, then rate the onset of the delirium symptoms.

0. No significant change from usual or longstanding baseline behavior

1. Gradual onset of symptoms, occurring over a period of several weeks to a month

2. Acute change in behavior or personality occurring over days to a week

3. Abrupt change in behavior occurring over a period of several hours to a day

15. Fluctuation of symptom severity

Rate the waxing and waning of an individual or cluster of symptom(s) over the time frame being rated. Usually applies to cognition, affect, intensity of hallucinations, thought disorder, language disturbance. Take into consideration that perceptual disturbances usually occur intermittently, but might cluster in period of greater intensity when other symptoms fluctuate in severity.

0. No symptom fluctuation

1. Symptom intensity fluctuates in severity over hours

2. Symptom intensity fluctuates in severity over minutes

16. Physical disorder

Rate the degree to which a physiological, medical or pharmacological problem can be specifically attributed to have caused the symptoms being assessed. Many patients have such problems but they may or may not have causal relationship to the symptoms being rated.

0. None present or active

1. Presence of any physical disorder that might affect mental state

2. Drug, infection, metabolic disorder, CNS lesion or other medical problem that specifically can be implicated in causing the altered behavior or mental state

DELIRIUM MOTOR SUBTYPE SCALE-4 (DMSS-4)

(a) Hyperactive subtype defined by the presence of either (i) or (ii)

(i) Increased activity levels evidenced by a positive response to *either*:

Is (s)he more active than before?

Does (s)he seem overactive?

(ii) Loss of control of activity evidenced by a positive response to *either*:

Are his / her movements unproductive or lacking in purpose

Has (s)he lost a sense of control over their actions?

(b) Hypoactive subtype defined by the presence of either (iii) or (iv):

(iii) Decreased speed of actions evidenced by a positive response to *either*:

Is (s)he moving more slowly than before?

Does it take longer than previously to perform simple tasks?

(iv) Decreased amount of speech evidenced by a positive response to *either*:

Does (s)he speak less than before?

Is (s)he lacking in spontaneous speech? E.g. only speaks when spoken to.

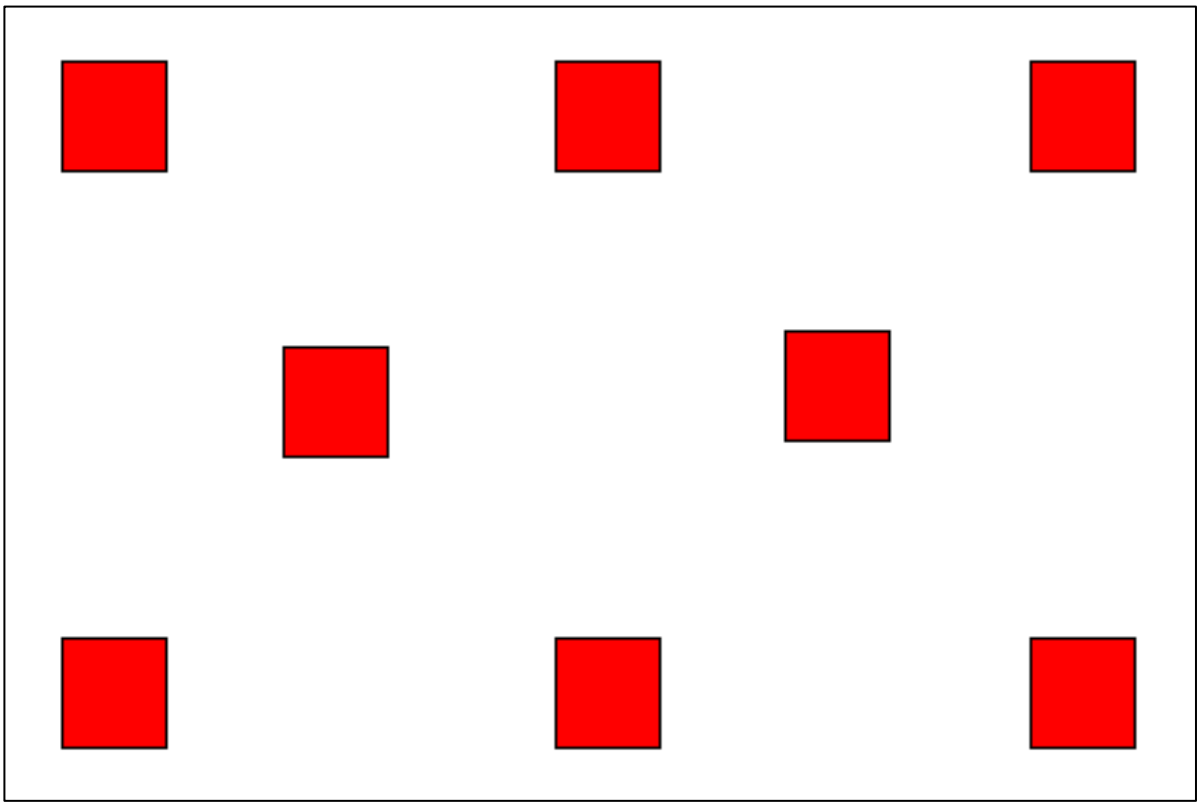
(c) Mixed subtype defined by the presence of both hyperactive and hypoactive criteria as outlined in (a) and (b) above.

(d) No subtype if neither hyperactive nor hypoactive criteria as outlined in (a) and (b) above.

SIX-ITEM COGNITIVE IMPAIRMENT TEST (6-CIT)

Instruction	**Date→**							
1. What year is it?	Score 0 if correct Score 4 if incorrect							
	Patient's answer							
2. What month is it?	Score 0 if correct Score 3 if incorrect							
	Patient's answer							
3. Repeat this address (*choose one)**: a. Mary /O'Brien/ 42/ High Street/ Waterford b. John/ Daly/ 77/ Lake View/ Killarney c. William/ Murphy/ 53/ College Road/ Galway d. Tom/ O'Shea/ 38/ Station Road/ Kilkenny e. Anne/ Hurley/ 29/ Church Street/ Limerick *(I used a variety of different addresses to minimise learning effect) **Try to remember this address. I'll ask you to recall it at the end of the test**								
4. About what time is it *(without looking at watch or clock*)?	Score 0 if patient is correct to within 1 hour Score 3 if patient is incorrect							
	Patient's answer							
5. Count backwards 20 down to 1 *20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1*	Score 0 if no mistakes Score 2 if 1 mistake Score 4 if 2 or more mistakes							
6. Say the months of the year in reverse order *Dec Nov Oct Sept Aug July June May April Mar Feb Jan*	Score 0 if no mistakes Score 2 if 1 mistake Score 4 if 2 or more mistakes							
7. Repeat the address I asked you to remember earlier	Score 2 for each error 0, 2, 4, 6, 8, 10							
	Total score	/28	/28	/28	/28	/28	/28	/28

SPATIAL SPAN FORWARDS TEST CARD



SPATIAL SPAN FORWARDS INSTRUCTIONS FOR USE

1. Show the A5 sized card to the patient and introduce the test by saying; " I would like to do a short test of your concentration. Can you see the squares on the piece of card? I am going to point to a sequence of squares with my finger and I would like you to repeat what I do by pointing with your finger to the same sequence of squares in the same order as me. For example: (point to the second square for one second and then slowly move your finger to the sixth square for one second saying) "I would like you to copy this" (point to the same two squares again as if you are the patient)

2. "Does that make sense?" Explain again if any uncertainty

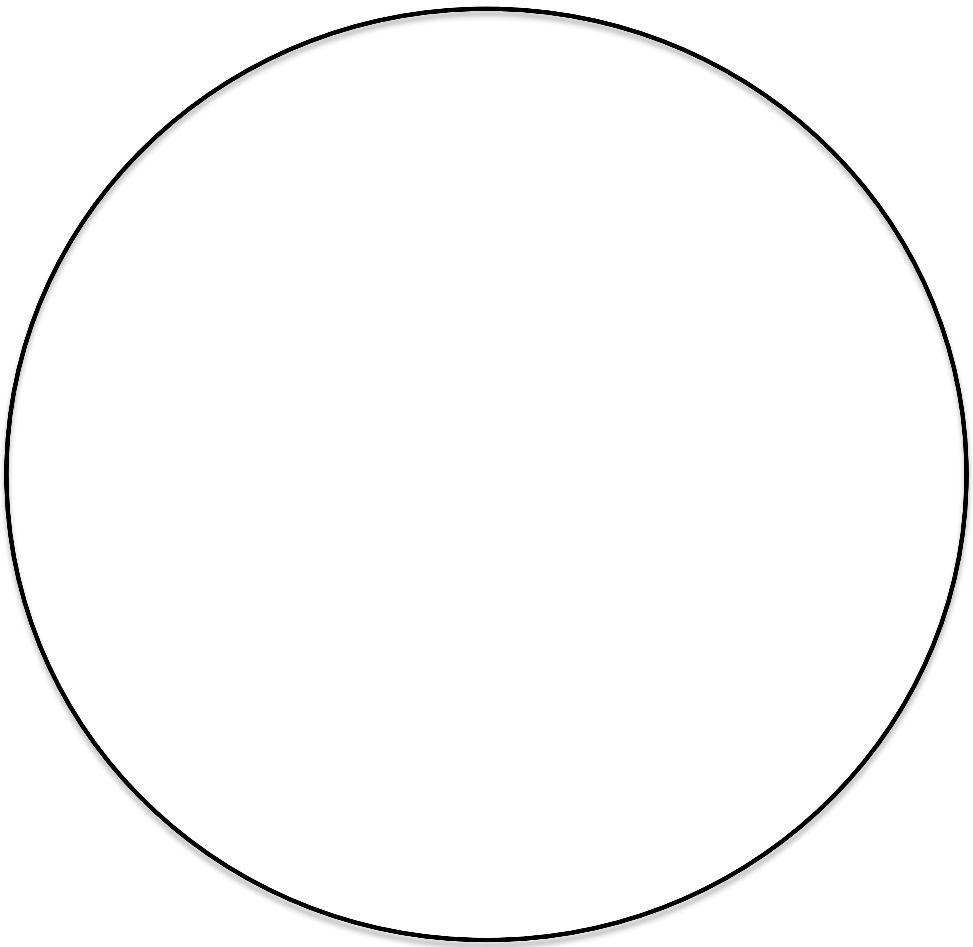
3. "Are you comfortable and ready to start? The test starts with just 2 squares but I will keep making the sequence longer until you get stuck- don't worry when that happens as that is normal"

4. Point to the sequences in this order, lingering on each square for 1 second:
   2-6; 2-7-5; 3-2-8-4; 5-3-4-6-1 ; 1-7-2-8-5-4

5. Keep going until the patient makes an error; note this and then try the second test of this trial (in column B below) i.e. if the patient fails the sequence of 4 (3-2-8-4), you should then perform the sequence of 4 from column B (2-6-1-5). If the patient fails the second attempt, stop and mark them as the last correctly repeated sequence, in this case the patient scores 3. If the patient succeeds at the second attempt, proceed to the sequence of 5 in column A. Hence, the patient is allowed 2 trials if necessary at every stage in order to proceed to the next stage.

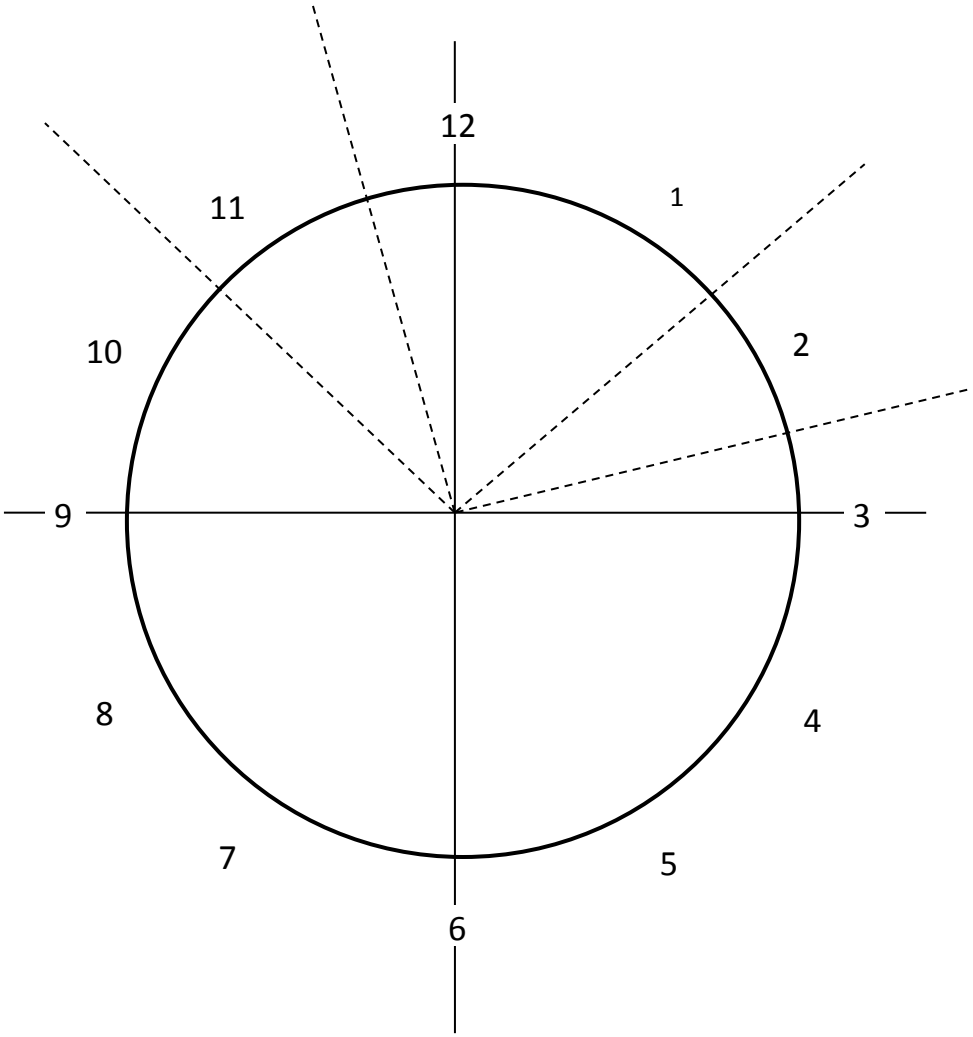
Column A- Trial 1	Column B- Trial 2
2-6	8-4
2-7-5	8-1-6
3-2-8-4	2-6-1-5
5-3-4-6-1	3-5-1-7-2
1-7-2-8-5-4	7-3-6-1-4-8
8-2-5-3-4-1-6	4-2-6-8-3-7-5

Please put numbers in the circle so it looks like the face of a clock



CLOCK DRAWING TEST SCORING TEMPLATE

Molloy DW. The Quick Mild Cognitive Impairment Screen (Qmci) Administration and Scoring Manual.21st September 2011.



Scoring

Place this scoring template over the completed clock with the template's "12 o'clock" line placed over the subject's 12. Adjust the template to maximize the score for the numbers and hands. The total score is 15. Record scores on the score sheet as follows:

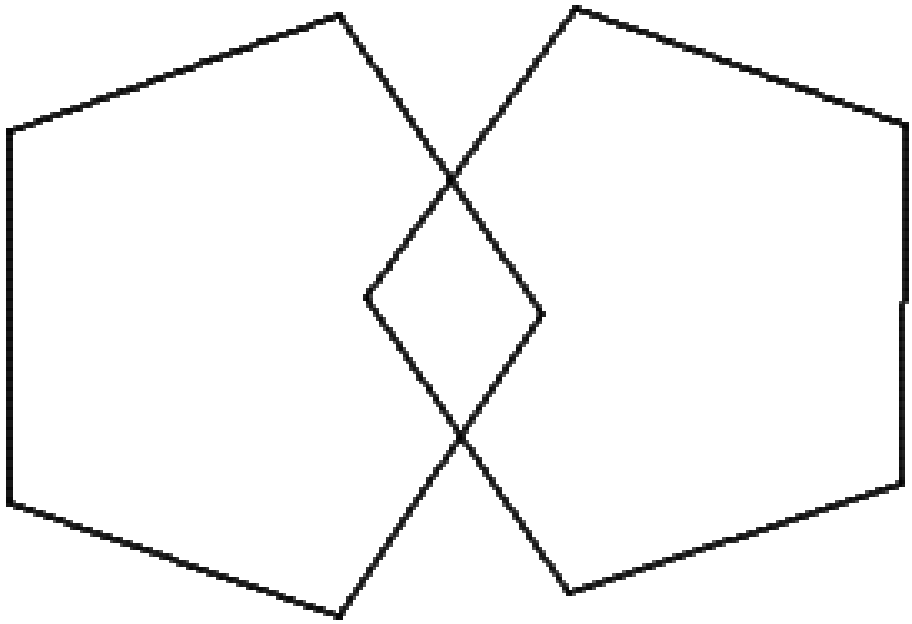
Numbers

- For the numbers 12, 3, 6, and 9 score one (1) point if they touch their respective lines, zero (0) point if missed, and zero (0) if the number is omitted.
- For the numbers 1, 2, 4, 5, 7, 8, 10, and 11 score one (1) point for each number in the correct quadrant, zero (0) point if the number is outside the quadrant, and zero (0) if the number is omitted.
- **Subtract one point for each number repeated or more than 12.**

Hands

Score the placement of the entire hand. If the hands are drawn within range, score one (1) point for each hand; if the hands are drawn outside the hatched line or are omitted score zero (0); Give one (1) point if the hands join at the pivot

Please copy this diagram



ENVIRONMENTAL VISUOSPATIAL QUESTIONS TEST

Five of the following questions were asked daily and the subject was given a mark for each correct answer. The test was scored out of five.

1. Where is the toilet?

2. Where is the nurses' station?

3. Where is the way out?

4. Which is bigger, ……* or …….*?

5. Which is closer to you, the window or the door?

6. Which of my hands is closer to you?

7. Which is taller, ….. *or ……*?

8. Which is closer to you, ……* or …….*?

*Objects in room or on bedside table are used here

STANDARDISED MINI MENTAL STATE EXAMINATION (SMMSE)

Time allowed for each question is given in brackets

Section 1- Orientation (10 seconds allowed for each question)

1.a. What year is this?	☐/1	2.a. What country are we in?	☐/1
b. Which season is this?	☐/1	b. What county are we in?	☐/1
c. What month is this?	☐/1	c. What city / town are we in?	☐/1
d. What is today's date?	☐/1	d. What is the name of this place?	☐/1
e. What day of the week is this?	☐/1	e. What floor are we on?	☐/1

Section 2- Cognition

3. SAY: "I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes." Say the following words slowly at 1 second intervals: ball / car / man. (20 seconds)

Word 1 _____ ☐/1

Word 2 _____ ☐/1

Word 3 _____ ☐/1

4. Spell the word 'WORLD'. Now spell it backwards. (30 seconds)

DLROW _____ ☐/5

5. Now what were the three objects I asked you to remember? (10 seconds)

Word 1 _____ ☐/1

Word 2 _____ ☐/1

Word 3 _____ ☐/1

6. SHOW wristwatch. Now ASK: "What is this called?" (10 seconds) ☐/1

7. SHOW pencil. Now ASK: "What is this called?" (10 seconds) ☐/1

8. SAY "I would like you to repeat this phrase after me:
No ifs, ands, or buts" (10 seconds) ☐/1

9. SAY “Read the words on the page and then do what it says.” Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads but does not close their eyes, repeat up to three times. Score only if subject closes eyes. (10 seconds)

Subject closes eyes ☐/1

10. HAND the person a pencil and paper. SAY: “Write any complete sentence on that piece of paper.” Note: the sentence must make sense. Ignore spelling errors. (30 seconds)

Sentence ☐/1

11. Place design, eraser and pencil in front of the person. SAY: “Copy this design please.” Allow multiple tries. Wait until the person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between 2 5-sided figures.
(1 minute)

Copies design ☐/1

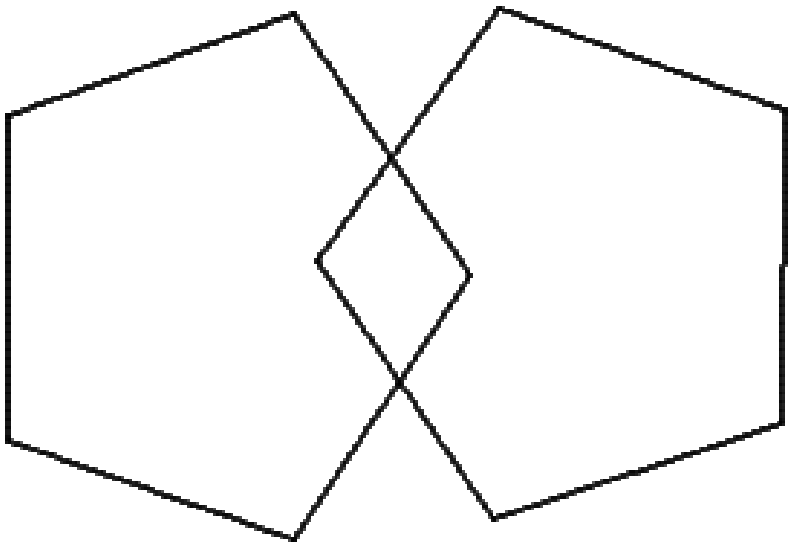
12. ASK the person if he / she is right or left-handed. Take a piece of paper and hold it up in front of the person. SAY: “Take this paper in your right / left hand (whichever is non-dominant), fold the paper in half once with both hands and put the paper down on the floor.” Score 1 point for each instruction executed correctly. (30 seconds)

Takes in correct hand ☐/1 Folds paper in half ☐/1 Puts paper on floor ☐/1

CLOSE YOUR EYES

Write a sentence

Copy this diagram



BARTHEL INDEX

		Date	Date	Date	Date	Date	Date	Date
Bowels	0= incontinent, 1= occasional accident (1 per week), 2= continent							
Bladder	0= incontinent or catheterized & unable to manage, 1= occasional accident (max 1 per 24 hours), 2= continent for over 7 days							
Grooming	0= needs help, 1= independent (face, hair, teeth, shaving)							
Toilet use	0= dependent, 1= needs some help but can do something, 2= independent (on & off, dressing, wiping)							
Feeding	0= unable, 1= needs help cutting, spreading butter, etc, 2= independent							
Transfer	0= unable, 1= major help (1-2 people, physical), 2= minor help (verbal or physical), 3= independent							
Mobility	0= immobile, 1= wheelchair independent including corners etc, 2= walks with help of 1 person (verbal/ physical), 3= independent (but may use aid, e.g. stick)							
Dressing	0= dependent, 1= needs help but can do half unaided, 2= independent							
Stairs	0= unable, 1= needs help (verbal, physical, carrying aid), 2= independent up & down							
Bathing	0= dependent, 1= independent							
	Score (__/20)							

MINI NUTRITIONAL ASSESSMENT- SHORT FORM

A. Have you been eating less than normal over the past 3 months? Is it much less or only a little less?

Severe decrease	0
Moderate decrease	1
No decrease	2

B. Have you lost weight recently without trying? How much?
Was that in the last few months or over the last year?

Weight loss >3kg	0
Does not know	1
Weight loss 1 to 3kg	2
No weight loss	3

C. Mobility

Bed / chair bound	0
Able to get up but not out	1
Goes out	2

D. Psychological stress/ acute disease
(e.g. bereavement / moved house / recent illness)

Yes	0
No	1

E. Neuropsychological problems (medical notes / collateral history)

Severe dementia / depression	0
Mild dementia	1
Nil	2

F1. Body Mass Index _____ **OR** **F2.** Calf Circumference (cm)

Weight (kg)	_____		_____
Height (m)	_____		
Demispan (cm)	_____		
BMI <19	0	<31 cm	0
BMI 19-21	1		
BMI 21-23	2		
BMI ≥23	3	≥31 cm	3

➔ **MNA SCORE _____**

AB CLINICIAN DEPRESSION SCREEN (ABCDS)

1. Do you often feel downhearted and blue?

No □ **➔Depression ruled out with 95% certainty**

Yes □ **➔ Ask the following questions:**

2.	Do you often feel helpless?	Yes	□	No	□
3.	Do you feel that your life is empty?	Yes	□	No	□
4.	Do you feel happy most of the time?	Yes	□	No	□
5.	Are you basically satisfied with your life?	Yes	□	No	□

Score 1 or 2 / total of 5 questions: Not depressed

Score 4 or 5 / total of 5 questions: Depressed.

Score of 3/5: proceed to Geriatric Depression Scale

GERIATRIC DEPRESSION SCALE: SHORT FORM

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? YES / **NO**
2. Have you dropped many of your activities and interests? **YES** / NO
3. Do you feel that your life is empty? **YES** / NO
4. Do you often get bored? **YES** / NO
5. Are you in good spirits most of the time? YES / **NO**
6. Are you afraid that something bad is going to happen to you? **YES** / NO
7. Do you feel happy most of the time? YES / **NO**
8. Do you often feel helpless? **YES** / NO
9. Do you prefer to stay at home, rather than going out and doing new things? **YES** / NO
10. Do you feel you have more problems with memory than most? **YES** / NO
11. Do you think it is wonderful to be alive now? YES / **NO**
12. Do you feel pretty worthless the way you are now? **YES** / NO
13. Do you feel full of energy? YES / **NO**
14. Do you feel that your situation is hopeless? **YES** / NO
15. Do you think that most people are better off than you are? **YES** / NO

Answers in bold indicate depression. Score 1 point for each bolded answer.

A score > 5 points is suggestive of depression.

A score ≥ 10 points is almost always indicative of depression.

A score > 5 points should warrant a follow-up comprehensive assessment.

Source: http://www.stanford.edu/~yesavage/GDS.html

THE MODIFIED CUMULATIVE ILLNESS RATING SCALE (M-CIRS).

Body system	Score				
1. Cardiac (heart only)	0	1	2	3	4
2. Hypertension (rating is based on severity; organ damage is rated separately)	0	1	2	3	4
3. Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics)	0	1	2	3	4
4. Respiratory (lungs, bronchi, trachea below the larynx)	0	1	2	3	4
5. EENT (eye, ear, nose, throat, larynx)	0	1	2	3	4
6. Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes)	0	1	2	3	4
7. Lower GI (intestines, hernias)	0	1	2	3	4
8. Hepatic (liver and biliary tree)	0	1	2	3	4
9. Renal (kidneys only)	0	1	2	3	4
10. Other GU (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11. Muscolo-skeletal-integumentary (muscle, bone, skin)	0	1	2	3	4
12. Neurological (brain, spinal cord, nerves, do not include dementia)	0	1	2	3	4
13. Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
14. Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

PRODROMAL CHECKLIST

(0 = not present; 1 = possibly or somewhat present; 2 = definitely present)

A. General complaints.	**0/1/2**	**D. Sleep/ activity changes**	**0/1/2**
In the last 24 hours, have you noticed any changes in the patient's general wellbeing? 1. Appetite 2. Pattern of pain / discomfort 3. Frequency of requests for analgesia 4. Frequency of help seeking OR calling for attention 5. Other non-specific changes (e.g. general malaise, 'not themselves') 6. Does the patient have nocturnal worsening of symptoms? **B. Affect / emotional changes.** In the last 24 hours, have you noticed any changes in the patient's mood? 1. Tearfulness / sadness 2. Irritable / grumpy 3. Fear 4. Excess anxiety or worry 5. Inappropriate elation or euphoria 6. Excess remorse or guilt **C. Demeanour or cognitive changes** In the last 24 hours, have you noticed any changes in the patient's ….. 1. Awareness of surroundings or situation? 2. Being apathetic or disinterested? 3. Being easily distractible or going 'off-track'? 4. Level of confusion or 'fogginess'? 5. Needing prompting / encouragement to do usual tasks?		In the last 24 hours, have you noticed any changes in the patient's sleep / activity? 1. Poor sleep pattern at night (max 2) 1-3 hours awake (1) >3 hours awake (2) Nightmares (1) Difficulty getting to sleep (>30 minutes) (1) Seems to be tired in the morning (1) 2. Drowsiness during the day some of the time (1) a lot of the time (2) 3. Being 'fidgety', restless or wandering 4. Being combative or resisting care 5. Being less active than usual / expected 6. Slower movements 7. Does the patient SHIFT suddenly from low to high activity or vice versa? Over minutes (2) Over hours (1) 8. Does the patient SHIFT suddenly from wakefulness to drowsiness or vice versa? Over minutes (2) Over hours (1) **E. Speech/ Talk disturbance** In the last 24 hours, have you noticed any changes in the patient's conversation? 1. Ability to find the right words or name things properly? 2. Understanding you 3. Holding a conversation 4. Saying odd things that don't make sense 5. Rambling off the point 6. Saying very little or nothing, lack of spontaneous speech	

INFORMANT QUESTIONNAIRE FOR COGNITIVE DECLINE IN THE ELDERLY – SHORT FORM (IQCODE-SF)

Source: http://www.alz.org/documents_custom/shortiqcode_english.pdf

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 19__. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

	1	2	3	4	5
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
6. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
7. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse

8. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
9. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
12. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Using his / her intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

DELIRIUM ETIOLOGY CHECKLIST

Trzepacz P, Meagher D. Neuropsychiatric aspects of delirium. In: Eds Yudofsky S, Hales R, editors. American Psychiatric Association Manual of Neuropsychiatry. 1st ed. Washington DC: American Psychiatric Publishing Press; 2012.

This checklist accounts for the multifactorial etiologies in causing delirium by allowing a weighted approach for documenting the range of potential inputs in any single case. Therefore, raters may indicate multiple categories as contributing toward reaching the threshold for delirium. The relative importance of history, examination, and tests in supporting the significance of any particular causative factor will vary among cases so that the certainty of causation will depend on the judgement of the clinician involved based on all available information. Specific disorders assigned to categories are noted on the reverse side of this page.

Please "X" a box for each row as appropriate.

	[1]Definite Cause	[2]Likely Cause	[3]Present and Possible Contributory	[4]Present but Apparently not Contributory	[5]Ruled Out/Not Present/Not Relevant
Drug Intoxication					
Drug Withdrawal					
Metabolic/Endocrine Disturbance					
Traumatic Brain Injury					
Seizures					
Infection (intracranial)					
Infection (systemic)					
Neoplasm (intracranial)					
Neoplasm (systemic)					
Cerebrovascular					
Organ Insufficiency					
Other CNS					
Other					

See other side for a more detailed list of conditions grouped under each of the above categories and please check each one you considered as a contributory (definite, likely, or possible) factor.

Drug Intoxication

1θ Alcohol
2θ Sedative - hypnotic
3θ Opiate
4θ Psychostimulant
5θ Hallucinogenic
6θ Prescribed drug _____
7θ Other _____
8θ OTC _____

Drug Withdrawal

1θ Alcohol
2θ Sedative-hypnotic
3θ Prescribed drug _____
4θ Other drug _____

Metabolic/Endocrine Disturbance

1θ Volume depletion
2θ Volume overload
3θ Acidosis
4θ Alkalosis
5θ Hypoxia
6θ Uremia
7θ Anemia
8θ Avitaminosis _____
9θ Hypervitaminosis _____
10θ Hypoglycemia
11θ Hyperglycemia
12θ Hypoalbuminemia
13θ Hyperalbuminemia
14θ Bilirubinemia
15θ Hypocalcemia
16θ Hypercalcemia
17θ Hypokalemia
18θ Hyperkalemia
19θ Hyponatremia
20θ Hypernatremia
21θ Hypomagnesiemia
22θ Hypermagnesiemia
23θ Hypophosphatemia
24θ Hypothyroidism
25θ Hyperthyroidism
26θ Hypoparathyroidism
27θ Hyperparathyroidism
28θ Cushing's Syndrome
29θ Addison's Disease
30θ Other _____

θ **Traumatic Brain Injury**

θ **Seizures**

Intracranial Infection

1θ Meningitis
2θ Encephalitis
3θ Abscess
4θ Neurosyphilis
5θ HIV
6θ Other _____

Systemic Infection

1θ Bacteremia
2θ Sepsis
3θ Fungal
4θ Protozoal
5θ Viral
6θ Respiratory
7θ Urinary
8θ Other _____

Intracranial Neoplasm

1θ Primary
Histology _____
2θ Metastasis
Site _____
3θ Meningeal Carcinomatosis

Extracranial Neoplasm

Site of primary lesion _____
θ Paraneoplastic Syndrome

Cerebrovascular Disorder

1θ Transient Ischemic Attack
2θ Subarachnoid Hemorrhage
3θ Stroke
4θ Subdural Hemorrhage
5θ Cerebral Edema
5θ Intraparenchymal hemorrhage
6θ Cerebral Vasculitis
7θ Other _____

Organ Insufficiency

1θ Cardiac
2θ Pulmonary
3θ Hepatic
4θ Renal
5θ Pancreatic
6θ Other _____

Other CNS

1θ Parkinson's Disease
2θ Huntington's Disease
3θ Multiple Sclerosis
4θ Wilson's Disease
5θ Hydrocephalus
6θ Other _____

Other Systemic

1θ Heat stroke
2θ Hypothermia
3θ Radiation
4θ Post-operative state
5θ Immunosuppressed
6θ Other _____
7θ Fractures

EXCERPT FROM NICE GUIDELINES: CG103

Delirium: Diagnosis, prevention and management. London: National Institute for Health and Clinical Excellence, 2010 CG103 Contract No.: CG103.

Risk factor assessment [Recommendation 1.1.1.]

When people first present to hospital or long-term care, assess them for the following risk factors. If any of these risk factors is present, the person is at risk of delirium.

- Age 65 years or older.
- Cognitive impairment (past or present) and/or dementia. If cognitive impairment is suspected, confirm it using a standardised and validated cognitive impairment measure.
- Current hip fracture.
- Severe illness (a clinical condition that is deteriorating or is at risk of deterioration).

Indicators of delirium: at presentation [Recommendation 1.2.1]

At presentation, assess people at risk for recent (within hours or days) changes or fluctuations in behaviour. These may be reported by the person at risk, or a carer or relative. Be particularly vigilant for behavior indicating hypoactive delirium (marked*). These behavior changes may affect:

- Cognitive function: for example, worsened concentration*, slow responses*, confusion.
- Perception: for example, visual or auditory hallucinations.
- Physical function: for example, reduced mobility*, reduced movement*, restlessness, agitation, changes in appetite*, sleep disturbance.
- Social behaviour: for example, lack of cooperation with reasonable requests, withdrawal*, or alterations in communication, mood and/or attitude.

If any of these behavior changes are present, a healthcare professional who is trained and competent in diagnosing delirium should carry out a clinical assessment to confirm the diagnosis

Indicators of delirium: daily observations

Observe at least daily, all people in hospital or long-term care for recent (within hours or days) changes or fluctuations in usual behaviour (see recommendation 1.2.1). These may be reported by the person at risk, or a carer or relative. If any of these behaviour changes is present, a healthcare professional who is trained and competent in the diagnosis of delirium should carry out a clinical assessment to confirm the diagnosis. **[1.4.1]**

NICE-BASED QUESTIONNAIRE

NICE: Questions to nursing staff ***Study number_____***

First use open questions and document response. Then ask more specific questions.

1. Has there been a recent change or any fluctuations in the patient's cognition?

Describe_____

a.	Has the patient been more confused than usual in the last 24 hours?	Y / N
b.	Does it seem harder for them to focus on what you're saying or on a task?	Y / N
c.	Are their responses to you slower than before?	Y / N

2. Has the patient had any perceptual disturbances?

Describe_____

a.	Have they complained of any hallucinations?	Y / N
b.	Does it seem that they are responding to things that are not there?	Y / N

3. Has there any changes in the patient's physical function?

Describe_____

a.	Have they become less active or have they slowed down in general?	Y / N
b.	Have they been restless or agitated at all?	Y / N
c.	Has there been any change in their sleep pattern?	Y / N
d.	Have they lost their appetite?	Y / N

4. Has there been any changes in their social behaviour?

Describe _____

a.	Have they become withdrawn or disinterested?	Y / N
b.	Have they become less cooperative / need more prompting than usual?	Y / N
c.	Have there been any changes in their mood / attitude towards you?	Y / N
d.	Has there been any changes in their level of communication with you?	Y / N

B. Details on How Delirium Instruments were Scored in this Study

- CAM Scoring
- DRS-R98 Scoring

CAM SCORING

To score the attention component of the CAM, I used only the 'Months of the Year Backwards (MOTYB)' supplemented by observations of level attentiveness / distractability during the assessment. MOTYB was considered incorrect if the patient failed to get back as far as July without error or major hesitation. Questions requiring abstract answers based largely on the CAM-ICU (The Confusion Assessment Method for the ICU) training manual[1] were used to discern if there was disorganised thinking present. This item was scored positively if any of these questions were answered incorrectly or if there was clear evidence of disorganised thought processes during the assessment. Level of alertness was considered abnormal if there was either evidence of drowsiness or hyperalertness or if collateral history suggested evidence of this over the previous 24-hour period. Patients were not considered drowsy if they had one nap after a meal and were easily roused during this nap. Acuity of onset and fluctuating course were assessed using collateral history from the caregiver and nursing staff.

[1]Ely EW. Confusion Assessment Method for the ICU (CAM-ICU). The Complete Training Manual. 2001 [updated October 2010; cited 2011 30th July]; Available from: http://www.icudelirium.org/docs/CAM_ICU_training.pdf.

DRS-R98 SCORING

In this study, in keeping with guidelines for its use, each DRS-R98 item was scored according to the training manual[1]. Items 1 (sleep-wake cycle disturbance); 2 (perceptual disturbances and hallucinations); 3 (delusions); 4 (lability of affect); 7 (motor agitation); 8 (motor retardation); 14 (temporal onset of symptoms); 15 (severity of fluctuations); and 16 (physical disorder) were scored using the anchored descriptions and suggested questions in the manual. Other items are scored using formal testing coupled with observations made during the interview: items 5 (language); 6 (thought process abnormalities); and the cognitive items (9 to 13). The following is a description of how each of these latter items were scored.

Item 5 (Language)

The patient was asked to firstly name two items shown to them (e.g. pen; watch; glass; jug; or other items found at the bedside) and secondly to follow a three-stage command (e.g. 'Close your eyes, stick out your tongue and raise your right hand in the air'; or 'Take this piece of paper, fold it in half and leave it on the bed'). Correct responses to these assessments were scored 0. Mild impairments were scored 1, e.g. mild word finding difficulty or hesitancy in following the command. A score of 2 was given if both items were named incorrectly or the three-stage command was incorrectly followed. A score of three was rarely given and was reserved for those with severe dysphasia (in which case they were generally excluded from the longitudinal study).

Item 6 (Thought Process Abnormalities)

Item 6 was scored by asking the patient to interpret a proverb or saying and to answer two questions requiring an abstract answer. Examples of the proverbs or sayings used included 'Every cloud has a silver lining'; 'Don't judge a book by its cover'; 'A stitch in time saves nine';

'Actions speak louder than words'; 'Blood is thicker than water'; 'The grass is always greener on the other side'. Some of the questions I used were based on the CAM-ICU training manual[2] and included 'Would a stone float on water?'; 'Would two pounds of flour weigh more than one pound?'; 'Can you use a hammer to pound a nail?'; 'Would you find fish in the sea?'. Other questions I used included 'Would a good pair of wellies (wellington boots) let water in?' and 'Is a cat bigger than a rat?'; 'Would you use a spoon to eat soup?'; 'Would you use a fork to eat soup?'; and 'Would you find sand on a beach?'. A score of 0 was given when thought process was normal, the proverb was interpreted correctly and the two questions answered correctly. A score of 1 was given if the patient was either circumstantial or tangential in their output or if they didn't entirely interpret the proverb correctly but got both abstract questions correct. A score of two was given if they got one or both of the abstract questions incorrect and / or the proverb was completely incorrect and / or there was demonstrable thought disorder (e.g. loosening of associations) at times during the conversation. Patients were rarely scored 3 and only if they had severe thought disorder such that full formal delirium assessment was challenging.

Item 9 (Orientation)

Scoring item 9 (orientation), was based on questions relating to the day, month, year and place as per the scoring manual. A patient scored 0 if he / she was fully orientated to time, place and person. A score of 1 was given if he / she was disoriented to time (e.g. by more than 2 days or wrong month or wrong year) or to place (e.g. name of building, city, county), but not both, whereas a score of 2 was given if the patient was disoriented to both time and place. A score of 3 was reserved only for those who could not identify who they themselves were (which was very rare).

Item 10 (Attention)

In this study, I incorporated multiple tests of attention (see later), however to score attention on the DRS-R98 I used only the 'days of the weeks backwards (DOTWB)' (in which a patient is asked to recite the days of the week in reverse order starting with Sunday); and '20 to 1' (in which a patient is requested to count backwards from 20 down to one), as well as a clinical assessment of their attention / distractability during the interview. Patients scored 0 if they were able to perform both tests without any error or hesitation and there was no evidence of distractability during the interview. A score of 1 was given if they made one error on one or both of the tests and / or there was mild distractability during the assessment. A score of 2 was given if the patient managed to finish the tests with more than one error, with or without prompting or if there was evidence of distractability requiring refocusing, during the interview. A score of three was given to those who were unable to finish the tests even with prompting or those who were so distractable that they were unable to engage with the tests.

Item 11 (short-term memory)

Item 11 was scored using the patient's ability to remember a five-point address (from the 6-CIT). If the five points were recalled correctly, the patient scored 0. If three or four items were recalled, a score of 1 was given, whereas a score of 2 was given to those who recalled only one to two items from the address. A score of 3 was given to those who could not remember any of the address.

Item 12 (long-term memory)

Item 12 was scored by asking the patient three questions pertaining to long-term memory, including 'What date is St. Patrick's Day?'; 'What year was the Easter Rising?'; 'What's the name of the Taoiseach / President?'. Sometimes these were substituted with questions

pertaining to the patient's personal history (e.g. 'What are the names of your children?'; 'What year did you return to live in Ireland from London?'; 'What year did you get married?'; 'What operations have you had in the past?'), if the patient indicated that they didn't want to answer questions about history or politics, but for the most part the first three questions were asked. A score of 0 was achieved if all three questions were answered correctly. If two questions were answered correctly, a score of 1 was given; if one question was answered correctly a score of 2 was given and if all questions were answered incorrectly a score of 3 was given.

Item 13 (Visuospatial Ability)

Item 13 was scored by considering the patients performance on each of 3 tests, the Clock-Drawing Test (CDT); the overlapping pentagons test (OPT) and a set of questions designed to verbally assess visuospatial function. An overall impression of the severity of impairment was decided upon and a score given accordingly.

[1]Trzepacz PT MJ, Kean J, Abell M, Meagher DJ. . The Delirium Rating Scale- Revised- 98 (DRS-R98) Administration Manual. A guide to increase understanding of how to solicit delirium symptoms to administer the DRS-R98. Indianapolis, IN, USA: Paula Trzepacz ®; 2009.

[2]Ely EW. Confusion Assessment Method for the ICU (CAM-ICU). The Complete Training Manual. 2001 [updated October 2010; cited 2011 30th July]; Available from: http://www.icudelirium.org/docs/CAM_ICU_training.pdf.

C. DATA RECORDING FILES

All data collection forms are included in the following pages:

- Baseline data collection form
- Longitudinal assessment forms
- Screening assessment forms
- Daily assessment forms
- Weekly assessment forms

BASELINE DATA COLLECTION FORM

"A Prospective Study of the Incidence, Prodrome, Characterisation, Risk Factors and Outcomes of Delirium in Older People in an Acute Hospital Setting"

A two-centre, prospective cohort study of delirium in acute hospitals in Cork City.

Hospital:

Initials :

Study ID:

Consent Form ○

Note for chart ○

Patient Info leaflet ○

Study number _____

Baseline

- ○ Nursing notes
- ○ Social/ educational hx
- ○ Medical History
- ○ M-CIRS
- ○ DEC
- ○ MNA
- ○ weight & demispan /calf
- ○ Waterlow / Braden
- ○ Frailty
- ○ Dynamometer
- ○ Standing
- ○ Depression
- ○ sMMSE
- ○ QOL

Collateral

- ○ Delirium
- ○ IQCODE-SF
- ○ Barthel / iADL
- ○ Dysf. Behaviour
- ○ Burden
- ○ MNA
- ○ Prodrome
- ○ *Other info patient unable to supply*

Weekly

Assessment	**Date →**							
ABDS (Depression)								
Possible interval delirium								
Barthel Score **(**discharge)								

Study number _____

Overall Clinician assessment...

The patient:

☐**1. Never develops delirium**

☐**2. Develops Subsyndromal Delirium**

☐**3. Develops Full-blown delirium**

If the patient develops full-blown or subsyndromal delirium:

1. **Fill the Delirium Etiology Checklist (full-blown mainly)**
2. **What day / date does he / she become delirious?_____**
3. **Which day of assessments is that? _____**
4. **What is the duration (3 consecutive days with DRS-R98 total score <12 being resolution)?**

   _____

Prodromal Features:

_____
_____
_____
_____

Comments:

_____
_____
_____
_____

"Gut Feeling"

_____
_____
_____
_____

Study number _____

C.2 Barthel Index (Baseline is day of admission)

		Date	Date	Date	Date	Date	Date	Date
Bowels	0= incontinent, 1= occasional accident (1 per week), 2= continent							
Bladder	0= incontinent or catheterized & unable to manage, 1= occasional accident (max 1 per 24 hours), 2= continent for over 7 days							
Grooming	0= needs help, 1= independent (face, hair, teeth, shaving)							
Toilet use	0= dependent, 1= needs some help but can do something, 2= independent (on & off, dressing, wiping)							
Feeding	0= unable, 1= needs help cutting, spreading butter, etc, 2= independent							
Transfer	0= unable, 1= major help (1-2 people, physical), 2= minor help (verbal or physical), 3= independent							
Mobility	0= immobile, 1= wheelchair independent including corners etc, 2= walks with help of 1 person (verbal/ physical), 3= independent (but may use aid, e.g. stick)							
Dressing	0= dependent, 1= needs help but can do half unaided, 2= independent							
Stairs	0= unable, 1= needs help (verbal, physical, carrying aid), 2= independent up & down							
Bathing	0= dependent, 1= independent							
	Score (__/20)							

Study number _____

1.0 Baseline Assessment

A. Demographics/ Medical History

a) **Gender:** Male ❑ Female ❑ b) married / widowed / single

c) **Age** :_____ years DOB (dd/mm/yy): ____/_____/____

d) **Date of Admission** ___/___/ ___

e) Arrived to A/E _____ Arrived to ward _____

LOS in A&E _____ hrs

f) **Reason for Admission** _____

_____

g) **Working Diagnosis**_____

_____

h) **Medical diagnoses**

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Study number _____

m) Modified Cumulative Illness Rating Scale

(include presenting complaints and past medical history). If not sure how to score, write in details.

Body system	Score				
1. Cardiac (heart only)	0	1	2	3	4
2. Hypertension (rating is based on severity; organ damage is rated separately)	0	1	2	3	4
3. Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics)	0	1	2	3	4
4. Respiratory (lungs, bronchi, trachea below the larynx)	0	1	2	3	4
5. EENT (eye, ear, nose, throat, larynx)	0	1	2	3	4
6. Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes)	0	1	2	3	4
7. Lower GI (intestines, hernias)	0	1	2	3	4
8. Hepatic (liver and biliary tree)	0	1	2	3	4
9. Renal (kidneys only)	0	1	2	3	4
10. Other GU (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11. Muscolo-skeletal-integumentary (muscle, bone, skin)	0	1	2	3	4
12. Neurological (brain, spinal cord, nerves, do not include dementia)	0	1	2	3	4
13. Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
14. Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

Score

_____

Study number _____

i) **Medications**

On admission:

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Changes since admission (Before recruitment):

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Study number _____

j) **Place of residence**

home alone	☐	home with _____	☐
sheltered accommodation	☐	nursing home	☐

k) **Social supports (if known)**

None	☐	PHN	☐	how often	_____
Home help	☐	amount	_____		
MOW	☐	Private carer	☐		
Family support	☐				

Details _____

l) **Education level**

Age left school _____

Primary school	☐	Inter Cert	☐
Leaving Cert	☐	3rd level	☐

m) **Smoking history**

Current	☐	how many /day _____how many years_____
Ex	☐	When started?_____When stopped?_____ How many? _____
Never	☐	

n) **Alcohol History**

Teetotaller ☐ Currently drinks ☐ (amount)_____

History of alcohol excess ☐

Study number _____

B) Baseline Patient Assessment

B.1 Sensory screening

1. Hearing

Can you understand me/ Can you hear me? ☐

No hearing impairment ☐

Known hearing impairment ☐

Wears 1 / 2 hearing aids ☐

2. Vision

No visual impairment ☐

Known visual impairment ☐

Blind or near-blind ☐

Wears glasses ☐

Can you see these objects?

Pen ☐

Watch ☐

Can you read this? ☐

(patient should use reading glasses if they usually wear them)

The quick brown fox jumps over the lazy dog

Study number _____

B.5. AB Clinician Depression Screen (ABCDS)

1. Do you often feel downhearted and blue?

No ☐ **➔Depression ruled out with 95% certainty**

Yes ☐ ➔ Ask the following questions:

2.	Do you often feel helpless?	Yes	☐	No	☐
3.	Do you feel that your life is empty?	Yes	☐	No	☐
4.	Do you feel happy most of the time?	Yes	☐	No	☐
5.	Are you basically satisfied with your life?	Yes	☐	No	☐

Score 1 or 2 / total of 5 questions: Not depressed

Score 4 or 5 / total of 5 questions: Depressed.

Score of **3/5**: proceed to **Geriatric Depression Scale**

Date _____ **Result** _____

Date _____ **Result** _____

Date _____ **Result** _____

Study number _____

B.2 Nutrition: Mini- Nutrional Assessment- Short form

A. Have you been eating less than normal over the past 3 months?
Is it much less or only a little less?

Severe decrease	0
Moderate decrease	1
No decrease	2

B. Have you lost weight recently without trying? How much?
Was that in the last few months or over the last year?

Weight loss >3kg	0
Does not know	1
Weight loss 1 to 3kg	2
No weight loss	3

C. Mobility

Bed / chair bound	0
Able to get up but not out	1
Goes out	2

D. Psychological stress/ acute disease (e.g. bereavement / moved house / recent illness)

Yes	0
No	1

E. Neuropsychological problems (medical notes / collateral history)

Severe dementia / depression	0
Mild dementia	1
Nil	2

F1. Body Mass Index _____ **OR** **F2.** Calf Circumference (cm)

Weight (kg)	_____		_____
Height (m)	_____		
Demispan (cm)	_____		
BMI <19	0	<31 cm	0
BMI 19-21	1		
BMI 21-23	2		
BMI ≥23	3	≥31 cm	3

➔ **MNA-SF SCORE** _____

B.5 Standardised Mini-Mental State Examination (SMMSE)

Study number _____ DATE_____

Time allowed for each question is given in brackets

Section 1- Orientation (10 seconds allowed for each question)

1.a. What year is this?	☐/1	2.a. What country are we in?	☐/1
b. Which season is this?	☐/1	b. What county are we in?	☐/1
c. What month is this?	☐/1	c. What city / town are we in?	☐/1
d. What is today's date?	☐/1	d. What is the name of this place?	☐/1
e. What day of the week is this?	☐/1	e. What floor are we on?	☐/1

Section 2- Cognition

3. SAY: "I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes." Say the following words slowly at 1 second intervals: ball / car / man. (20 seconds)

Word 1 _____ ☐/1

Word 2 _____ ☐/1

Word 3 _____ ☐/1

4. Spell the word 'WORLD'. Now spell it backwards. (30 seconds)

DLROW _____☐/5

5. Now what were the three objects I asked you to remember? (10 seconds)

Word 1 _____ ☐/1

Word 2 _____ ☐/1

Word 3 _____ ☐/1

6. SHOW wristwatch. Now ASK: "What is this called?" (10 seconds) ☐/1

7. SHOW pencil. Now ASK: "What is this called?" (10 seconds) ☐/1

8. SAY “I would like you to repeat this phrase after me:
No ifs, ands, or buts” (10 seconds) ☐/1

9. SAY “Read the words on the page and then do what it says.” Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads but does not close their eyes, repeat up to three times. Score only if subject closes eyes. (10 seconds)

Subject closes eyes ☐/1

10. HAND the person a pencil and paper. SAY: “Write any complete sentence on that piece of paper.” Note: the sentence must make sense. Ignore spelling errors. (30 seconds)

Sentence ☐/1

11. Place design, eraser and pencil in front of the person. SAY: “Copy this design please.” Allow multiple tries. Wait until the person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between 2 5-sided figures.
(1 minute)

Copies design ☐/1

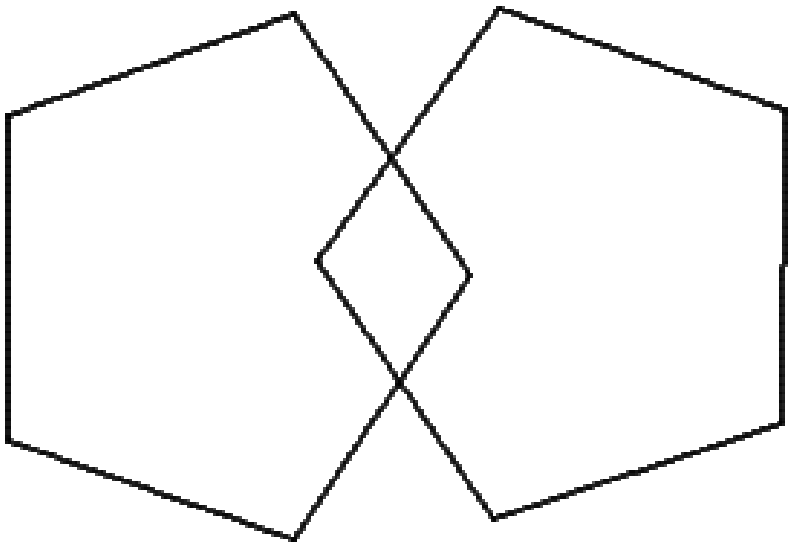
12. ASK the person if he / she is right or left-handed. Take a piece of paper and hold it up in front of the person. SAY: “Take this paper in your right / left hand (whichever is non-dominant), fold the paper in half once with both hands and put the paper down on the floor.” Score 1 point for each instruction executed correctly. (30 seconds)

Takes in correct hand ☐/1 Folds paper in half ☐/1 Puts paper on floor ☐/1

CLOSE YOUR EYES

Write a sentence

Copy this diagram



Study number _____

C) Baseline- collateral history

IQCODE-SF

Score = _____ **Mean score = _____**	Much Improved	A bit improved	Not much change	A bit worse	Much worse
	1	2	3	4	5
Remembering things about family					
Remembering recent events					
Recalling conversations a few days later					
Remembering own address/ phone number					
Knowing day/ month					
Remembering where things are usually kept					
Remembering where to find things that are in a different place than usual					
Knowing how to work familiar machines around the house					
Learning how to use a new gadget around the house					
Learning new things in general					
Following a story in a book or on TV					
Making decisions on everyday matters					
Handling money for shopping					
Handling financial matters, eg: pension					
Handling other everyday arithmetic					
Using intelligence to understand/ reason					

LONGITUDINAL ASSESSMENTS

	Study number _____ DATE / DAY→ **Sample questions**							
Sleep	Did you sleep well? Were you awake during the night? Did you feel well-rested this morning? Do you have trouble staying awake during the day?							
Del/ Hall	Do you feel alright in yourself? Has anything strange happened that you think might not be real? Any nightmares / vivid dreams? Do you feel safe here? Have you been treated well here?							
Mood	Has anything upset you? Are you annoyed about anything? Do you feel in control of your emotions?							
MA	Have you felt agitated / restless / fidgety? Do you feel the need to keep moving?							
MR	Have you slowed down? Are you moving around less than usual?							
Speech	Has your speech changed in anyway?							
Thought	Have you noticed any changes in your ability to think clearly?							

	Study number _____ DATE /DAY→							
Observation	Bed location (1= window, 2= middle, 3= door, 4= 2-bedded, 5= single room)							
	Bed move							
	Clock / watch (1= yes, 0= no)							
	IV line (number, 4= central)							
	Restraint: 0 =none; 1=tray; 2=bedrail; 3=both; 4=other							
	Feeding: 0=oral; 1= fast; 2=NGT; 3=PEG; 4=TPN; 5= unable to eat (e.g. nausea)							
	Catheter (0= none; 1 = urethral; 2 = s-pub)							
	O2 (0= none; 1=continuous; 2 = intermittent)							
6-item CIT Orientation	Year							
	Month							
	Place							
6-item CIT Registration	Address (or 3 items)							
6-item CIT Attention	20-1							
	Months Backwards							
6-item CIT Orientation	Time of day							
6-item CIT Recall	Address							

Nurse	Study number _____ DATE /DAY→							
CAM1	Any changes in last 24 hours- confusion, drowsiness, behaviour?							
	Any fluctuations / waxing & waning?							
Sleep	Sleeping well? Any confusion during the night? Any drowsiness or hyperalertness during the day?							
Del/ Hall	Any hallucinations or delusions? Do they seem preoccupied with / upset about anything?							
Mood	Any tearfulness / inappropriate emotions?							
Language	Any difficulty in conversing?							
MA	Any agitation / restlessness? Are they constantly trying / asking to get out of the chair / bed?							
MR	Initiate any activity (scratching / eye contact / personal needs)? Does poor spontaneous movement interfere with care?							
Attention	Is the patient easily distracted by things going on in the room?							

Prodromal Checklist

(0 = not present; 1 = possibly or somewhat present; 2 = definitely present)

A. General Complaints	Date → Baseline							
1. Appetite								
2. Pain / discomfort Describe								
3. Frequency of requests for analgesia How often?								
4. Frequency of help seeking How often?								
5. Other changes Describe								
6. Nocturnal worsening of symptoms								
B. Affect / emotions								
1. Sadness / tearfulness								
2. Irritability / grumpiness								
3. Fear								
4. Excess anxiety / worry								
5. Inappropriate elation / euphoria								
6. Excess remorse or guilt								
C. Demeanour / Cognition								
1. Awareness of surroundings, etc								
2. Apathy / disinterest								
3. Distractability / going 'off-track'								
4. Confusion / 'fogginess'								
5. Needing prompting / encouragement								

D. Sleep / activity	Date → Baseline							
1. Poor sleep pattern (1= 1-3 hours awake, 2= >3 hours awake, nightmare-1, difficulty falling asleep [>30 mins]-1, seems tired in the morning) [Any 2 of the above =2]								
2. Drowsy during the day (1= some of the time, 2= a lot of the time)								
3. Fidgety or restless or wandering								
4. Combative / resisting care								
5. Less active than usual / expected								
6. Slower movements								
7. Shifts in wakefulness / drowsiness (1= over hours, 2= over minutes)								
8. Low activity / high activity (1= over hours, 2= over minutes)								
F. Speech / talk								
1. Finding the right word / naming								
2. Understanding you								
3. Holding a conversation								
4. Saying odd things that don't make sense								
5. Rambling off the point								
6. Saying less than usual, lack of spontaneous speech								

STUDY NUMBER _____ DMSS-4 Date										
Day										
Hypoactive										
Decreased speed of actions Moving around slowly, as if in slow motion A simple task takes a long time to do due to slow body movements										
Decreased amount of speech Speaks less than before Lacks spontaneous speech Speaks only when spoken to, doesn't initiate a chat Speaks only in monosyllables or short sentences (not due to aphasia)										
Hyperactive										
Increased activity levels More active than before Seems overactive Moves around a lot Seems to be "on the go" a lot of the time										
Loss of control of activity Movements are unproductive / lacking in purpose Impulsive body movements (perhaps in an unsafe manner) Seems to have lost control over his / her own body movements										

SCREENING ASSESSMENT

Date _____

Collateral from family member

Acute changes?

Increased confusion (forgetfulness / disorientation / recognise)?

Fluctuations?

Hallucinations/ delusions?

Change in activity levels (high / low)?

Changes in speech?

Change in sleep pattern?

Drowsiness during the day?

Easily distracted?

Emotional changes?

Getting lost?

Nurses

Plans for discharge?

Patient

Sleeping ok? Drowsy during the day?

Upset / emotions? Del / Hall?

Any confusion / difficulty thinking clearly?

Naming 1. _____ Thinking: Proverb _____

2. _____ 1. _____

Command _____ 2. _____

STM 1. _____ 2. _____ 3. _____

LTM 1. _____ 2. _____ 3. _____

Day Month Year Place

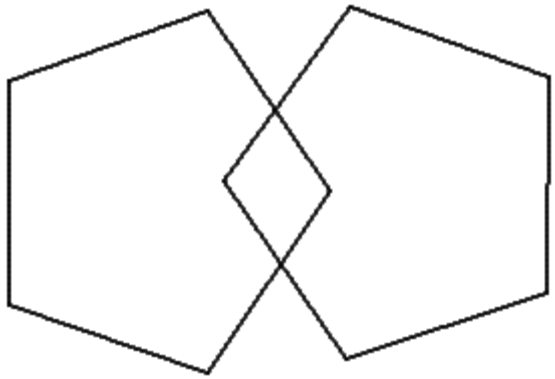
Days backwards

Months backwards

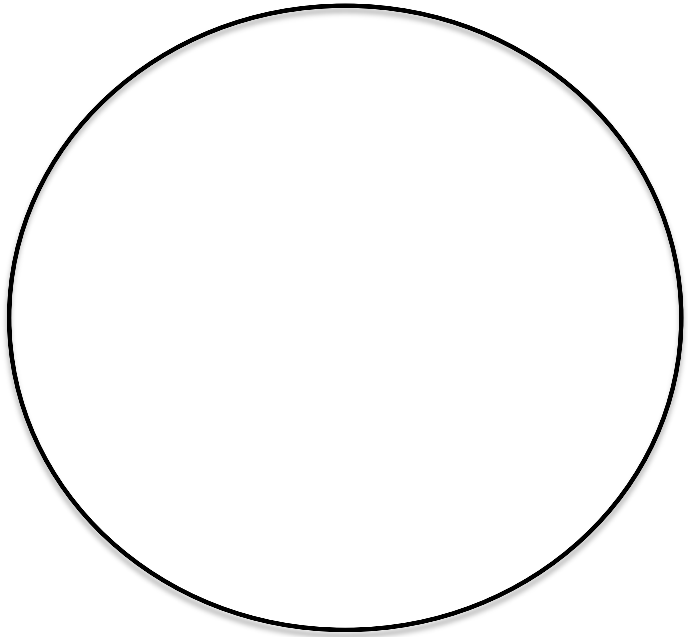
Way out? Bigger? Closer?

SSF Score _____ Attempt _____

Please copy this diagram



Please put numbers in the circle so it looks like the face of a clock



Study number _____ Date _____ Assessment Day _____

Study number _____ Date _____ Day of assessment _____

DAILY ASSESSMENT

CAM Scoring sheet

Positive ☐ **Negative** ☐

(1a OR 1b) AND 2 AND (3 OR 4) [CAM sensitive]

Item 1

(c) **Acute onset** Y O N O [acute on chronic O] _____

(d) **Fluctuation** Y O N O

Item 2

Inattention Y O N O _____

Months Forwards

J F MH A MY JE JY A S O N D

_____

Months Backwards

D N O S A JY JE MY A MH F J

_____

Item 3

Disorganised Thinking Y O N O _____

Proverb (cloud / meat / stitch / blood / vessels / actions / book / chickens / leopard / cat)

Questions (stone / leaf / wellingtons / elephants / hammer / fish / flour / bird / bigger / fork)

Details:

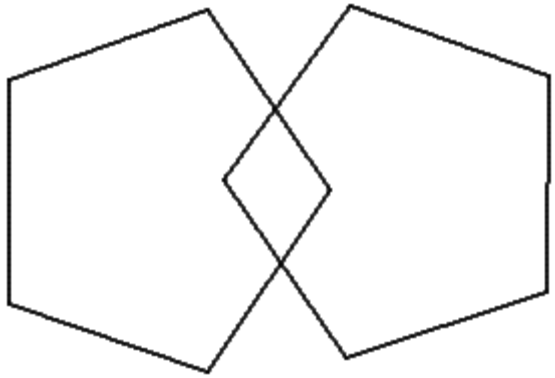
_____

Item 4

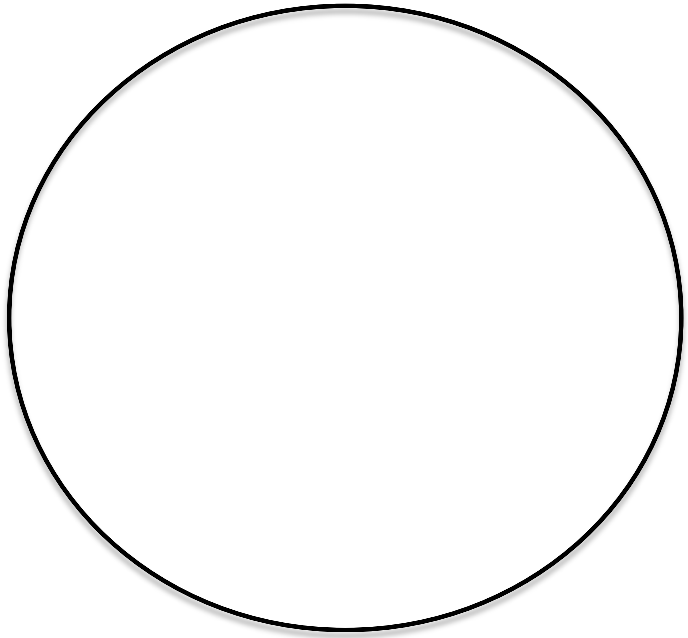
Consciousness **Alert** Y O N O Other _____

(hyperalert or vigilant/ lethargic but readily rousable/ stuporose or comatose)

Please copy this diagram



Please put numbers in the circle so it looks like the face of a clock



Study number _____ Date _____ Assessment Day _____

WEEKLY ASSESSMENT

Date _____

Nurses

Acute changes?

Increased confusion (forgetfulness / disorientation / recognise)?

Fluctuations?

Hallucinations/ delusions?

Change in activity levels (high / low)?

Changes in speech?

Change in sleep pattern?

Drowsiness during the day?

Easily distracted?

Emotional changes?

Getting lost?

Plans for discharge?

Barthel Index □ **Burden** □ **Behaviour** □

Patient

Sleeping ok? Drowsy during the day?

Upset / emotions? Del / Hall?

Any confusion / difficulty thinking clearly?

Naming 1. _____ Thinking: Proverb _____

2. _____ 1. _____

Command _____ 2. _____

STM 1. _____ 2. _____ 3. _____

LTM 1. _____ 2. _____ 3. _____

Day Month Year Place

Days backwards

Months backwards

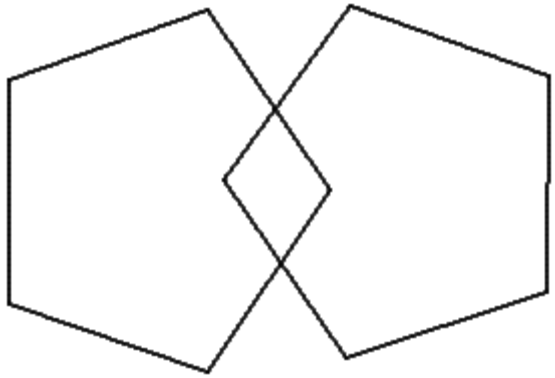
Way out? Bigger? Closer?

SSF Score _____ Attempt _____

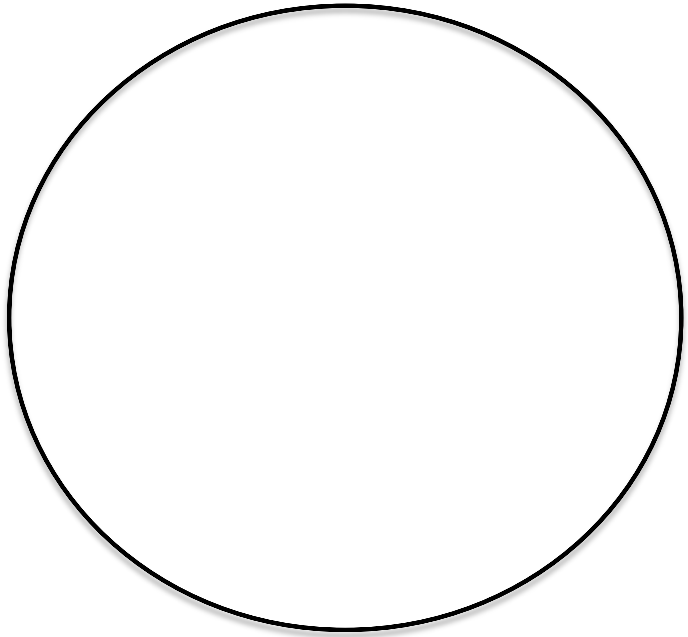
Depression □ **QOL** □

Study number _____ Date _____ Assessment Day _____

Please copy this diagram



Please put numbers in the circle so it looks like the face of a clock



Study number _____ Date _____ Assessment Day _____

D. ETHICAL CONSIDERATIONS

- Patient Information Leaflet
- Consent Form
- Note for Medical Chart
- Letter of Ethical Approval

PATIENT INFORMATION SHEET:

A Prospective Study of the Incidence, Prodrome, Characterisation, Risk Factors and Outcomes of Delirium in Older People in an Acute Hospital Setting

(Dr. Niamh O'Regan)

What is delirium?

Delirium is a sudden, temporary reduced memory and awareness of surroundings during an illness. There are many different symptoms such as confusion, agitation, hallucinations (seeing things that are not there) and poor sleeping and it can vary in severity from day to day. Common causes of delirium include infection, some medications and a change in a person's surroundings.

Why are we doing this study?

Delirium is common in hospital, particularly in older people, and can be very distressing for patients and families. It leads to higher risk of death, dementia and need for nursing home care which can be reduced by early diagnosis and treatment. However it is often difficult to diagnose correctly. Little research has been done in delirium in Ireland to date. In our study we hope to identify early signs of delirium, assess the impact of delirium on patients and carers, and examine ways to improve its detection. We hope that this will lead to better detection and treatment of delirium in Ireland.

Why am I being considered for this study?

Any patient of 70 years of age and older who is admitted to this ward is being asked to take part in the study. To fully understand delirium, we need to study a large number of patients, so every participant is very important to us.

What do I need to do if I'm interested?

Simply agree to take part in our study. This involves a series of interviews during your hospital stay. The first interview should be less than 30 minutes and the other interviews, sometimes daily, should last only 10 minutes. We may also need to interview your next-of-kin/ carer. After you are discharged, we will ask you to come to a special clinic to be reviewed twice (at 6 months and 1 year after discharge). We will arrange for the clinic to be as close as possible to where you live and transport will be arranged for you and a carer on each occasion.

Will all details be confidential?

Yes. The recorded interview details will not include your name or hospital number.

Is there any risk?

The study only involves being interviewed. There will be no procedure and no risk to you. We will stop the interview at any time if you wish to stop.

Thank you for reading this leaflet.

We deeply appreciate your interest and time.

Clinical Research Ethics Committee of The Cork Teaching Hospitals

---

This is a Consent Form

Participant's Name: ……

Study Title: A Prospective Study of the Incidence, Prodrome, Characterisation, Risk Factors and Outcomes of Delirium in Older People in an Acute Hospital Setting

Chief Investigators: Dr. Suzanne Timmons Tel No: 021 4205976

Dr. ……. has given me a full explanation of the nature, purpose and duration of this study. I have also received and read the patient information leaflet. I was able to ask him/ her questions regarding all aspects of the study.

I consent to the study investigators interviewing me on several occasions during my hospital stay, as well as discussing my case with the nursing staff caring for me. I also consent to the investigators speaking to my family about my health and functional abilities before I was admitted.

I accept that data recorded during this study may be processed on a computer by the investigators. My identity will never be disclosed and the data collected will remain confidential. I agree that I will not seek to restrict the use to which results of the study may be put.

After due consideration, I agree to participate in this study and co-operate with the testing required. I understand that at any time I may withdraw from this study without giving a reason.

_____

Signature of investigator **Date**

_____

Signature of participant **Date**

_____

Assent from next of kin **Date**

NOTE FOR MEDICAL CHART

"A Prospective Study of the Incidence, Prodrome, Characterisation, Risk Factors and Outcomes of Delirium in Older People in an Acute Hospital Setting"

Dear Doctor,

Your patient _____ has been included in the above study, with their consent / a relative's assent.

The aim of the study is to **identify incident delirium in hospital** and involves daily cognitive and delirium assessments of each recruited patient for at least the first week of their admission. Collateral history will also be sought from a close relative. This study has been approved by the Cork Research Ethics Committee and the EMB of the Mercy University Hospital.

Any **clinically pertinent results / scores from my assessments** will be entered on this page. Should you have any questions, **please don't hesitate to contact me at 087 9736620.**

Yours sincerely,

Dr. Niamh O'Regan (IMCN 189937), Geriatric Medicine Research Fellow, University College Cork

---

IQCODE-SF _____ (≥3.5 indicates pre-existing dementia) SMMSE _____

Depression screen positive **Yes / no**

Develops delirium **Yes / no** If yes: Date _____ Medical team contacted Yes / no

Date _____

LETTER OF ETHICAL APPROVAL

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Our ref: ECM 4 (uu) 01/02/11

Centre for Gerontology and Rehabilitation
20 JUL 2011
University College Cork

26th January 2011

Dr Suzanne Timmons
Senior Lecturer in Gerontology & Rehabilliation
School of Medicine
University College Cork
Brookfield Health Science Complex
College Road
Cork

Re: A prospective study of the incidence, detection, characteristation, risk factors and outcomes of delirium in older people in an acute hospital setting.

Dear Dr Timmons

Expedited approval is granted to carry out the above study in:

- Cork University Hospital
- Mercy University Hospital.

The following documents were approved:

- Application Form
- Study Protocol
- Timetable
- Data Collection Sheets
- Plan of Assessment
- Patient Information Sheet
- Consent Form.

The co-investigators involved in this study will be:

- Dr Niamh O'Regan, Professor David Meagher and Professor William Molloy.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

E. PUBLICATIONS

Early Detection of Delirium: Prodromal Features

Published In: Alonso R, editor. Delirium Diagnosis, Management and Prevention. New York: Nova Science Publishers, Inc.; 2014. p. 35-68.

Niamh A. O'Regan, Geriatric Medicine Research Fellow, Centre for Gerontology and Rehabilitation, School of Medicine, University College Cork, St. Finbarr's Hospital, Cork, Ireland

James Fitzgerald, Department of Medicine, University of Limerick, Limerick, Ireland

Prof. D.W. Molloy, Professor of Geriatric Medicine, Centre for Gerontology and Rehabilitation, School of Medicine, University College Cork, St. Finbarr's Hospital, Cork, Ireland

Prof. David Meagher, Professor of Psychiatry, University of Limerick, Limerick; Cognitive Disorders Research Group, Centre for Interventions in Infection, Inflammation & Immunity (4i), Graduate Entry Medical School, University of Limerick, Ireland

Dr. Suzanne Timmons, Senior Lecturer in Geriatric Medicine, Centre for Gerontology and Rehabilitation, School of Medicine, University College Cork, Cork, Ireland

ABSTRACT

Delirium is a serious neuropsychiatric condition, with a point prevalence of 20% in the general inpatient population, rising to almost 50% in older patients. It is independently associated with a range of adverse outcomes, including prolonged length of hospital stay, increased dependency and increased mortality. Despite its significance, delirium is often underrecognised in the hospital setting, with up to two thirds missed or misdiagnosed across treatment settings. This underdetection contributes significantly to poorer outcomes. Early identification and multifaceted intervention can reduce the degree and duration of delirium, but once a patient develops established delirium, even the best quality medical and nursing care can only modestly impact on long-term sequelae. Multicomponent systemised strategies to identify those at risk and minimise modifiable risk factors have been shown to halve delirium incidence, and hence improve outcomes. Hence, delirium prevention is key to attentuating its long-term impact.

One of the most typical features of delirium is its acute onset, however, there is growing evidence to suggest that delirium is preceded by a prodrome of varying duration. The proposed symptoms have differed from one report to the next, some being part of the delirium cluster, both cognitive and non-cognitive, and others more somatic in nature. Lipowski described a prodromal period characterised by poor concentration, restlessness, irritability, fatigue, malaise, hypersensitivity to stimuli, sleep-wake cycle abnormalities and perceptual phenomena and suggested that a longer prodrome heralded a delirium secondary to systemic illness or metabolic abnormalities, rather than that caused by more mechanical or surgical aetiology. Over the last thirty years or so, studies in differing patient populations, and designed for other purposes, have described a variety of other potential prodromal features including headaches and general uneasiness; inattention and other cognitive features; changes in activity levels; frequent calls for assistance; perceptual disturbances; mood changes; language and thought disorder and disruption in sleep-wake pattern. Additionally, recent prospective studies have shown that

patients who go on to develop delirium tend to have subsyndromal features in the days or weeks before full diagnostic criteria are met.

Greater recognition of the symptoms that characterise emerging delirium can facilitate proactive detection and prompt intervention; so that, in effect, we may be able to treat delirium pre-emptively. Further work is required to accurately define these early indicators and to ascertain whether intervening at this prodromal stage can lead to a meaningful improvement in outcomes.

INTRODUCTION

Delirium, a complex neuropsychiatric syndrome caused by acute illness or injury, is one of few conditions to permeate across all treatment settings, occurring in one-fifth of all hospital inpatients (1), in up to half of the hospitalised elderly (2) and at higher rates in the critically ill (3). It is independently associated with adverse sequelae including increased mortality, institutionalisation and cognitive decline (4). Despite this, case identification remains poor, with up to two-thirds being missed or misattributed to dementia, depression and other neuropsychiatric diagnoses (5).

One of the major barriers to delirium detection is that, to the untrained eye, it is difficult to recognise and can present in many guises. The more subtle hypoactive form, although most prevalent and most prognostically significant, is commonly mistaken for depression. Symptoms undulate in severity over the course of the day which can be deceptive to clinicians, as the delirium symptoms which so often present more floridly at night, can appear almost fully resolved during a morning ward round. Another obstacle to improved detection is that delirium in itself is not often acknowledged as causing serious healthcare, economic and personal burden. It is commonly seen purely as a manifestation of underlying illness, and not as a medical emergency in it own right. Unfortunately, confusion in ill older people can be viewed as the norm due to its high prevalence, and, hence, is often passively overlooked during medical review.

The under-detection of delirium is one of the major challenges facing delirium care today for several reasons. Firstly, non-detection is associated with particularly poor outcomes, including mortality (6). Secondly, it is well-recognised that delirium duration has a direct relationship with poor outcomes, such that the longer a patient goes undiagnosed, the higher their risk of adverse sequelae. This is most

starkly illustrated in a study by Gonzalez et al, which found that for each additional forty-eight hours of delirium, mortality was increased by 11% (7). Kiely et al found that patients with persistent delirium were almost three times more likely to die within one year than those whose delirium resolved early, independent of other confounders.(8)

Additionally, early and more optimal intervention in delirium has been shown to improve short-term outcomes, for example delirium duration and severity (9). However, in order to impact significantly on long-term outcomes, delirium prevention is the key, but for the most part this involves the implementation of systematic and widespread delirium prevention programmes(10), which in turn requires that delirium as a serious healthcare concern is recognised by clinical leaders and senior hospital management, as well as on the ground.

The development of strategies for prevention and early intervention of delirium has been informed by multiple studies of factors which increase delirium risk. Hence, strategies are targeted at patients and populations most predisposed to delirium development. Although a wide range of risk factors have been identified, differing slightly across treatment settings and patient groups, the most consistent independent predisposing factors for delirium development are advancing age and premorbid cognitive decline(11). Our ageing population means that the proportion of hospitalised patients over the age of seventy years is steadily rising, leading to higher proportions of at risk patients. Hence, efforts at delirium prevention are commonly spread thinly. Fine-tuning the ability to identify delirium-prone patients could facilitate a more streamlined and efficient approach towards delirium prevention and identification.

One of the most characteristic features of delirium is that its onset is typically acute, with symptoms occurring over hours to days and, indeed, this contextual feature is one of the core criteria for delirium diagnosis

using any of the available diagnostic systems. Somewhat converse to this construct is the concept of a delirium prodrome, where in some patients full-syndromal delirium is preceded by a range of cognitive and other varied symptoms. This concept has appeared in the literature for decades, however it has yet to be fully characterised. Improved understanding of the features, context and duration of this prodrome may lead to advances in strategies promoting the prevention and detection of delirium.

Subsyndromal delirium

Subsyndromal delirium (SSD) is described broadly as evidence of delirium features without full diagnostic criteria for delirium diagnosis. Accurate definition remains challenging as it is unclear as to the number, type and severity of symptoms required to warrant a label of SSD. Some features of delirium can occur in isolation, for instance in the setting of illness (e.g. drowsiness, hypoactivity) and other symptoms can occur either alone or in clusters as components of non-delirium diagnoses (e.g. hypomania, acute psychosis). Hence, in order to accurately identify SSD, we must be able to tease out what it is that distinguishes it from delirium and other diagnoses. Previous studies have used a variety of different approaches to define and measure SSD, including categorical and dimensional methods. Categorical methods are underpinned according to the presence of core or key diagnostic features (12-18) whereas dimensional approaches are based on symptom severity scores on a spectrum from absence of delirium to presence of the full-syndromal state (19-25). Studies have shown that SSD differs from full-blown delirium, and also from no delirium, in symptom profile and severity (26, 27). Although it remains unclear as to which mechanism for diagnosis is most appropriate, one study suggests that the features are relatively consistent regardless of the diagnostic system used (26).

The clinical relevance of SSD is illustrated in multiple studies outlining its prognostic significance, with SSD patients experiencing adverse outcomes intermediate between those with delirium and normal controls (14, 17, 21, 28, 29). The relationship of SSD to delirium is not yet fully understood as some patients with SSD symptoms resolve fully without progression to delirium, and others experience subsyndromal features in the prodromal and post-dromal (or recovery period)(19) phases of delirium. Recently, a randomised controlled trial of risperidone versus placebo in SSD post cardiac surgery showed significantly reduced transition to full delirium in the intervention group (25). This landmark study indicates that improving understanding and recognition of SSD may increase opportunities to prevent delirium and hence help to mitigate its accompanying cognitive, functional and social burden.

Current concepts in early diagnosis

Given its high prevalence and clinical significance, all at-risk patients should be routinely and frequently assessed for delirium. Unfortunately, definitive diagnosis is challenging due to its nuanced and commonly complex presentation. There are two standard diagnostic systems for the diagnosis of delirium, the Diagnostic and Statistical Manual of Mental Disorders criteria(30) and the International Classification of Diseases (ICD)-10(31), neither of which are easily applicable in day-to-day practice, and require specific training and experience in their use. In order to make delirium identification more feasible in a practical setting, a two-phase approach to detection is now recommended by experts. A preliminary step where all patients at high risk for delirium are screened for key features using a short easily applicable test, would then be succeeded by full formal assessment in those who screen positive. The recent NICE (National Institute for Clinical Excellence, UK)(32) guidelines advocate this approach, and although multiple screening tools for delirium

have been developed, consensus remains lacking as to which screening method should be used. These seminal guidelines proposed a screening approach based on daily observation of all at-risk patients for specific delirium indicators. Although the theory behind this approach, developed by a panel of experts, is rooted in common sense and highlights a number of important delirium features, it has yet to be validated and operationalized for practical use.

Whichever method is employed, a crucial property is high sensitivity in order to curtail the risk of missing cases, as with any screening process for a serious condition. There are multiple bedside screening tests for delirium, the most widely used screening test being the Confusion Assessment Method (CAM)(33, 34), which has been validated in several languages and a wide range of settings, for example, intensive care (35), emergency department(36, 37) and long-term care settings (14). Designed originally for diagnostic use, and based on DSM-IIIR (Diagnostic and Statistical Manual of Mental Disorders, third edition) criteria, its application requires semi-structured patient interview and accurate collateral history for accurate application. Hence, it lacks the brevity required for routine ward use. Importantly, its accuracy is also closely related to the training level of those using it, such that sensitivities drop to 50% in the minimally trained (38). Recently, a systematic review of its diagnostic accuracy reported a high specificity (99%, 95% CI 87-100%) and only moderate to high sensitivity (82%, 95% CI 69-91%), advising against reliance on the CAM in isolation and concluding that its use should not replace clinical judgement. The 'SQiD' or 'Single Question in Delirium' is a useful screening question for family members or carers. It is simple and does not require training, and although its diagnostic accuracy has only been reported in one study, sensitivity was as high as 80%(39). Some screening tools have been developed for use by nursing staff, which is intuitive given that nurses have most exposure to patients round the clock and have more opportunity to notice a significant change in behaviour or cognition than medical staff. The Nu-DESC (The Nursing Delirium Screening Scale) is an observational five-item scale which was

designed to be completed quickly by nursing staff(40). It measures symptoms of disorientation, inappropriate behaviour and communication, illusions / hallucinations and psychomotor retardation. A strength of this tool is its recognition of the significance of hypoactivity, which can be difficult to detect and linked to poorer outcomes (41). Additionally, its sensitivity of up to 96%, associated specificity of 79% and easy applicability makes it very practical for general use. The NEECHAM is another nursing based tool used mainly in post-operative patients(42). It incorporates the measurement of physiological markers of illness severity and hence can take longer to perform.

Recently attempts to simplify screening approaches in order to improve penetration across healthcare settings on the ground are showing promising results. Tests of attention are quick, easy to perform and require minimal training in their use and because inattention is a cardinal compulsory feature of delirium, these tests seem an obvious choice for investigation. Recent and on-going studies have been aimed at examining the predictive validity of simple attention tests in the diagnosis of delirium. One such study suggests that simply asking a patient to recite the months of the year in reverse order has a sensitivity of 83.3% and a specificity of 90.8% in detecting full syndromal delirium in general hospital patients (43). Examples of useful attention tests are shown in Table 1.

The Role of Biological Markers in Early Diagnosis of Delirium

Although there are many hypotheses as to the pathophysiology of delirium, the exact process has not yet been clearly defined. Theories include imbalances in the neurotransmitter system; altered brain responses to peripheral inflammatory processes; dysregulation of the hypothalamic pituitary adrenal axis; and direct cerebral insults such as hypoxia. It is likely that each of these theories contribute in varying

degrees to delirium development and that initial triggering mechanisms ultimately culminate in a final common pathway of neurotransmitter imbalance. Multiple studies of biomarkers and genetic polymorphisms have been conducted, indicating relationships with delirium incidence, course and severity (44, 45). Studies of peripheral inflammatory mediators have shown some promise in relation to heralding emerging delirium. Studies in hip fracture patients illustrated higher levels of IL-8 and cortisol in patients with delirium, with peak levels occurring prior to delirium onset (46, 47). A study in older medical patients found that elevated C-reactive protein (C-RP) independently predicted the onset of delirium, however numbers of incident cases were very small(48). More recently, Zhang et al found that changes in the C-RP of >8.1 in the first 24 hours of admission to intensive care were independently associated with an increased risk of developing delirium, however predictive ability of C-RP was poor (AUC 0.68) (49). Studies of the cytoprotectant peptide Insulin-like growth factor I (IGF-I) have shown that low baseline levels are associated with a greater delirium risk (50) and that patients with delirium have lower levels that controls (51), however a study in intensive care patients found that IGF-I levels were not predictive of delirium onset (52). It is clear that further studies are necessary to fully understand the neurobiological processes underpinning delirium and to examine the role of biological markers in delirium detection, before we can assess the utility of these markers in predicting delirium onset.

Concept of a prodromal state

As aforementioned, although coupling delirium screening with appropriate early intervention policies is important in reducing adverse outcomes, in order to truly harness the short- and long-term effects of delirium, prevention strategies are key. Identifying the features of the delirium prodrome may help to refine these preventative strategies to those most at risk, however as yet, these warning symptoms have not been fully characterised. Over the past few decades, the features of this

prodromal phase have been studied or referenced in only a small number of works. Most studies alluding to this prodrome were principally designed for other purposes and other works have given anecdotal descriptions based on clinical experience. Lipowski referred to a prodromal period characterised by difficulties with concentation, restlessness, irritability, fatigue and sleep-wake cycle disruption, perceptual abnormalities, malaise, and hypersensitivity to light and sound (53). Other authors have described a variety of other features. Broadly, the various proposed symptoms can be divided into four major domains: cognitive features, non-cognitive delirium features, somatic features and non-specific emotional features. Some features are recognised delirium symptoms, however when present during this prodromal phase, occur in the absence of full delirium diagnostic criteria. Depending on the type and severity of these features during the prodromal period, they may be considered part of a subsyndromal delirium presentation. Other prodromal features are less related to the delirium cluster and are more somatic or non-specific in nature. Hence, the prodrome is even more polymorphic than the delirium itself increasing the challenge of detection. Below, the various potential prodromal features, based on existing literature, are outlined and considered conceptually as components of four respective symptom domains: Cognitive; non-cognitive; somatic; and non-specific emotional changes.

Cognitive symptoms

Attentional deficit / clouding of consciousness

Considering the significance of impaired attention span in the diagnosis of delirium, it is unsurprising that it is also the most commonly referenced feature of the delirium prodrome, either distinctly, or as an element of the phenomenon known as 'clouding of consciousness'. In his 1990 textbook, Lipowski discusses the history of how delirium came to be viewed as a disorder of consciousness in the latter nineteenth century, and describes how the term 'clouding of consciousness' evolved to mean a disturbance in level of alertness coupled with inability to concentrate or attend to

happenings in the environment(53). His report of the prodromal state includes a wide spectrum of features including poor concentration. Similarly, Crammer, a retired emminent psychiatrist, in describing his subjective experience of a delirious state, refers to a 'declining awareness of the environment' as delirium approached(54). Mermelstein's case series of clarithromycin-induced delirium describes a prodrome in one patient who had 'difficulty focusing' the day prior to delirium onset(55).

Duppils et al showed that although clouding of consciousness did not feature prominantly in older hip surgery patients, when it did occur it was only in those about to develop delirium. Conversely, in two other studies of delirious hip fracture patients, inattention was found to be one of the dominant features of the prodromal period. Firstly, de Jonghe et al found that poor concentration, measured using the digit span, was common in the prodromal phase, occurring in 53% of delirious patients two days before delirium onset (OR 3.9, CI: 1.6-9.8) and in 81.8% of patients on the day before delirium (OR 13.0, CI 4.9-34.7) (56). In a more recent study, conducted by Lee et al, almost all DRS-R98 (Korean version) features were present during the delirium prodrome, with inattention, accompanied by some other cognitive and non-cognitive features, occurring as early as four days prior to delirium onset(57). In a more general older study population of 91 delirious medical and surgical patients, 15.9% experienced a prodrome which included inattentiveness (58).

Studies in bone marrow transplant (BMT) patients have also illustrated attentional deficits to be a central feature of the delirium prodrome. Fann et al used a multifaceted approach, including assessments of mood, pain and delirium features, to identify prodromal features in a cohort of 90 BMT patients, half of whom went on to have a delirium episode(59). Decreasing attention span and cognitive decline was noted in the days before delirium onset in the delirium group. In 2010, Beglinger et al conducted a prospective case-control study of delirium in 54 BMT patients aiming to describe the cognitive performance of patients during the delirium phase compared to non-delirious BMT patients and 10 healthy

controls(60). A comprehensive battery of neuropsychological tests were administered at baseline pre-transplantation, including Modified Mini Mental State Examination (3MS); Trail-making tests (TMT) A and B; The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); The Wechsler Abbreviated Scale of Intelligence (WASI); as well as a visual analog scale of thinking clarity. Subsequently subjects were assessed twice weekly for up to four weeks post transplantation, using an abbreviated version of the baseline assessment (TMT; 3MS; RBANS list learning, Coding, Fluency, List Recall and List Recognition subsets). Patients who developed delirium showed a consistent drop in scores on all measures throughout the post-transplant period. TMT B, list recall and coding scores decreased significantly in these patients from the second visit to the visit just before delirium. At baseline, there was no significant difference between groups for age, education level and WASI IQ, however, those patients who went on to develop delirium performed significantly more poorly than non-delirious BMT patients on list learning and list recall. This indicates that acquired deficits in attention domains (particularly divided attention, complex scanning and visual tracking), along with impairments in psychomotor speed, learning and memory occurred in the prodromal period before delirium onset.

Disorientation

Another frequently observed cognitive feature of impending delirium is disorientation. Eden and Foreman recorded in detail a case of tardily diagnosed delirium in the intensive care setting, aiming to highlight barriers to early recognition(61). The 69-year old elective renal endartectomy patient began to exhibit prodromal delirium symptoms on the first post-operative night, having been documented as being "confused at times, but reoriented easily". Although, the first mention of delirium in his case-notes was on the fourth post-operative day, and no formal neuro-cognitive assessment took place, it appears from the report that delirium began on post-operative day two, hence, his early disorientation was likely to be part of a prodrome. Disorientation was also one of the key prodromal features in Levkoff et al's prospective cohort of

325 older general medical and surgical patients(58). Of 91 cases of delirium, 69.2% experienced a prodrome based on daily longitudinal assessment using the Delirium Symptom Interview. Almost half of these prodromal patients had evidence of disorientation, most commonly to place, just prior to delirium onset. In delirious hip surgery patients, disorientation has been a consistent and significant feature of the delirium prodrome. In an observational study recording behavioural changes before and during the course of delirium in hip surgery patients, disorientation was significantly more represented in the delirium group in the 48 hours preceding diagnosis, and additionally was one the the most dominant features of the prodromal period in these patients(62). Subsequently, de Jonghe et al assessed older hip fracture patients on a daily basis for incident delirium using the DRS-R98, MMSE and digit span(56). In this study, disorientation preceded delirium by as early as four days and became more prevalent as delirium approached, occuring in over eighty per cent of delirium prodrome patients the day before full diagnosis. This finding of early onset disorientation in the prodromal phase was recently replicated in Lee et al's study of Korean hip surgery patients(57).

Registration and Memory impairment

Deficits in registration and memory have been indicated as features of the delirium prodrome in some of the aforementioned articles. Crammer's account of his subjective experience refers to the onset of retrograde amnesia and impaired registration before delirium emerged(54). Both short- and long-term memory impairments feature substantially in the prodrome to delirium in de Jonghe et al's hip fracture cohort(56). In Lee et al's Korean cohort, long-term memory deficits appeared first and persisted throughout the prodromal phase, while short-term memory declined just before delirium onset(57). In Beglinger et al's detailed investigation of neurocognitive performance in BMT patients, significant declines in immediate recall and verbal long-term memory functions scores were recorded during the assessment prior to delirium

diagnosis(60). Additionally, in a recent study of long-term care patients, using serial CAM assessments to detect delirium, worsening of registration (measured by requesting immediate recall of three words) was significantly associated with emerging delirium (OR 2.59; 95% CI 1.24-5.41)(63).

Visuospatial deficits

Visuospatial impairments appear to be less prevalent and less prominent than other features in the delirium prodrome. A decline in TMT B in prodromal BMT patients reflects poor visuomotor processing speed but not necessarily visuospatial impairment(60). Mild deficits in visuospatial ability have been reported in prodromal hip surgery patients however the magnitude of clinical change was less than that of declines in other cognitive domains (57).

Non-cognitive features

The 'non-cognitive' domain is made up of neuropsychiatric symptoms which are key components of delirium phenomenology but, as expected, are not relating to deficits in cognition. Amost all non-cognitive delirium symptoms have been reported in the prodromal phase, though some feature more prominently than others. Perceptual abnormalities; psychomotor disturbances; and disruption in the sleep-wake cycle are the most prevalent non-cognitive prodromal features, whereas delusons; speech problems; thought disorder; affective lability; and evidence of fluctuations are reported with less frequency.

Motor changes

Psychomotor disturbance in delirium has long been recognised as central to clinical presentation. The ancient Greeks coined the phrases 'lethargicus' and 'phrenitus' to indicate decreased and increased motor activity profiles respectively. Over the years, other delirium classification

symptoms have been proposed and studied, however, most work has focused on subtyping based on motor activity profile. Not only are motor features more visible than other signs, delirium subtypes based on motor profile differ distinctly in relation to many important clinical parameters including aetiology, duration and outcomes. Hence, if delirium phenomenology is also heavily represented in its prodrome, it is intuitive that psychomotor symptoms would predominate.

A few studies have suggested a prodrome characterised by hypoactivity, however, restlessness or hyperactivity has most frequently appeared in the prodromal literature. It is important to note that although the hypoactive subtype of delirium is now known to be more prevalent, especially in older populations, it remains the least detected. Hypoactivity presents less of a challenge to staff and is often incorrectly not considered pathological. Understanding of the subtle signs of delirium is rare, withdrawal and poor mobility often attributed solely to concommitant illness. Hence, although hyperactivity has been described more frequently, it is possible that hypoactivity has simply gone largely unnoticed in the prodromal literature.

In a study of older general hospital patients, changes in psychomotor activity occurred in 54% of patients who went on to develop delirium(58). Hyperactive features predominated slightly and, in particular, restlessness. Restlessness has featured significantly in case studies or accounts of the prodromal phase. Lipowski included it in his 1990 characterisation of the delirium prodrome(53) and in Eden and Foreman's case study, restlessness was one of first features of impending delirium, increasing in severity as delirium approached(61). In Miller's case series of three delirium tremen patients, restlessness was a chief feature of the prelude to delirium(64). Increased psychomotor activity has also been described in the prodromal phase in hip fracture patients (57, 62) and in Matsushima's small study of 20 coronary care unit patients, almost all in the delirium group had evidence of hyperactivity during the prodromal phase(65). Conversely, Osse at al showed using wrist actigraphy in elective cardiac surgery patients that those with delirium had lower mean

activity levels and reduced restlessness in the first post-operative day and night(66). In was unclear from this report, however, whether the these changes were, in fact, recorded in early delirium or just preceding it.

Sleep-wake cycle disturbance

Disruptions in the sleep-wake cycle are also common during the delirium prodrome and have been illustrated in orthopaedic, cardiology and general hospital patients. In Levkoff et al's cohort, 25.4% of prodromal patients experienced problems in this domain, in particular describing difficulties getting to sleep and staying asleep during the night (58). Nocturnal insomnia has also been described as part of the prodromal phase (53, 61).

Perceptual abnormalities

Perceptual disturbance is the most prevalent psychiatric feature of the delirium prodrome and can vary in severity from fleeting illusions to disturbing hallucinations. Although other cognitive and non-cognitive features occur with more consistency in this phase, the presence of perceptual abnormalities is the most convincing evidence for the existence of a delirium prodrome and that the features of this phase are not simply due to illness behaviour. Lipowski described prodromal symptoms including vivid dreams and nightmares and difficulty differentiating between dreaming and waking imagery or true perceptions. He asserts that the fleeting illusions and hallucinations that may occur during this phase contribute to a decline in an individual's sense of control over both cognitive processes and the ability to make sense of the environment. Perceptual abnormalities of varying severity have been found in the prodromal phase in many patient groups, including hip surgery patients (57, 62); bone-marrow transplant patients (59); long-term care patients (63) and older general hospital patients (58). The reports in delirium tremens patients are most dramatic, for example one case report describes a patient's recurrent sensation of being grabbed from behind,

while another report depicts recurrent frightening visual hallucinations involving large black rocks hurtling towards the patient's head(64).

Other non-cognitive symptoms

Other delirium symptoms have been observed in the prodromal phase but with less consistency. Incoherent speech and tangentiality were common in Levkoff et al's cohort occurring in 49.2% and 22% of prodromal patients respectively(58). Mermelstein reported a prodrome including 'confused speech' in one of his cases of clarithromycin-induced delirium(55) and incoherence was also recognised in one study of hip fracture patients(56). A second study of hip surgery patients found disorganised thinking, delusions and lability of affect in the prodromal phase(57). Prodromal suspiciousness was recorded in one of Miller's cases of delirium tremens(64) and new-onset disorganised thinking was a feature in Voyer et al's long-term care cohort(63), whereas Fann and colleagues reported evidence of variability of symptoms in BMT patients(59).

Somatic or physical features

A wide range of somatic features have been reported in the delirium prodrome, so much so that they vary disparately from study to study and very few features have been documented with any regularity. The most consistent report is that of pain. In Sirois' evaluation of 100 consecutive cases of delirium referred to liaison psychiatry, it was observed that unexplained headaches preceded delirium onset in a number of subjects(67). Lumbar or thoracic back pain as well as discomfort at catheter sites was described in prodromal coronary care patients(65). Fann et al reported that pain (measured using a ten-point Likert Scale) preceded delirium in BMT patients by approximately three days and increased in severity as delirium approached(59). Lipowski's constellation of prodromal features include fatigue, malaise and hypersensitivity to light and sound(53), whereas delirium tremens patients describe disturbing

limb sensations in the prodromal phase, accompanying the expected diaphoresis, nausea and vomiting (64).

Non-specific emotional symptoms

One of the reasons the delirium prodrome has not yet been characterised, despite being recognised as a concept for decades, is that there are elements that difficult to define and quantify. Many clinicians, and indeed family members, note that in the days before delirium a patient may seem 'not quite right' or 'not quite him / herself'. Usually these observations are made retrospectively as the non-specific nature of the signs and symptoms do not lend themselves well to measurement or, indeed, to detection in a prospective fashion. When these reported non-specific symptoms are studied and distilled down, the vast majority include an element of emotional change. These reported emotional changes include irritability (53, 64), fear (64), anxiety (61, 65), and dysphoria (68). Anxiety is documented with the most frequency. Reported in cardiology patients(65) and also in Eden and Foreman's case study of an ICU patient(61), anxiety, manifesting as urgent calls for attention, was also a key feature of the delirium prodrome in one study of hip surgery patients (62). Apathy, dysphoria and withdrawal were observed in the prodromal phase of delirium in children and adolescents in an urban sub-Saharan setting(68). Fann described (using the Profile of Mood States) an increase in all negative emotional states in BMT patients as delirium approached, indicating a marked rise in distress levels in these patients(59). The most non-specific symptom was described by Sirois, who reported that complaints of 'general uneasiness' preceded delirium in many cases(67).

Prodrome Overview

From the above, we can see that the delirium prodrome is composed of a constellation of features which vary from study to study,

challenging efforts to derive a definition. Some features appear consistently across the literature, whereas some of the symptoms are observed in only one study. Figure 1 illustrates a schematic representation of the features of the delirium prodrome based on the literature to date. Many of the symptoms also occur in delirium, so conceptually it can be difficult to distinguish some prodromal episodes from subsyndromal delirium. De Jonghe and colleagues suggest that a differentiating factor is the impact of symptom severity on daily functioning, with delirium diagnosed when function is impaired(56). Another obstacle to defining the delirium prodrome is that many of the described somatic and emotional features could be influenced by other patient factors. Illness behaviour may explain fatigue and malaise; an unwell patient may experience understandable anxiety in relation to prognosis; and low mood may be contributed to by reduced function when physically compromised. Hence, further studies are required to elucidate the specific features that herald a delirium episode.

Another aspect of this prodrome which remains unclear is its duration in relation to the onset of delirium. Lipowski suggested that a longer prodrome preceded delirium secondary to systemic illness or metabolic abnormalities, and that delirium secondary to mechanical or surgical aetiology was likely to be more acute in onset(53). Studies looking at delirium in hip surgery populations dispute this, with prodromal symptoms occurring in many cases three to four days before delirium diagnosis and varying in type and severity on a daily basis(56, 57). A similar duration has been reported in BMT patients (59, 60), whereas in general hospital patients, mean duration was 2.7 days (SD 3.3) with a range of one to nineteen days (58). Prodromal symptoms occurred between a few days to over a week in ill children and adolescents(68) and were described between one and two weeks prior to delirium diagnosis in long-term care patients (63), so defining duration based on aetiology may not be accurate. Noted in many studies and case reports is that prodromal features tend to increase in number and severity as delirium proximity increases. This is best illustrated by Fann et al(59), whose data show a precipitous rise in all prodromal features from four days prior to delirium diagnosis. Most of these features continue to worsen during delirium and

then tail off in the post-dromal period. In Duppils et al's study in hip fracture patients, although behavioural changes were common in all patients, the changes were different and more repeatedly observed in those with emerging delirium(62). Additionally, there was increased frequency and evidence of behavioural changes in these patients with increased delirium proximity.

CONCLUSION

Delirium is a serious highly prevalent condition which has a significant impact on medical, social and personal outcomes, as well as on increasingly stretched health budgets. Our ageing population is leading to increasing age profiles across all medical settings, which in turn will generate higher case complexity across the board and increased prevalence rates of all age-related co-morbidities. Delirium rates are hence likely to increase dramatically, given that advancing age, pre-existing cognitive impairment and comorbidity are all significant risk factors for its development. This makes improving delirium care a key factor in delivering enhanced care quality to this growing proportion of older patients. Prognosis is linked to delirium duration, underlining the importance of early detection and appropriate intervention, yet we are still hampered by a lack of awareness and understanding of delirium on the ground. Delirium prevention has the potential to yield great long-term benefits on both personal and population-based levels, but strategies to prevent delirium must be multifactorial and system-wide in order to be effective and must include educational initiatives to improve comprehension of its significance both at staff level and at institutional level.

Understanding early indicators of delirium, specifically the features of the delirium prodrome, may facilitate the development of more streamlined

initiatives to identify those in the early stages of delirium. Although, the studies as described above have outlined the landscape, further work is needed to definitively characterise this prodromal period with regard to symptom profile and duration and whether or not these characteristics differ according to delirium aetiology or other factors. We also must investigate why some patients experience a prodrome, yet others do not. Is this related to acuity of onset of the underlying precipitant or do all patients with delirium traverse through a prodromal period of varied duration and symptom profile? Once we understand the nature of the prodrome in more depth, we must turn our efforts towards investigating if intervening at this pre-delirium phase has meaning in relation to improving patient outcomes. Prospective studies of incident delirium focussing on the characterisation of the prodromal period are necessary to as a starting point in comprehending its clinical significance.

Table 1: Useful attention tests

Cognitive tests	**Description**
Digit Span forwards (DSF)/ backwards (DSB)	Patient must repeat a sequence of numbers read out by examiner (same order for DSF, reverse order for DSB) Abnormal: DSF <5 or DSB <3 on 2 trials
Spatial Span forwards (SSF)/ backwards (SSB)	A visual version of the digit span, using a card with 8 coloured squares. Sequences are tapped out for the patient to repeat. Useful in patients with communication difficulties. Abnormal: SSF <5 or SSB <3 on 2 trials
Months of the year backwards	Recite the months of the year in reverse order starting with December. Failure to reach July without error is abnormal
Days of the week backwards	Recite the days of the week backwards. Any error is abnormal
20 to 1	Count backwards from 20 to 1. Any error is abnormal

Figure 1: The features of prodromal delirium

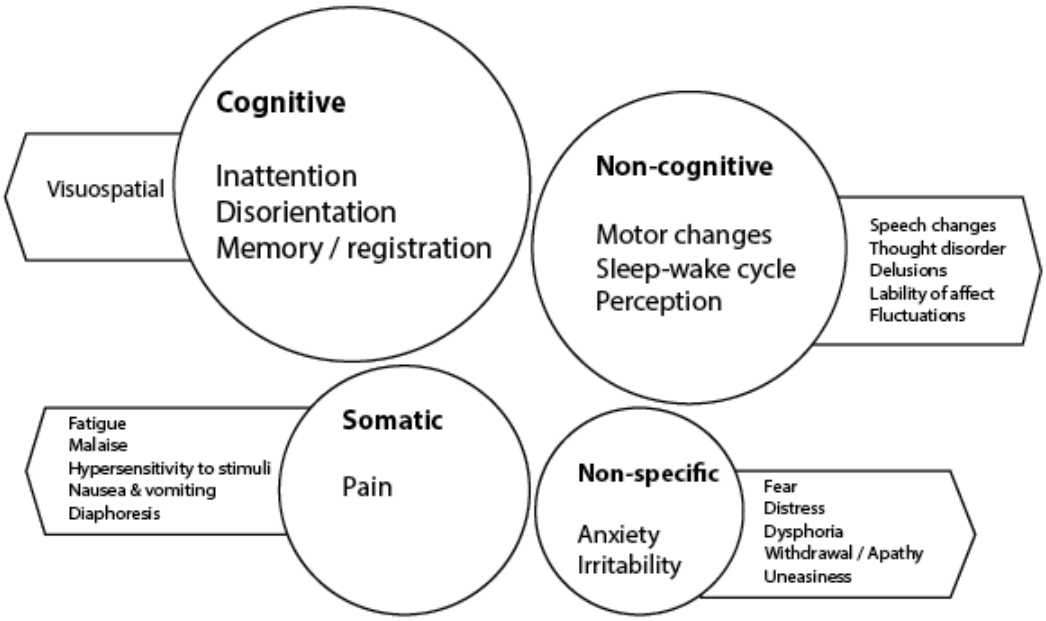


Table 2: Studies of delirium prodrome

	Study design	Population	No. of cases	Reference standard (delirium)	Assessments used	Frequency of Assessments	Outcomes	Prodromal features	Prodromal duration
Sirois, 1988(67)	Retrospective cohort study	100 liaison psychiatry referrals	100	DSM-III criteria	Not specified	Not specified	Not specified	• Headaches • General uneasiness	Not specified
Levkoff et al, 1994(69)	Prospective cohort study	325 older medical and surgical inpatients	91	DSM-III criteria	Delirium Symptom Interview	Daily	69.2% of cases experienced a prodrome.	• Changes in psychomotor activity • Speech and thought disorder • Disorientation • Sleep disturbance • Inattentiveness • Perceptual disturbance:	Range 1-19 days Mean 2.7 days (SD 3.3)
Matsushima et al, 1997(65)	Prospective cohort study	20 CCU patients	10	Psychiatry assessment , DSM-III-R	MMSE; EEG and eye movement recordings; Assessment of clinical symptoms	Daily on days 1,2,3 and 4 of admission to CCU and a subsequent control recording	Slowing of background EEG activity and Increased R and RS group eye movements in delirium group.	• Anxiety ($p<0.05$) • Increased body activity ($p<0.05$) • Sleep disturbance ($p<0.05$) • Slowing of background EEG activity	1-3 days
Duppils, et al 2004(62)	Prospective, descriptive observational study	103 older hip surgery patients	32	DSM-IV criteria	Baseline MMSE; Structured observation protocol assessing for behavioural changes	3 to 8 times daily	BCs were more frequent in delirium group.	• Disorientation ($p<0.05$) • Urgent calls for attention ($p<0.05$) • Increased psychomotor activity (ns) • Perceptual disturbance (ns)	Up to 48 hours
Fann et al, 2005(59)	Prospective cohort study	90 HSCT patients	45	DRS	DRS, MDAS, POMS, numerical pain score (0-10)	Three times weekly	Factor analysis revealed a 3-factor structure: psychosis-behaviour; cognitive; mood-consciousness	• Impairments in attention • Perceptual disturbance • Changes in cognition • Evidence of variability of symptoms. • Pain • Distress symptoms	5 days
De Jonghe et al(56)	Prospective cohort study	101 older hip fracture patients	66	DSM-IV criteria	MMSE, DRS-R-98, Digit span	Daily	Marked increase in mean DSR-R98 scores on the day before delirium.	• Disorientation • Difficulty concentrating • Short & long-term memory impairment • Incoherence	1-3 days

Osse et al, 2009(66)	Prospective cohort study	70 older elective cardiac surgery patients	38	CAM-ICU	Actiwatch® actigraphy on non-dominant wrist	Continuous data for 1st post-operative day and night	Number of immobility minutes was higher and mean activity level was lower for the delirious group compared to non-delirious group	• Lower nocturnal mean activity levels ($p<0.05$) • Reduced restlessness ($p<0.05$) • Higher immobility minutes (ns) • Lower daytime mean activity levels (ns)	Unclear if prodrome or actual early delirium
Beglinger et al, 2010(60)	Prospective case-control study	54 HSCT patients 10 healthy controls	19	Unclear Used DRS; DRS-R98; MDAS	3MS, TMT A and B; RBANS; WAIS; A visual analog scale of thinking clarity‡	Twice weekly	Trails B, List recall, and coding z-scores (from RBANS) show a significant drop from the second visit to the visit just before delirium.	• Deficit in psychomotor speed • Learning and memory impairment • Attention / working memory impairment Slight increase in DRS and MDAS scores prior to delirium onset	2-5 days
Lee et al, 2011(57)	Prospective cohort study	65 older hip surgery patients	18	DSM-IV and Korean-DRS-R98	K-DRS-R98; MMSE-K; APACHE III	Daily until post-operative day 5	Increasing K-DRS-R98 symptoms and severity scores as delirium approached with no change in the non-delirious group.	• Day -4: sleep-wake, thought process, orientation, attention, LTM impairment • Del -3: lability of affect • Del -2: perceptual disturbances, hallucinations and visuospatial ability • Del -1: delusions, motor agitation, STM	1-4 days
Voyer et al, 2012(63)	Nested case-control study	593 LTC patients	85	CAM	MMSE; HDS; BI; CAM	Weekly	There were more new-onset delirium symptoms prior to delirium in the delirium group, but the prevalence was still very low (<15%)	• Perceptual disturbances (9.4%) • Disorganised thinking (8.3%) • Impaired registration (14.2%)	<2 weeks

(DSM-III: Diagnostic and Statistical Manual for Mental Disorders (Third Edition); DSM-IIIR: Diagnostic and Statistical Manual for Mental Disorders (Third Edition)- Revised; DSM-IV: Diagnostic and Statistical Manual for Mental Disorders (Fourth Edition); CCU: Coronary Care Unit; MMSE: Mini Mental State Examination; EEG: Electroencephalogram; BC(s): Behavioural change(s); HSCT: Haematopoeitic Stem Cell Transplantation; DRS: Delirium Rating Scale; DRS-R98: Delirium Rating Scale-Revised '98; MDAS: Memorial Delirium Assessment Scale; CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; 3MS: Modified MMSE; TMT A and B: Trail Making Tests A and B; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; WAIS: The Wechsler Abbreviated Intelligence Scale; DRS-R98: Korean version of the Delirium Rating Scale-Revised '98; MMSE-K: Korean version of the MMSE: APACHE II: Acute Physiology and Chronic Health Evaluation II; HDS: Hierarchic Dementia Scale; BI: Barthel Index; CAM: Confusion Assessment Method)

Table 3: Case studies of delirium prodrome

Case Studies	Study design	Patient group	Number of cases	Outcomes	Prodromal features	Prodromal duration
Miller, 1982(64)	Case series	Delirium tremens patients	3	N/A	• Recurrent visual and / or tactile hallucinations • Motor agitation • Fear • Suspiciousness / argumentativeness • Disturbing sensation in limbs • Diaphoresis • Nausea and vomiting	Perceptual abnormalities: 1-6 months Other symptoms: 1-2 days
Eden et al, 1996(61)	Case study	ICU	1	N/A	• Restlessness • Anxiety • Nocturnal insomnia • Intermittent disorientation	3 days
Mermelstein, 1998(55)	Case series	Clarithromycin-induced delirium	3	One patient had an apparent prodrome	• Difficulty focusing • Confused speech	24 hours
Crammer, 2002(54)	Case report	ICU (Subjective experience)	1	N/A	• Retrograde amnesia • Declining awareness of the environment • Impaired registration	At least 24 hours
Hatherill et al, 2010(68)	Prospective case series	Paediatric referrals to consultation liaison psychiatry (Sub-saharan Africa)	23	22% (n=5) patients presented with an apparent prodrome.	• Apathy • Dysphoria • Withdrawal	A few days to a week or more

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