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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

**Title**: Determinants of quality of life in patients with incurable cancer.

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## Abstract

**Background:** Optimising quality of life (QoL) remains the central tenet of care in patients with incurable cancer, however determinants of QoL are not clear. The aim of the present study was to examine which factors influence QoL in patients with incurable cancer.

**Methods:** A multi-centre study of adult patients with advanced cancer was conducted in Ireland and the United Kingdom between 2011-2016. Data were collected from patients at study entry and included patient demographics, Performance Status (ECOG-PS), nutritional parameters [weight loss (%WL) and muscle parameters assessed using computed tomography images (skeletal muscle index (SMI) and skeletal muscle attenuation (MA)], inflammatory markers [modified Glasgow Prognostic score (mGPS)] and QoL data (EORTC QLQ-30). The relationship between clinical, nutritional and inflammatory parameters with QoL was assessed using the Spearman-rank correlation coefficient and multivariate binary logistic regression. Components of the EORTC-QLQ (physical function, fatigue and appetite loss) and the summary QoL score were mean-dichotomised for the logistic regression analyses.

**Results:** Data were available on 1027 patients (51% male, median age 66 years). Gastrointestinal cancer was most prevalent (40%), followed by lung (26%) and breast (9%). Distant metastatic disease was present in 87% of patients had metastatic disease. %WL, ECOG-PS and mGPS were significantly correlated with deteriorating QoL functional and symptom scales (all $p<0.001$). On multivariate regression analysis, >10% WL (OR 2.69 [95% CI:1.63-4.42]), ECOG-PS 3-4 (OR 14.33 [95% CI:6.76- 30.37]) and mGPS 2 (OR 1.58 [95% CI:1.09- 2.29]) were independently associated with poorer summary QoL score. These parameters were also independently associated with poorer physical function, fatigue and appetite loss (all $p<0.05$). Low MA was independently associated with poorer physical functioning (OR 1.67 [95% CI:1.09-2.56]), but muscle parameters were not independently associated with fatigue, appetite loss or QoL summary score.

**Conclusions:** These findings indicate that QoL is determined (at least in part) by WL, ECOG-PS and the systemic inflammatory response in patients with advanced cancer. Identifying early predictors of poor QoL may allow the identification of patients who may benefit from early referral to palliative and supportive care, which has been shown to improve QoL.

## INTRODUCTION

The European Society of Medical Oncology (ESMO)[1] advocate integrating supportive and palliative patient centred care into overall anti-cancer treatment at all stages of the disease. ESMO acknowledges that oncology patients' needs are not being adequately met and that oncology care should encompass patient-centred supportive and palliative care from initial diagnosis to throughout the entire trajectory of the disease. Importantly, cancer care should not only aim to deliver the best quality anticancer treatment, but cancer care should now also consider the impact of a cancer diagnosis and its treatment on each patient's life[1].

In patients who have an incurable cancer, the fundamental aim of treatment is to optimise quality of life (QoL). If this can be attained in unison with prolonged survival then this is clearly desirable, however if prolonged survival comes at the expense of impaired QoL then this may not be in the best interests of patients. Importantly, QoL is increasingly being recognised as an important prognostic indicator, and QoL has been shown to be associated with reduced survival in a variety of cancer sites, even after adjusting for known prognostic clinical variables[2-5].

The now, almost routine adoption of patient reported outcome measures (PROMs) of QoL into cancer clinical trials, has enhanced our understanding of this area.[6] The European Organisation for the Research and Treatment of Cancer (EORTC) have now developed over 60 QoL modules, including the universal EORTC Quality of Life Questionnaire C-30 (EORTC QLQ-C30)[7]. Using this, it has been shown that both physical function (performance score) and measures of the systemic inflammatory response (modified Glasgow Prognostic Score

[mGPS]) have a differential association with QoL.[8,9] In a large cohort of 2,520 patients with advanced cancer, increasing mGPS and deteriorating performance status (ECOG) were associated with deterioration in quality-of-life parameters such as global health, role, physical and social functioning, and fatigue, pain, appetite symptoms ($P < .001$). The association with Increasing systemic inflammation and poorer quality-of-life parameters was independent of PS[8]. It has also been reported that other aspects including weight loss, body mass index and loss of muscle (sarcopenia) influence QoL in patients with cancer.[10-12]

It has been argued that the host-tumour interaction and the resulting systemic inflammatory response is key in the genesis of how symptoms/quality of life are influenced in patients with cancer. Indeed work to date has supported this hypothesis demonstrating that the magnitude of the systemic inflammatory response influences the magnitude of symptoms in patients with cancer.[8] Based on this, markers of the systemic inflammatory response are now advocated as key assessment criteria for staging nutritional status[13] and as stratification factors in randomised clinical trials.[14] In the same way that the tumour is staged, it has been argued that the host should be staged, as inflammatory status is likely to influence treatment outcomes and magnitude of symptoms.[15]

However, a comparison of all factors known to influence QoL has yet to be done. Elucidation of those factors, which adversely influence QoL, may allow the identification of patients who may benefit from early referral to palliative and supportive care, which has been shown to improve QoL.[16,17] Therefore, the aim of the present study was to examine the relationship between clinical, nutritional, inflammatory factors, and QoL, in patients with incurable cancer.

## METHODS

### Study sample

Data were collected across 18 sites in Ireland and Scotland (cancer centres, hospitals, and specialist palliative care units) over a period of 5 years (2011-2016). Patients were over 18 years of age and had a diagnosis of incurable cancer. Incurable cancer was defined as metastatic disease or locally advanced disease being treated with palliative intent. Both inpatients and outpatients were recruited and a convenience sampling approach was adopted. Willing participants provided written informed consent. Exclusion criteria included patients that were under the age of 18 years of age and those that were unwilling or unable to participate due to cognitive impairment. Ethical approval was given for the data collection at all sites and was conducted according to good clinical practice and applicable laws.

### Procedure and Assessment

Demographic data and clinical data were recorded and this included primary tumour site, stage and extent of metastatic disease (if present). The EORTC QLQ-C30 (version 3.0) was used to assess QoL.[3] This 30-item cancer specific questionnaire includes five functional scales (physical, emotional, cognitive, social and role), three symptom scales (fatigue, pain, nausea/vomiting), a global health/QoL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact of disease). The 28 items measuring functional and symptom scales have a numeric scale: 1 (not at all), 2 (a little), 3 (quite a bit) and 4 (very much). The 2 items concerning global QoL have a scale of 1 (very poor) to 7 (excellent). The raw scores were linearly transformed to give standard scores in the range of 0-100 for each of the scales and single items as described by the EORTC[18]. Higher scores for the functional or global QoL scale represent a high level of functioning or QoL, whereas higher scores on the symptom scales represent worse symptomatology. The summary score of the EORTC QLQ-C30, which is comprised from the mean of 13 of the 15 QLQ-C30 scales (global

QoL scale and financial impact scale are not included), was used to assess overall summary QoL. with a maximum score of 100.[19] The summary score was only calculated if all of the required 13 scale scores were available and the scoring of the QLQ-C30 summary score was calculated as follows: QLQ-C30 Summary Score=(Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ 100-Fatigue+ 100-Pain+ 100-Nausea_Vomiting+ 100-Dyspnoea+ 100-Sleeping Disturbances+ 100-Appetite Loss+ 100-Constipation+ 100-Diarrhoea)/13.[19]

Nutritional parameters were also assessed. Patient's weight, height and body mass index (BMI) (weight (kg)/height [$m^2$]) were recorded. Patients were categorised according to their BMI as underweight (<20 kg/$m^2$), normal weight (20-24.9 kg/$m^2$), overweight (≥25-29.9 kg/$m^2$) or obese (≥30 kg/$m^2$). Weight loss (WL) in the preceding 3 months was reported by patients, and when possible verified from patients' medical records.

C-reactive protein (mg/L)(CRP) and albumin (g/L) were used as markers of the systemic inflammatory response and were drawn by a venous blood sample at time of consent. Using both CRP and albumin, a modified Glasgow prognostic score (mGPS) was calculated accordingly.[20] Patients who had both elevated CRP (>10 mg/L) and hypoalbuminemia (<35 g/L) were assigned a score of 2. Patients with only an elevated CRP (>10 mg/L) and without hypoalbuminemia (albumin >35 g/L) were assigned a score of 1. Patients with neither of these abnormalities (i.e. CRP <10 mg/L and Albumin >35 g/L) were assigned a score of 0.[21] The limit of detection of CRP was <5 mg/L. An increasing score is related to increasing systemic inflammation.[20]

Performance status (PS) was assessed using the Eastern Oncology Cooperative Group (ECOG) score.[22] Scores were assigned according to patient-reported daily physical function: 0= fully active with no restrictions; 1= restricted in physically strenuous activity but ambulatory and able to carry out light work; 2= ambulatory and capable of all self-care but

unable to carry out any work activities; 3= capable of only limited self-care; 4= completely disabled and totally confined to bed or chair.

**Body composition assessment**

Abdominal Computerized Tomography (CT) images, taken as part of routine patient care within 12 weeks of QoL assessment, were used to assess body composition as previously described.[23] The third lumbar vertebrae (L3) was chosen as the standard landmark and two consecutive transverse CT images where both transverse processes were clearly visible were analysed using OsiriX software version 4.1.1 (Pixmeo, Geneva, Switzerland) and ImageJ software version 1.47 (National Institutes of Health, MD, USA). Both imaging software packages have been shown to provide excellent agreement for body composition measures.[24] L3 was used as a standard landmark because it correlates best with whole body measures of muscle mass.[25,26] Skeletal muscle area ($cm^2$)(SMA) was manually outlined and segmentation of SMA was based on Hounsfield unit (HU) thresholds (-29 to +150 HU).[27] SMA was normalized for stature to compute the skeletal muscle index (SMI)($cm^2/m^2$). Mean muscle attenuation (MA) in HU was assessed in all patients with a contrast enhanced CT image and was reported for the entire SMA at L3. Gender and BMI specific cut points were used to define low SMI (sarcopenia) and low MA according to Martin *et al.*(2013).[28] Measurements were performed by two individuals (RD and LD) and inter-rater reliability was assessed in a sample of 20 patient images using inter-class correlation coefficients (ICCC)(SMA ICCC=0.986, SMD ICC=0.964). Investigators were blinded to patient's demographic and clinic-pathological status.

**Statistical Analysis**

Statistical analysis was conducted using SPSS (version 24.0, SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation (SD) or median [interquartile range,

IQR] where appropriate. Comparisons between groups of patients were assessed using Chi-squared test for categorical variables and unpaired *t* tests and Mann-Whitney U tests to test for differences in continuous variables. Correlations were investigated using Spearman's coefficient for non-parametric QoL data. The correlation coefficient ($\rho$) was used to determine the strength of the correlations. Cohen's guidelines were employed when interpreting effect size and strength of correlations. These suggest that $r$=0.1-0.29 indicates a small effect size or correlation, $r$=0.3-0.49 indicates a medium effect size and $r$=0.5-1.0 indicates a strong effect size or correlation. Components of the EORTC-QLQ (physical function, fatigue and appetite loss) and the summary QoL score were mean-dichotomised for the logistic regression analyses assessing clinical, nutritional and inflammatory predictors of QoL. Patients with a score below the mean for physical function and QoL summary score, and above the mean for fatigue and appetite loss were given a score of 1, while those with a score above the mean for physical function and QoL summary score and below the mean for fatigue and appetite loss, were given a score of 0. Thus, odds ratios greater than 1.0 indicate a greater likelihood of worse QoL. Independent variables that had significance on univariate analysis were eligible for inclusion in multivariate analysis. All statistical tests were two-sided, and significance was taken at the level $p<0.05$.

## RESULTS

*Patient characteristics and demographics*

A total of 1027 patients with advanced cancer were recruited. Baseline demographic, clinical, nutritional and QoL characteristics are presented in Table 1. Patients were a median of 4.6 months from diagnosis when they entered the study (IQR 3.0-13.0 months). In brief, 51% of patients were male and the median age was 66 (IQR 57-74) years. Gastrointestinal cancer was most common (40%) and metastatic disease was present in 87% of patients. In total, 830

patients (81%) were on active chemotherapy treatment (chemotherapy in the preceding 4 weeks).

*Anthropometry and body composition*

Patients exhibited a wide variation in BMI (12.3-47.4 kg/m$^2$). Half (51%) of all patients were overweight or obese (BMI ≥25 kg/m$^2$), while only 13% had a BMI <20.0 kg/m$^2$. Weight loss >5% in the preceding 3 months occurred in 277 (29%) patients, with 14% experiencing severe WL >10%. In terms of body composition, CT scans within 12 weeks of QoL assessment were available in 428 patients (contrast enhanced CT images for MA assessment available in 413 patients). Overall, 192 (45%) patients were considered to have a low SMI (sarcopenia) and 223 (54%) had low MA.

*Relationship between clinical, nutritional and inflammatory parameters with QoL*

The relationship between clinical, nutritional and inflammatory parameters to PROMs is displayed in Table 2.

Within our cohort, female sex was significantly negatively correlated with poorer physical function (ρ=-.112, $p$=0.001), emotional function (ρ=-.071, $p$=0.024) and summary QoL score (ρ=-.080, $p$=0.012), and positively correlated with more nausea and vomiting (ρ=.123, $p$=0.001) and pain (ρ=0.068, $p$=0.030). Overall the strength of these correlations were small (ρ<0.3). Increasing age, negatively correlated with poorer physical (ρ=-.143, $p$=0.001) and role function (ρ=-.063, $p$=0.047) and positively with better emotional functioning (ρ=0.070, $p$=0.012). In terms of symptom scales, age was positively correlated with more fatigue (ρ=0.70, $p$=0.024), dyspnoea (ρ=0.089, $p$=0.005) and constipation (ρ=0.073, $p$=0.020). The presence of distant metastatic disease (vs. locoregional incurable disease) was not statistically significantly correlated with any EORTC functional or symptom scale.

Percentage WL, ECOG-PS and mGPS were negatively correlated with almost all EORTC functional scales ($p$<0.05). Importantly, medium to strong correlations (ρ>.30) were observed between ECOG-PS and mGPS with physical function (ρ=-.557, $p$<0.001 and ρ=-.312, $p$<0.001, respectively), and ECOG-PS with role function (ρ=-.494, $p$<0.001), social function (ρ=-.334, $p$<0.001), global health (ρ=-.410, $p$<0.001) and importantly summary QoL scores (ρ=-.500, $p$<0.001). The presence or absence of metastatic disease was not related to any of the PROMs. Interestingly, reduced EORTC reported physical functioning was more strongly correlated with low MA compared with low SMI (ρ=-.244 vs. ρ=-.164). Low SMI was not significantly associated with any other PROMS, whereas low MA was associated with role function (ρ=-.145, $p$=0.003), global health (ρ=-.175, $p$<0.001) and QoL summary score (ρ=-.135, $p$=0.006).

Table 3 depicts the relationship between the symptom components of the EORTC-QLQ and clinical, nutritional and inflammatory parameters. In line we what we observed in the PROMs functional scales, % WL, ECOG-PS, and mGPS were associated with increasing symptoms scores ($p$<0.05). Medium correlations (ρ>.30) were observed between ECOG-PS and fatigue (ρ=.476, $p$<0.001) and pain (ρ=.309, $p$<0.001), and as expected between % WL and anorexia (ρ=.311, $p$<0.001). Low MA was associated with more fatigue (ρ=.150, $p$=0.002) and dyspnoea (ρ=.150, $p$=0.002).

In the multivariate logistic regression analyses, the QoL summary score was dichotomised by the mean (73.8). Odds ratios above 1.00 show an association with poorer overall QoL. On multivariate regression analysis, %WL (WL >5% OR:1.59 (95% CI: 1.01-2.51) , $p$=0.048; WL >10% OR: 2.69 (95% CI: 1.63-4.42), $p$<0.001), ECOG-PS (PS 2: OR 3.32 (95% CI: 2.34-4.70), $p$<0.001; PS 3-4: OR 14.33 (95% CI: 6.76-30.37), $p$<0.001), and mGPS (mGPS 1 OR: 2.05 (95% CI: 1.26-3.32), $p$=0.004; mGPS 2: OR 1.58 (95% CI: 1.09-2.29), $p$=0.0016) were independently predictive of an overall QoL summary score below the mean (table 4).

In terms of physical function (<68.4), WL >10% (OR 1.92 (95% CI: 1.16-3.19), *p*=0.039), ECOG-PS (PS 2: OR 3.93 (95% CI: 2.77-5.58), *p*<0.001; PS 3-4: OR 18.07 (95% CI: 7.91-41.28), *p*<0.001), mGPS 2 (OR 2.01 (95% CI: 1.39-2.93), *p*<0.001) and female sex (OR: 1.56 (95% CI: 1.10-2.19), *p*=0.011), were independent predictors of poorer physical function on multivariate analysis (eTable 1).

Examining predictors of fatigue (>42.3), on multivariate analysis WL >10% (OR 2.53 (95% CI: 1.53-4.19), *p*<0.001), ECOG-PS (PS 2: OR 2.89 (95% CI: 2.06-4.07), *p*<0.001; PS 3-4: OR 18.67 (95% CI: 7.79-44.7), *p*<0.001), and mGPS 2 (OR 1.57 (95% CI: 1.09-2.25), *p*<0.001) were independent predictors of more fatigue (eTable 2).

On multivariate analysis, factors associated with more appetite loss (>27.3) were WL (WL >5%: OR 2.38 (95% CI: 1.51-3.76, *p*<0.001); WL >10%: OR 2.51 (95% CI: 1.58-3.99), *p*<0.001), ECOG-PS (PS 2: OR 1.86 (95% CI: 1.26-2.74), *p*=0.002; PS 3-4: OR 2.59 (95% CI: 1.48-4.55), *p*=0.001) and mGPS (mGPS 1: OR 1.72 (95% CI: 1.02-2.91), *p*=0.043; mGPS 2: OR 1.64 (95% CI: 1.09-2.48), *p*=0.017)(eTable 3).

On assessment of the relationship between muscle parameters and QoL (*n*=428), on univariate analysis low SMI was associated with poorer physical functioning (OR 1.72 (95% CI: 1.27-2.33), *p*<0.001) but not fatigue, appetite loss or summary QoL score (all *p*>0.05). However, on multivariate assessment (controlling for WL, ECOG-PS, mGPS, and low MA), low SMI was no longer associated with poorer physical functioning (OR 1.14 (95% CI: 0.74-1.73), *p*=0.555). On univariate analysis, low MA was associated with poorer physical function (OR 2.31 (95% CI: 1.69-3.18), *p*<0.001), fatigue (OR 1.66 (95% CI: 1.22-2.25), *p*=0.001), appetite loss (OR 1.94 (95% CI: 1.33-2.84), *p*=0.001) and poorer summary QoL score (OR 1.41 (95% CI: 1.03-1.92), *p*=0.032). However, after adjustment for % WL, ECOG-PS, mGPS, and low SMI, low MA was only independently associated with poorer physical functioning (OR 1.67 (95% CI: 1.09-2.56), *p*=0.018).

## DISCUSSION

Our study reports, for the first time, a comprehensive analysis of tumour and host factors and their effect on QoL in a large cohort of patients with incurable disease. Our finding indicate that QoL is determined (at least in part) by weight loss, performance status and the systemic inflammatory response in patients with advanced cancer. Muscle mass and attenuation were significantly associated with some QoL domains on univariate analysis, however, on multivariate analysis, there was no significant independent association with fatigue, appetite loss or QoL summary score. Our findings suggest that interventions to mitigate the systemic inflammatory response and weight loss in patients with incurable cancer might have a positive impact on patients QoL.

As expected, better ECOG-PS (scores 0-1) correlated with better physical, role, emotional and social functioning, global heath scores, and less fatigue, pain, anorexia and constipation (all $p<0.001$). Considering ECOG-PS is designed to determine a patient's ability to carry out activities of daily living and general well-being, it is no surprise that ECOG-PS is associated with items of the EORTC QLQ-C30, and this relationship has been reported previously.[8,29,30]

Our findings also demonstrate that the systemic inflammatory response, as evidenced by mGPS scores ≥1, is correlated with almost all EORTC functional and symptom scales. Furthermore, the mGPS was independently associated with physical functioning, fatigue, appetite loss and the QoL summary score. Our findings echo those previously reported in advanced cancer. Laird *et al.* reported that C-reactive protein was significantly associated with all of the functional components of the EORTC QLQ-C30, and a number of the symptoms including appetite loss, pain and fatigue.[31]

In some instances, individual cytokines implicated in the pro-inflammatory response have been associated with clinical symptoms e.g. Interleukin-6 (IL-6) and CRP with

anorexia[32], IL-1ra with fatigue[32] and IL-6 with major depression.[33,34] However, whether these cytokines exert their impact on symptoms in isolation or in combination is unclear. The reasons why systemic inflammation worsens QoL in patients with cancer has recently been reviewed[35] and evidence from a variety of preclinical and clinical studies suggest that the systemic inflammatory response has a direct role in the development of cancer associated symptom clusters including pain, fatigue, mood, anorexia and physical function.[35] Importantly, the effect of systemic inflammation on QoL was independent of ECOG-PS, consistent with previous reports that showed the systemic inflammatory response (mGPS) to be associated with poorer QoL even in those with a good performance score.[8] Research is warranted to determine if attenuating the systemic inflammatory response is capable of producing clinically relevant improvements in symptoms that may represent a new therapeutic approach to symptom management in patients with advanced cancer.

We report herein that WL was associated with poorer QoL in almost all functional and symptom domains. In particular WL in excess of 10% in the preceding 3 months was independently associated with poorer physical function, fatigue, appetite loss and overall poorer QoL summary score. Weight loss is a frequent manifestation of malnutrition and is an important criterion for the diagnosis of cancer cachexia, a multifactorial syndrome characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism[36]. In patients with cancer, cancer cachexia is often defined based on a single criterion, WL >5% over a period of 6 months. The adverse impact of WL on QoL has long been recognised in patients with cancer and WL has been associated with deterioration in patients' performance status and psychosocial well-being.[37-39] In a recent systematic review examining the impact of WL and QoL, a negative relationship between %WL and QoL was reported in 23 of the 27 studies included in the analysis.[11] However, the mode by which WL exerts its influence on QoL is not fully understood but may relate to muscle atrophy associated with cachexia and weight loss leading to fatigue or reduced

functional capacity.[40] Importantly, interventions aimed at targeting nutritional status and attenuating WL have proven successful in improving aspects QoL in patients with cancer.[41] In addition, novel cachexia treatments, such as Anamorelin, an oral ghrelin-receptor agonist with appetite enhancing and anabolic activity have shown a favourable clinical response in alleviating anorexia-cachexia symptoms.[42,43]

When examining the impact of muscle parameters and QoL outcomes, low SMI was associated with poorer physical function and more insomnia, while low MA was correlated with poorer physical function, role function, global health and summary QoL and also with more fatigue and dyspnoea (all $p<0.05$). Low MA was independently associated with poorer EORTC reported physical functioning [HR 1.67 (95% CI: 1.09-2.56), $p=0.018$], whereas low SMI was not. This is consistent with previous reports that low MA is associated with physical functional impairments as evidenced by improvements in timed up and go, stair climb and walking.[44]. Inconsistent reports on this relationship between muscle parameters and QoL have been published in the literature.[10,12,45,46] Parsons and colleagues reported no significant associations between low SMI and symptom burden or functional life domains assessed by the MD Anderson Symptom Inventory (MDASI) in a cohort of 104 patients with advanced cancer.[45] However, in a study of 734 advanced lung cancer patients, low SMI was non-linearly associated with lower global QoL, physical function and role function, and associated with more symptoms (fatigue and pain), while low MA was associated with poor physical function and more dyspnoea.[10] Our findings may be explained by the fact that low SMI, at one time point, is not reflective of a dynamic measure of loss and may be influenced by patient's intrinsic level of muscularity. Within our study, the composition of WL, which influenced QoL was unknown, and perhaps losses of muscle over time may better reflect poor QoL. A growing body of evidence favours measures of muscle loss over time as prognostic of poor survival in patients with cancer compared with single point measurements. [47,48]

The strengths of this study include the collection of numerous variables measured with appropriate methods simultaneously in a relatively large sample of patients with incurable cancer. In addition, using the QoL summary score to examine differences in QoL can avoid problems that may arise with multiple testing when otherwise making comparisons based on the 15 outcomes generated by the EORTC-QLQ questionnaire[19]. However, study limitations are also present. The aetiology of QoL is extremely complex given the web of determinants that influence it, and although we accounted for a number of clinical and nutritional parameters, the list of variables examined was not exhaustive. Given the convenient recruitment strategy, patients may have been at different time points of their disease trajectory when QoL was assessed (81% received chemotherapy in the previous 4 weeks), in addition patients may have received prior treatments, and this may have influenced QoL scores.'

**Conclusion**

In summary, the findings herein provide evidence of the independent role of WL, ECOG-PS and systemic inflammation (mGPS) in predicting poorer physical functioning, more fatigue and appetite loss, and poorer overall QoL summary score in patients with incurable cancer. Our findings indicate potential targets for interventions aimed at safeguarding the QoL of patients with advanced cancer. Future work should focus on targeting the systemic inflammatory response, attenuating WL and improving performance status in patients with incurable cancer as a means of improving PROMs and reducing symptom burden.

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**Table 1** Demographic and clinical characteristics of patients included in this study

| | ***n* (%)** |
|---|---|
| **Sex** | |
| Male | 524 (51) |
| **Age (years)** | |
| <65, 65-74, >75 | 483 (47), 300 (29), 244 (2) |
| **Primary cancer** | |
| Gastrointestinal | 411 (40) |
| Lung | 266 (26) |
| Other* | 350 (34) |
| **Metastatic disease** | |
| Yes | 862 (87) |
| **Performance status (ECOG-PS)[a]** | |
| 0-1/ 2/ 3/ 4 | 575 (59), 292 (30), 96 (10), 16 (1) |
| **mGPS[b]** | |
| 0, 1, 2 | 353 (43), 139 (17), 329 (40) |
| **BMI (kg/m$^2$)[c]** | |
| <20.0, 20.0-24.9, 25-29.9, >30 | 122 (13), 348 (37), 299 (31), 180 (19) |
| **Weight loss (%)[d]** | |
| <5%, 5-10%, >10% | 674 (71), 143 (15), 134 (14) |
| **Sarcopenia[e]** | 192 (45) |
| **Low muscle attenuation[f]** | 223 (54) |

| **Quality of life domains (*n*=1000)** | **Mean (SD)** |
|---|---|
| **Functioning scales** | |
| Physical functioning | 68.4 (26.2) |
| Role functioning | 59.4 (35.8) |
| Emotional functioning | 79.4 (22.7) |
| Cognitive functioning | 79.2 (24.7) |
| Social functioning | 66.0 (31.9) |
| **Cancer-related symptom scales** | |
| Fatigue | 42.3 (28.6) |
| Nausea & vomiting | 13.6 (21.5) |
| Pain | 25.3 (31.3) |
| Dyspnoea | 24.3 (32.1) |
| Insomnia | 28.6 (33.6) |
| Anorexia | 27.3 (33.7) |
| Constipation | 21.0 (30.4) |
| Diarrhoea | 12.3 (23.8) |
| **Global health status** | 60.6 (24.1) |
| **Quality of life summary score** | 73.8 (18.1) |

[a]ECOG available in 979; [b]mGPS available in 821; [c]BMI available on 949; [d]%WL available in 951.
[e]CT scans available for muscle mass (sarcopenia) assessment in 428 patients
[f]Contrast enhanced CT image available for muscle attenuation assessment in 413 patients
ECOG, The Eastern Oncology Cooperative Group; mGPS, modified Glasgow Prognostic Score; BMI, Body Mass Index *Other group consists of Breast, Gynaecological, Genitourinary, Neurological, Haematological, Melanoma, Unknown primary and other

**Table 2** Relationship between clinical, nutritional and inflammatory parameters with EORTC-QLQ functional scales.

| Variable | *n* | Physical | | Role | | Emotional | | Cognitive | | Social | | Global health | | Summary QoL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value |
| **Sex** | | | | | | | | | | | | | | | |
| Male/female | 1027 | -.112 | **0.001** | -.028 | 0.379 | -.071 | **0.024** | -.049 | 0.121 | -.035 | 0.272 | .027 | 0.397 | -.080 | **0.012** |
| **Age (years)** | | | | | | | | | | | | | | | |
| <65/65-74/>75 | 1027 | -.143 | **0.001** | -.063 | **0.047** | .079 | **0.012** | -.011 | 0.724 | -.054 | 0.089 | -.058 | 0.065 | -.037 | 0.247 |
| **Metastatic disease** | | | | | | | | | | | | | | | |
| Yes/No | 994 | -.013 | 0.691 | -.034 | 0.286 | -.010 | 0.766 | -.031 | 0.339 | -.008 | 0.797 | -.005 | 0.871 | .003 | 0.927 |
| **ECOG-PS** | | | | | | | | | | | | | | | |
| 0-1/2/3/4 | 979 | -.577 | **0.001** | -.494 | **0.001** | -.255 | **0.001** | -.298 | **0.001** | -.334 | **0.001** | -.410 | **0.001** | -.500 | **0.001** |
| **mGPS** | | | | | | | | | | | | | | | |
| 0/1/2 | 821 | -.312 | **0.001** | -.272 | **0.001** | -.069 | 0.051 | -.163 | **0.001** | -.158 | **0.001** | -.276 | **0.001** | -.267 | **0.001** |
| **Weight loss (%)** | | | | | | | | | | | | | | | |
| <5/5-10/>10 | 952 | -.208 | **0.001** | -.216 | **0.001** | -.111 | **0.001** | -.147 | **0.001** | -.135 | **0.001** | -.207 | **0.001** | -.291 | **0.001** |
| **BMI (kg/m$^2$)** | | | | | | | | | | | | | | | |
| <20, 20-24.9, 25-29.9, >30 | 949 | .020 | 0.545 | .086 | **0.008** | .052 | 0.113 | .053 | 0.106 | .085 | **0.009** | .072 | **0.028** | .077 | **0.018** |
| **Low SMI** | | | | | | | | | | | | | | | |
| No/Yes | 428 | -.164 | **0.001** | -.070 | 0.149 | -.078 | 0.103 | -.026 | 0.592 | -.104 | 0.034 | -.052 | 0.282 | -.060 | 0.218 |
| **Low MA** | | | | | | | | | | | | | | | |
| No/Yes | 413 | -.244 | **0.001** | -.145 | **0.003** | .009 | 0.857 | -.006 | 0.902 | -.072 | 0.145 | -.175 | **0.001** | -.135 | **0.006** |

ECOG, Eastern Cooperative Oncology Group; mGPS, modified Glasgow Prognostic Score; BMI, Body Mass Index; SMI, Skeletal muscle index; MA, Muscle attenuation.

**Table 3** Relationship between clinical, nutritional and inflammatory parameters with EORTC-QLQ symptom scales.

| **Variable** | ***n*** | **Fatigue** | | **Nausea & Vomiting** | | **Pain** | | **Dyspnoea** | | **Insomnia** | | **Anorexia** | | **Constipation** | | **Diarrhoea** | | **Financial impact** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value | ρ | *p*-value |
| **Sex** | | | | | | | | | | | | | | | | | | | |
| Male/female | 1027 | .042 | 0.179 | .123 | **0.001** | .068 | **0.030** | .015 | 0.629 | .019 | 0.539 | .065 | 0.039 | .037 | 0.237 | .029 | 0.360 | -.022 | 0.481 |
| **Age (years)** | | | | | | | | | | | | | | | | | | | |
| <65/65-74/>75 | 1027 | .071 | **0.024** | -.041 | 0.189 | -.012 | 0.700 | .089 | **0.005** | -.060 | 0.059 | .040 | 0.203 | .073 | **0.020** | .011 | 0.735 | -.302 | **0.001** |
| **Metastatic disease** | | | | | | | | | | | | | | | | | | | |
| Yes/No | 994 | .008 | 0.794 | -.009 | 0.786 | -.057 | 0.076 | -.033 | 0.308 | -.023 | 0.477 | -.012 | 0.710 | .027 | 0.396 | .038 | 0.242 | -.073 | 0.023 |
| **ECOG-PS** | | | | | | | | | | | | | | | | | | | |
| 0-1/2/3/4 | 979 | .476 | **0.001** | .206 | **0.001** | .309 | **0.001** | .253 | **0.001** | .119 | **0.001** | .277 | **0.001** | .192 | **0.001** | .038 | 0.244 | -.017 | 0.601 |
| **mGPS** | | | | | | | | | | | | | | | | | | | |
| 0/1/2 | 821 | .248 | **0.001** | .147 | **0.001** | .207 | **0.001** | .199 | **0.001** | .033 | 0.346 | .210 | **0.001** | .095 | **0.007** | .011 | 0.760 | -.010 | 0.774 |
| **Weight loss (%)** | | | | | | | | | | | | | | | | | | | |
| <5/5-10/>10 | 952 | .232 | **0.001** | .198 | **0.001** | .167 | **0.001** | .110 | **0.001** | .117 | **0.001** | .311 | **0.001** | .123 | **0.001** | .064 | 0.051 | .057 | 0.082 |
| **BMI (kg/m$^{2)}$** | 94 | | | | | | | | | | | | | | | | | | |
| <20, 20-24.9, 25-29.9, >30 | 9 | -.072 | **0.027** | -.057 | 0.081 | -.025 | 0.438 | -.006 | 0.853 | .003 | 0.935 | -.167 | **0.001** | -.049 | 0.134 | -.056 | 0.084 | -.001 | 0.985 |
| **Low SMI** | | | | | | | | | | | | | | | | | | | |
| No/yes | 428 | .057 | 0.243 | -.040 | 0.413 | .035 | 0.473 | .012 | 0.806 | -.096 | **0.047** | -.033 | 0.490 | .032 | 0.513 | .020 | 0.682 | -.068 | 0.069 |
| **Low MA** | | | | | | | | | | | | | | | | | | | |
| No/Yes | 413 | .152 | **0.002** | -.049 | 0.323 | .054 | 0.277 | .150 | **0.002** | -.004 | 0.934 | .116 | 0.019 | .073 | 0.142 | -0.43 | 0.380 | -.184 | **0.001** |

ECOG, Eastern Cooperative Oncology Group; mGPS, modified Glasgow Prognostic Score; BMI, Body Mass Index. SMI, Skeletal muscle index; MA, Muscle attenuation.

**Table 4** Clinical, nutritional and inflammatory parameters related to poor QoL summary scores (below the mean <73.8) according to multivariable logistic regression analysis.

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | ***n*** | **OR** | **95% CI** | ***p* value** | **OR** | **95% CI** | ***p* value** |
| **Sex** | | | | | | | |
| Male | 510 | 1.00 | | | | | |
| Female | 490 | 1.35 | 1.05-1.73 | **0.019** | | | |
| **Age (years)** | | | | | | | |
| <65 | 476 | 1.00 | | | | | |
| 65-74 | 289 | 0.95 | 0.71-1.27 | 0.730 | | | |
| >75 | 235 | 1.01 | 0.74-1.38 | 0.956 | | | |
| **Metastatic disease** | | | | | | | |
| No | 127 | 1.00 | | | | | |
| Yes | 842 | 1.11 | 0.76-1.61 | 0.597 | | | |
| **ECOG-PS** | | | | | | | |
| 0-1 | 572 | 1.00 | | | 1.00 | | |
| 2 | 283 | 4.22 | 3.11-5.72 | **<0.001** | 3.32 | 2.34-4.70 | **<0.001** |
| 3-4 | 97 | 16.56 | 8.42-32.58 | **<0.001** | 14.33 | 6.76-30.37 | **<0.001** |
| **mGPS** | | | | | | | |
| 0 | 349 | 1.00 | | | | | |
| 1 | 132 | 3.03 | 1.99-4.61 | **<0.001** | 2.05 | 1.26-3.32 | **0.004** |
| 2 | 313 | 2.73 | 1.99-3.75 | **<0.001** | 1.58 | 1.09-2.29 | **0.016** |
| **BMI (kg/m$^2$)** | | | | | | | |
| 20.0-24.9 | 348 | 1.00 | | | | | |
| <20 | 122 | 1.95 | 1.28-2.98 | **0.002** | | | |
| 25-29.9 | 299 | 0.81 | 0.59-1.12 | 0.205 | | | |
| >30.0 | 180 | 1.25 | 0.86-1.79 | 0.242 | | | |
| **Weight loss (%)** | | | | | | | |
| <5% | 671 | 1.00 | | | | | |
| 5-10% | 140 | 2.17 | 1.50-3.15 | **<0.001** | 1.59 | 1.01-2.52 | **0.048** |
| >10% | 126 | 4.85 | 3.11-7.54 | **<0.001** | 2.69 | 1.63-4.42 | **<0.001** |

OR, odds ratio; CI, confidence interval; mGPS, modified Glasgow Prognostic Score; BMI, body mass index.

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**eTable 1.** Clinical, nutritional and inflammatory parameters related to poorer physical function (below the mean <68.4) according to multivariable logistic regression analysis.

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | ***n*** | **OR** | **95% CI** | ***p* value** | **OR** | **95% CI** | ***p* value** |
| **Sex** | | | | | | | |
| Male | 510 | 1.00 | | | 1.00 | | |
| Female | 490 | 1.52 | 1.18-1.95 | **0.001** | 1.56 | 1.10-2.19 | **0.011** |
| **Age (years)** | | | | | | | |
| <65 | 476 | 1.00 | | | | | |
| 65-74 | 289 | 1.34 | 0.99-1.79 | 0.052 | | | |
| >75 | 235 | 1.97 | 1.97-2.71 | **<0.001** | | | |
| **Metastatic disease** | | | | | | | |
| No | 127 | 1.00 | | | | | |
| Yes | 842 | 0.94 | 0.64-1.36 | 0.726 | | | |
| **ECOG-PS** | | | | | | | |
| 0-1 | 572 | 1.00 | 3.83-7.06 | | 1.00 | | |
| 2 | 283 | 5.19 | 14.48- | **<0.001** | 3.93 | 2.77-5.58 | **<0.001** |
| 3-4 | 97 | 30.52 | 64.32 | **<0.001** | 18.07 | 7.91-41.28 | **<0.001** |
| **mGPS** | | | | | | | |
| 0 | 349 | 1.00 | | | 1.00 | | |
| 1 | 132 | 2.25 | 1.50-3.38 | **<0.001** | 1.46 | 0.89-2.38 | 0.136 |
| 2 | 313 | 3.29 | 2.39-4.52 | **<0.001** | 2.01 | 1.39-2.93 | **<0.001** |
| **BMI (kg/m$^2$)** | | | | | | | |
| 20.0-24.9 | 348 | 1.00 | | | | | |
| <20 | 122 | 1.87 | 1.26-2.86 | **0.004** | | | |
| 25-29.9 | 299 | 0.91 | 0.66-1.25 | 0.565 | | | |
| >30.0 | 180 | 1.35 | 0.94-1.95 | 0.106 | | | |
| **Weight loss (%)** | | | | | | | |
| <5% | 671 | 1.00 | | | 1.00 | | |
| 5-10% | 140 | 1.61 | 1.11-2.32 | **0.011** | 1.03 | 0.64-1.65 | 0.910 |
| >10% | 126 | 3.12 | 2.09-4.64 | **<0.001** | 1.92 | 1.16-3.19 | **0.039** |

OR, odds ratio; CI, confidence interval; mGPS, modified Glasgow Prognostic Score; BMI, body mass index.

**eTable 2.** Clinical, nutritional and inflammatory parameters related to fatigue (above mean 42.3) according to multivariable logistic regression analysis.

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | ***n*** | **OR** | **95% CI** | ***p* value** | **OR** | **95% CI** | ***p* value** |
| **Sex** | | | | | | | |
| Male | 510 | 1.00 | | | | | |
| Female | 490 | 1.19 | 0.93-1.52 | 0.178 | | | |
| **Age (years)** | | | | | | | |
| <65 | 476 | 1.00 | | | | | |
| 65-74 | 289 | 0.99 | 0.75-1.34 | 0.996 | | | |
| >75 | 235 | 1.33 | 0.97-1.82 | 0.076 | | | |
| **Metastatic disease** | | | | | | | |
| No | 127 | 1.00 | | | | | |
| Yes | 842 | 1.04 | 0.72-1.51 | 0.840 | | | |
| **ECOG-PS** | | | | | | | |
| 0-1 | 572 | 1.00 | | | 1.00 | | |
| 2 | 283 | 4.09 | 3.04-5.53 | **<0.001** | 2.89 | 2.06-4.07 | **<0.001** |
| 3-4 | 97 | 26.14 | 12.4-54.9 | **<0.001** | 18.67 | 7.79-44.7 | **<0.001** |
| **mGPS** | | | | | | | |
| 0 | 349 | 1.00 | | | 1.00 | | |
| 1 | 132 | 2.00 | 1.34-3.01 | **0.001** | 1.28 | 0.79-2.06 | 0.307 |
| 2 | 313 | 2.70 | 1.98-3.69 | **<0.001** | 1.57 | 1.09-2.25 | **0.001** |
| **BMI (kg/m$^2$)** | | | | | | | |
| 20.0-24.9 | 348 | 1.00 | | | | | |
| <20.0 | 122 | 1.67 | 1.09-2.54 | **0.017** | | | |
| 25-29.9 | 299 | 0.76 | 0.56-1.04 | 0.088 | | | |
| >30.0 | 180 | 1.09 | 0.76-1.57 | 0.625 | | | |
| **Weight loss (%)** | | | | | | | |
| <5% | 671 | 1.00 | | | 1.00 | | |
| 5-10% | 140 | 1.65 | 1.15-2.38 | **0.007** | 1.09 | 0.69-1.71 | 0.704 |
| >10% | 126 | 3.93 | 2.59-5.95 | **<0.001** | 2.53 | 1.53-4.19 | **<0.001** |

OR, odds ratio; CI, confidence interval; mGPS, modified Glasgow Prognostic Score; BMI, body mass index.

**eTable 3.** Clinical, nutritional and inflammatory parameters related to more appetite loss (above mean 27.3) according to multivariable logistic regression analysis.

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | ***n*** | **OR** | **95% CI** | ***p* value** | **OR** | **95% CI** | ***p* value** |
| **Sex** | | | | | | | |
| Male | 510 | 1.00 | | | | | |
| Female | 490 | 0.86 | 0.64-1.15 | 0.300 | | | |
| **Age (years)** | | | | | | | |
| <65 | 476 | 1.00 | | | | | |
| 65-74 | 289 | 1.29 | 0.92-1.81 | 0.140 | | | |
| >75 | 235 | 1.43 | 0.99-2.05 | 0.052 | | | |
| **Metastatic disease** | | | | | | | |
| No | 127 | 1.00 | | | | | |
| Yes | 842 | 1.04 | 0.67-1.61 | 0.866 | | | |
| **ECOG-PS** | | | | | | | |
| 0-1 | 572 | 1.00 | | | 1.00 | | |
| 2 | 283 | 2.64 | 1.90-3.66 | **<0.001** | 1.86 | 1.26-2.74 | **0.002** |
| 3-4 | 97 | 4.45 | 2.85-6.96 | **<0.001** | 2.59 | 1.48-4.55 | **0.001** |
| **mGPS** | | | | | | | |
| 0 | 349 | 1.00 | | | 1.00 | | |
| 1 | 132 | 2.33 | 1.48-3.67 | **<0.001** | 1.72 | 1.02-2.91 | **0.043** |
| 2 | 313 | 2.41 | 1.69-3.44 | **<0.001** | 1.64 | 1.09-2.48 | **0.017** |
| **BMI (kg/m$^2$)** | | | | | | | |
| 20.0-24.9 | 348 | 1.00 | | | 1.00 | | |
| <20.0 | 122 | 1.67 | 1.07-2.59 | **0.024** | 1.35 | 0.80-2.29 | 0.258 |
| 25-29.9 | 299 | 0.54 | 0.37-0.79 | **0.002** | 0.63 | 0.40-0.99 | **0.046** |
| >30.0 | 180 | 0.63 | 0.41-0.99 | **0.045** | 0.71 | 0.43-1.18 | 0.182 |
| **Weight loss (%)** | | | | | | | |
| <5% | 671 | 1.00 | | | 1.00 | | |
| 5-10% | 140 | 3.28 | 2.20-4.88 | **<0.001** | 2.38 | 1.51-3.76 | **<0.001** |
| >10% | 126 | 4.24 | 2.83-6.36 | **<0.001** | 2.51 | 1.58-3.99 | **<0.001** |

OR, odds ratio; CI, confidence interval; mGPS, modified Glasgow Prognostic Score; BMI, body mass index.