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Authors	O'Keeffe, David;O'Donovan, D;Aherne, M;Hanley, Sinead;Goodwin, Emma;Shanahan, P;Twomey, A;Cronin, K;Meyer, F;Rey, R;Green, T;Finn, B;Stone, G;Mullane, D;Millar, S R;NiChroinin, M
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Longitudinal Improvements in Clinical Outcomes for Children with Cystic Fibrosis Aged Six Years

D. O'Keeffe[1], D. O'Donovan, M. Aherne, S. Hanley[1], E. Goodwin, P. Shanahan, A. Twomey, K. Cronin, F. Meyer[1], R. Rey[2], T. Green[1], B. Finn[1], G. Stone, D. Mullane[1], S.R. Millar, M. NiChroinin[1,2]

1. Department of Paediatrics, Cork University Hospital, Wilton, Co. Cork, Ireland.
2. University College Cork, College Rd., Co. Cork, Ireland.

Abstract

Background

Cystic Fibrosis (CF) is the most common life-shortening inherited lung disorder of Caucasian children. Advances in early diagnosis and management in the last twenty years have considerably improved the outcome of patients with CF. We aimed to assess whether outcomes for cystic fibrosis patients aged 6 years have improved in our centre since the introduction of these key measures over the past 20 years.

Methods

A retrospective observational study utilising a database of CF patients at Cork University Hospital (CUH).

Results

Over the 20-year period, age at CF diagnosis shifted markedly, with all patients in 2019–2023 diagnosed by newborn screening (20/20, 100%). Since 2014, mortality at age six has been eliminated (0/50, 0%) compared with 2/29 (6.9%) in 2002–2007 and 2/30 (6.7%) in 2008–2013, and chronic *Pseudomonas aeruginosa* colonisation fell to 0% from 3/29 (10.3%) in 2002–2007. CFTR modulator use rose from 0/29 (0%) to 10/20 (50.0%), though most recent patients had short treatment durations. Higher BMI was a statistically significant factor associated with better lung function (FEV_1 p=0.008; FVC p=0.006).

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Discussion
Improvements in outcomes for children aged 6 years are yet to be fully realised with the commencement of CFTR modulator therapy in the first year of life; however, more sensitive diagnostics will be needed to monitor clinical progression.

Introduction

Cystic Fibrosis (CF) is the most common life-shortening inherited lung disorder of Caucasian children, with an incidence in Ireland of approximately 4.5-5.6/10,000[1,2]. Advances in early diagnosis and management in the last twenty years have considerably improved the outcome of patients with CF[3,4]. Newborn screening for cystic fibrosis was introduced in Ireland in 2011, which aims to diagnose cystic fibrosis at 3 weeks of age**.** Further advances in medical care for children with CF include early and aggressive antibiotic eradication therapies targeting Pseudomonas aeruginosa (PsA). Eradication therapy, typically involving inhaled and/or oral antibiotics, aims to eliminate the organism at the first detection to prevent chronic colonisation and subsequent lung damage. It has been shown to reduce morbidity, including the development of bronchiectasis. However, the eradication protocol has its limitations, with failure reported in 10–40% of patients[5]. Patient segregation and isolation to reduce cross-infection have become the standard of care in the management of children with cystic fibrosis. Additionally, Cystic fibrosis transmembrane regulator (CFTR) modulator therapies have been developed and approved and are becoming available for younger patients. In the 2-6-year age bracket, Ivacaftor was made available in 2014, Lumacaftor/Ivacaftor (orkambi) in 2019, and elexacaftor-tezacaftor-ivacaftor (Kaftrio/Ivacaftor) therapy in 2024.

In 2017, we published a report on the improvements in clinical outcomes in children with CF ages six to sixteen years, showing improvements in FEV_1% predicted (forced expiratory volume in 1 second) and BMI (body mass index, kg/m^2) as well as a significant decline in the number of patients with chronic PsA in our population[6]. This was strongly associated with dietary support, nutritional supplementation and changes in antibiotic prescribing, including the use of inhaled therapy[7]. This improvement in clinical outcomes, as well as the introduction of CFTR modulators, has also been noted in other countries like Canada, reporting an increase in CF median survival age and age at death[7]. Accurately predicting the development of cystic fibrosis outcomes over the years is vital for early prevention and personalised care. Our study aimed to assess whether outcomes for cystic fibrosis patients have improved in our centre since the introduction of these key measures over the past 20 years. We included children at age six, as at this age, more

accurate interpretations of spirometry results were possible. Furthermore, as some children in the most recent cohort would have had exposure to modulator therapy, we were interested to know how many had access to modulator treatment, for how long and if it had any impact aged 6 years.

Table 1: Year of CFTR modulator therapy availability in Ireland for children ≤6years

Modulator Type	Ivacaftor	Ivacaftor/Lumacaftor	ETI
Age 2-6 years	2014	2019	April 2024
Age 1-2 years	2018	December 2023	Awaited
Age 4 months	May 2020	Awaited	Awaited

Methods

This is a retrospective observational study utilising a prospectively maintained database of CF patients at Cork University Hospital (CUH). The CF nurse specialists have documented information on all CF patients since the early 1980s. Approval to access patients' records was obtained from the Cork University Hospital Clinical Governance and Audit Office. Ethical approval was obtained from the local ethics committee (CREC Review Reference Number: ECM 4(a) & ECM 3 (fff)). Our inclusion criteria focused on children who turned six between January 1, 2002, and December 31, 2023, under the care of the CUH paediatric CF service.

The measured outcomes encompassed patient demographics, including date of birth, date of diagnosis, reason for presentation, genotype and initial sweat chloride result at the time of diagnosis. Lung function tests, including FEV_1% predicted and FVC (Forced Vital Capacity) % predicted at six years, respectively, for each cohort, were considered (Global Lung Index reference equations were used from 2017[8]). Additional parameters included in this study are BMI and six years for each cohort, PsA status (classified according to Leeds Criteria)[9], and diabetes diagnosis at six years of age, depending on the cohort, were included. PsA status was classified as never (no previous positive PsA sputum or cough swabs), free from (a previous positive PsA sample but none over the preceding 12 months), intermittent (<50% of sputum samples positive in the preceding 12 months) and chronic (>50% of sputum samples positive for PsA in the preceding 12 months). CF-related diabetes (CFRD) is defined using the ISPAD guidelines[10] based on either a two-hour oral glucose tolerance test blood glucose of >/= 11.1mmol/L/ fasting blood glucose of >/= 7mmol/L on two or more occasions or fasting blood glucose of >/=7mmol/L plus random blood glucose level of >/=11.1mmol/L or random BG levels of >/= 11.1mmol/L with symptoms of CFRD on two or more occasions when otherwise clinically well. The use of CFTR

modulators and duration of therapy, and transplant status, specifically lung transplants undertaken six years ago, were also analysed. Outcome measures including FEV_1 % predicted and BMI were recorded at the closest well visit at aged at least 6 years.

Statistical analysis involved descriptive statistics followed by linear regression analysis for both univariate and multivariable models, conducted using Stata SE Version 13 (Stata Corporation, College Station, TX, USA) for Windows. Features displaying a p-value of less than 0.05 in univariate analyses were subsequently incorporated into multivariable models.

Descriptive statistics were examined according to the period of data collection. Categorical variables are shown as a number and percentage, while continuous variables are shown as a mean plus or minus one standard deviation. Linear regression analyses were conducted to examine measured outcome relationships with forced expiratory volume % predicted and forced vital capacity levels % predicted. For each measured outcome, two models were run: Model 1 was a univariate model, while Model 2 adjusted for the period of data collection. Data analysis was conducted using Stata SE Version 13 (Stata Corporation, College Station, TX, USA) for Windows. For all analyses, a p-value (two-tailed) of less than .05 was considered to indicate statistical significance.

Results

With the introduction of the newborn blood spot screening for cystic fibrosis, all patients in the 2019-2023 group under the care of the Cork University Hospital paediatric cystic fibrosis unit were diagnosed at birth, compared with 25% being diagnosed at birth in the 2002-2007 group, 33.3% in the 2008-2013 group and 48.1% in the 2014-2018 group (Table 2). There were zero mortalities observed in the 2019-2023 cohort at 6 years, similar to the 2014-2018 group. We note there were two mortalities in 2002-2007 and 2008-2013, respectively. There were no patients transplanted or on transplant list in any of the groups.

PsA status was assessed in each patient group, and the results were as follows. The “Never” diagnosed group was 58.6% in the 2002-2007 group, 33.3% in 2008-2013, 43.3% in 2014-2018 and 50% in 2019-2023. In the group with successful eradication of PsA infection/colonisation “free from” group, the 2002-2007 group had the lowest number of patients in this group (10.3%), 26.7% in the 2008-2013 cohort, 50% in the 2014-2018 group and 30% in the 2019-2023 group.

Intermittent PsA infection/colonisation was noted to be mainly unchanged throughout the twenty years, except for the 2014-2018 group, which is noted to have only 6.7% of patients in this group when compared to higher levels across the other groups (2002-2007 - 20.7%, 2008-2013 36.7%, 2019-2023 20%). The 2014-2018 and 2019-2023 groups had no patients with chronic PsA infection/colonisation, whereas the 2002-2007 groups and 2008-2013 groups had 10.3% and 3.3% of patients with chronic infection, respectively (Table 2).

Use of CFTR modulator therapy was highest in the 2019-2023 group (50%) compared to 0%, 6.7%, and 13.3% in the 2002-2007 group, 2008-2013 group and 2014-2018 group. (Table 2). BMI throughout the four different groups remained mostly unchanged over the 20 years (16.1 ± 2.0, 16.1 ± 1.8, 15.5 ± 1.0, 15.7 ± 1.8) (Table 2). FEV_1% predicted and FVC % predicted have remained mostly the same across the groups when taking into consideration the standard deviation within the groups (Table 2). Although the 2014-2018 group was noted to have a slight improvement in FEV_1% predicted (100.9 ± 15.8) and FVC % predicted (102.8 ± 16.7) when compared to the other three cohorts (2002-2007 FEV_1 % predicted 90.7 ± 16.1 FVC % predicted 94.1 ± 14.6, 2008-2013 FEV_1 % predicted 99.3 ± 17.9 FVC % predicted 101.7 ± 15.2, 2019-2023 FEV_1% predicted 96.2 ± 14.5 FVC 93.2 ± 17.4) (Table 2).

Tables 3 and 4 use a linear regression model to extrapolate the significance of 4 different factors (Time to diagnosis, PsA status, use of CFTR modulators and BMI) for FEV_1 % predicted and FVC % predicted in 6-year-old patients with CF. The only statistically significant factor that impacted FEV_1% predicted and FVC % predicted was BMI, with a p-value of .008 and 95% CI of 0.66, 4.32 for FEV_1 % predicted and p-value of .006 with a 95% CI of 0.74, 4.35 for FVC % predicted. This would suggest an elevated BMI was associated with an improved FEV_1% predicted and FVC % predicted in 6-year-olds with CF. For our cohort time to diagnosis, PsA status (intermittent or chronic) and use of CFTR modulator therapy did not have a statistically significant impact on FEV_1% predicted and FVC % predicted in 6-year-olds with CF.

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Table 2. Characteristics of 6-year-old patients with cystic fibrosis, 2002–2023.

Outcome measured	2002–2007	2008–2013	2014–2018	2019–2023
Mortality (n)	2	2	0	0
Number of patients who reached six years (n)	29	30	30	20
Time to diagnosis:				
Before or at birth (%)	7 (25.0)	10 (33.3)	13 (48.1)	20 (100.0)
Before 1 year (%)	10 (35.7)	13 (43.3)	8 (29.6)	0 (0.0)
Between 1–2 years (%)	6 (21.4)	4 (13.3)	1 (3.7)	0 (0.0)
>2 years (%)	5 (17.9)	3 (10.0)	5 (18.5)	0 (0.0)
Pseudomonas (PsA) status:				
Never (%)	17 (58.6)	10 (33.3)	13 (43.3)	10 (50.0)
Free from (%)	3 (10.3)	8 (26.7)	15 (50.0)	6 (30.0)
Intermittent (%)	6 (20.7)	11 (36.7)	2 (6.7)	4 (20.0)
Chronic (%)	3 (10.3)	1 (3.3)	0 (0.0)	0 (0.0)
Use of CFTR modulator (%)	0 (0.0)	2 (6.7)	4 (13.3)	10 (50.0)
Ivacaftor number	0	2	4	1
Orkambi number	0	0	0	9
BMI, kg/m^2 (mean)	16.1 ± 2.0	16.1 ± 1.8	15.5 ± 1.0	15.7 ± 1.8
Forced expiratory volume % predicted (mean, SD	90.7 ± 16.1	99.3 ± 17.9	100.9 ± 15.8	96.2 ± 14.5
Forced vital capacity % predicted), (mean, SD)	94.1 ± 14.6	101.7 ± 15.2	102.8 ± 16.7	93.2 ± 17.4

Numbers and % are shown for time to diagnosis, PsA status and use of CFTR modulator. BMI forced Expiratory volume % predicted and forced vital capacity % predicted are shown as a mean ± one standard deviation.

Table 2a Duration of modulator treatment received when aged 6 years

	2008-2013	2014- 2018	2019-2023
< 1 year	2	3	5
1-2 years	-	1	4
>2 years	-	-	1

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Table 3. Factors associated with FEV $_1$% predicted in 6-year-old patients with cystic fibrosis – linear regression.

Outcome measured		Coefficient	Std Error	95% CI	p value
Model 1					
	Time to diagnosis*	-0.88	1.59	-4.04, 2.28	.582
	Pseudomonas (PsA) status**	-4.38	3.68	-11.68, 2.91	.236
	Use of CFTR modulator	5.4	4.48	-3.49, 14.29	.231
	BMI	2.27	0.92	0.44, 4.11	.016
Model 2					
	Time to diagnosis*	-0.11	1.75	-3.58, 3.36	.951
	Pseudomonas (PsA) status**	-3.52	3.74	-10.93, 3.90	.349
	Use of CFTR modulator	3.21	4.99	-6.69, 13.11	.522
	BMI	2.49	0.92	0.66, 4.32	.008

*Time to diagnosis included as a continuous 4-category variable: (1) before or at birth; (2) before 1 year; (3) between 1–2 years; and (4) >2 years.
**Either intermittent or chronic.
Model 1: Univariate.
Model 2: Adjusted for a period of data collection.
Two subjects were excluded from analyses due to missing outcome values.

Table 4. Factors associated with forced vital capacity levels in 6-year-old patients with cystic fibrosis – linear regression.

Outcome measured		Coefficient	Std Error	95% CI	p value
Model 1					
	Time to diagnosis*	1.80	1.56	-1.30, 4.90	.253
	Pseudomonas (PsA) status**	-3.82	3.62	-10.99, 3.35	.293
	Use of CFTR modulator	2.81	4.42	-5.96, 11.57	.526
	BMI	2.48	0.90	0.69, 4.26	.007
Model 2					
	Time to diagnosis*	2.22	1.73	-1.21, 5.64	.202
	Pseudomonas (PsA) status**	-3.81	3.70	-11.15, 3.53	.306
	Use of CFTR modulator	2.96	4.95	-6.85, 12.76	.551
	BMI	2.55	0.91	0.74, 4.35	.006

*Time to diagnosis included as a continuous 4-category variable: (1) before or at birth; (2) before 1 year; (3) between 1–2 years; and (4) >2 years.
**Either intermittent or chronic.
Model 1: Univariate.
Model 2: Adjusted for a period of data collection. Two subjects were excluded from analyses due to missing values. Two subjects were excluded from analyses due to missing outcome values.

Discussion

In the patient cohort turning six in 2019-2023, they were all diagnosed with CF at or before birth. Newborn screening for CF was established in Ireland in 2011, which explains the markedly higher rate of neonatal diagnosis in the 2019–2023 cohort (100%) compared to earlier cohorts (2002–2007: 25%, 2008–2013: 33.3%, 2014–2018: 48.1%) The reduced mortality seen may be a direct effect of newborn screening as was seen in the US when CF-related mortality was assessed in US states with and without newborn screening[11]. For the 2019-2023 cohort, the number of patients in this group were n=20, compared to n=29 or n=30 in the previous 3 other groups. The reduced number in the 2019-2023 group may be related to the change in geographic boundaries for CF centres in 2011 following the introduction of 6 designated CF centres nationally.

As this is a longitudinal study over 20 years different reference equations were used to measure lung function over the study period -most recently GLI reference equations from 2017[8]. Therefore, this needs to be taken in account when interpreting the comparisons of % predicted FEV_1 and FVC across groups over different time periods.

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The general trend observed in the 6-year-old patients from 2002- 2023 is a lower rate of chronic and intermittent PsA colonisation. 0 patients in the 2014-2018 group and 2019-2023 group had chronic PsA infection compared to 10.3% in the 2002-2007 cohort. Chronic early PsA infection in children with cystic fibrosis is associated with a significant increase in morbidity and mortality[12]. Interestingly, there was no reduction in patients who never had a PsA infection (58.6 % vs 33.3% vs 43.3% vs 50%), indicating that the prevalence of PsA is likely to be similar throughout 2002-2023, but there was a notable reduction of the groups with PsA infection progressing to have intermittent or chronic infection/colonisation. The reason for this is likely to be multifactorial, including the use of tobramycin nebulised therapy and IV eradication therapy. It is important to note that PsA diagnostics may have improved over the study period and may influence results. We could not exclude the poorly understood effects of the SARS–CoV–2 pandemic on the epidemiology of respiratory infection. There is some evidence that highly effective CFTR modulator therapy may reduce PsA acquisition rates in the future[13].

The use of CFTR modulators has been a paradigm shift in the evolution of CF care, with half of the 6-year-olds in the 2019-2023 cohort commencing CFTR modulators. However, the duration of modulator therapy received in this group ranged from 1 to 41 months, with 5 out of 10 patients receiving less than 1 year of modulator therapy at age 6 years, meaning that improvements in lung function and pancreatic function may have not been fully realised. None of the patient groups had received ETI, the highly effective modulator therapy, but this has been available in Ireland since early 2024 to prescribe from 2 years of age. Therefore, it is anticipated that future generations of children aged 6 will have had effective CF modulation. The long-term outcomes for CFTR modulators remain under review, but many clinical trials have already demonstrated they have a significant improvement in mortality and morbidity in children and adults with CF[14]. However, these drugs have been shown to have adverse effects, including changes in mood and behaviour and hepatic dysfunction[15,16].

In our study, BMI appeared to be the most significant factor to impact lung function outcomes and appeared more important than PsA status or time to diagnosis. This data further supports the longstanding target of optimising nutrition in early childhood as a key measure in CF care. Lean body and fat mass are emerging as more sensitive parameters and may be stronger predictors of FEV_1% predicted than BMI[17].

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This study highlights that patients with cystic fibrosis now have earlier diagnosis, reduced mortality and reduction in PsA colonisation rates. With improvements in treatment and earlier introduction of CFTR modulators, more sensitive outcome measures will be required in addition to spirometry and BMI. Future research will focus on the impact of earlier introduction of CFTR modulators on clinical outcomes and any associated drug side effects. Investigations such as lung clearance index, lean body and fat mass and CT imaging will be needed to monitor clinical progression in cystic fibrosis.

Declarations of Conflict of Interest:
None declared.

Corresponding Author:
David O'Keeffe
Department of Paediatrics,
Cork University Hospital,
Wilton,
Co. Cork,
Ireland.
E-Mail: davidt.okeeffe@hse.ie

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