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Predictors and trajectory of performance status in patients with advanced cancer: A secondary data analysis of the international European Palliative Care Cancer Symptom study

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Abstract

Background: Performance status, a predictor of cancer survival, and ability to maintain independent living deteriorate in advanced disease. Understanding predictors of performance status trajectory could help identify those at risk of functional deterioration, target support for independent living and reduce service costs. The relationship between symptoms, analgesics and performance status is poorly delineated.

Aim: The aim of this study is to determine whether demographics, analgesics, disease characteristics, quality-of-life domains and C-reactive protein predict the trajectory of Karnofsky Performance Status (KPS) in patients with advanced cancer.

Design: The study design is the secondary data analysis of the international prospective, longitudinal European Palliative Care Cancer Symptom study (ClinicalTrials.gov: NCT01362816). A multivariable regression model was built for KPS area under the curve per day (AUC).

Setting and participants: This included adults with advanced, incurable cancer receiving palliative care, without severe cognitive impairment and who were not imminently dying ($n = 1739$).

Results: The mean daily KPS AUC ($n = 1052$) was 41.1 (standard deviation = 14.1). Opioids ($p < 0.001$), co-analgesics ($p = 0.023$), poorer physical functioning ($p < 0.001$) and appetite loss ($p = 0.009$) at baseline were explanatory factors for lower KPS AUC. A subgroup analysis of participants with C-reactive protein data ($n = 240$) showed that only C-reactive protein ($p = 0.040$) and physical function ($p < 0.001$) were associated with lower KPS AUC.

Conclusion: This study is novel in determining explanatory factors for subsequent functional trajectories in an international dataset and identifying systemic inflammation as a candidate therapeutic target to improve functional performance. The effect of interventions targeting physical function, appetite and inflammation, such as those used for cachexia management, on maintaining functional status in patients with advanced cancer needs to be investigated.

Keywords

Karnofsky Performance Status, appetite, inflammation, neoplasms, opioids, analgesics

What is already known about the topic?

- Performance status and ability to maintain independent living deteriorate in advanced disease and are associated with cancer survival.
- Palliative care interventions may help support independent living and reduce health and social care costs.
- The relationships between symptoms, analgesics and performance status are poorly delineated.

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What this paper adds?

- Opioids, co-analgesics, poorer physical functioning and appetite loss at baseline were associated with a lower Karnofsky Performance Status over time.
- In a subgroup analysis which included C-reactive protein, only this and physical function were associated with a lower Karnofsky Performance Status over time.
- This study identifies systemic inflammation as a candidate therapeutic target to improve functional performance.

Implications for practice, theory or policy

- A thorough assessment of clinical and patient-reported data is needed to identify and subsequently manage issues potentially leading to a deteriorating performance status.
- The effect of interventions to improve physical function, appetite and inflammation, such as those used for cachexia management, on maintaining functional status in patients with advanced cancer needs to be investigated.
- Further research assessing this association and the impact of managing systemic inflammation on clinical outcomes is needed.

Introduction

Performance status is an independent predictor of cancer survival.[1–5] It is often impaired in patients with advanced disease.[4] Performing activities of daily living is an important patient priority; minimising burden on others was 'very important' for 89% patients.[6] Symptoms negatively impact function.[7,8] Pain is associated with decreased Karnofsky Performance Status (KPS).[9] Better symptom management could improve performance status. However, longitudinal data exploring the association between symptoms, analgesics and performance status are limited. Understanding predictors of performance status could help identify those at risk of deterioration, so palliative interventions can be planned.[10,11] If such interventions help maintain function sufficient for independent community-based living, health and social care costs could be reduced.[12] KPS is a measure of overall function (including impact of psychosocial factors), allowing patients to be classified according to their functional impairment.[13] C-reactive protein (CRP), as a marker of inflammation, has been associated with poorer performance.[14]

Aim

The aim of this study is to explore whether demographics, analgesics, disease characteristics and the palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core15 (EORTC QLQ-C15-PAL) items at baseline predict KPS trajectory in patients with advanced cancer and the effect of CRP on these relationships. Our null hypothesis is that there is no relationship between these variables and performance status over time.

Methods

Study design

The study design is the secondary data analysis of the prospective, longitudinal, multi-site European Palliative Care Cancer Symptom study (ClinicalTrials.gov: NCT01362816), which recruited from April 2011 to October 2013.[15] Detailed study methods have been published.[15] Eligible participants were consenting adults ($\geqslant$18 years) with advanced, incurable cancer receiving palliative care, not imminently dying and scoring $\geqslant$4/8 on the four-item Mini–Mental State Examination. Data registration consisted of registration of patients' medical data by healthcare providers, and patient self-reported data on key sociodemographic items: age, sex and living situation and questions about common cancer-related symptoms, quality of life and functional status. Assessments were performed upon study inclusion and monthly $\pm$1-week follow-up, either at hospital or by mailed postal questionnaires, for at least 6 months if possible.[15]

In total, the dataset included 1739 patients. The baseline characteristics have been published previously.[15] This analysis uses the full dataset, and records with occasional missing values for single variables were retained. Table 1 shows data collected at each visit.

Statistical analyses

The characteristics of the patients are presented for the baseline assessment using mean and standard deviation (SD), minimum and maximum, or *n* (%).

The dependent outcome measure was area under the curve (AUC) for performance status using KPS. All serial measurements of KPS were plotted against time. AUC from entry to the study to death (KPS of zero assigned) was calculated using the trapezoid rule.[17] The summary score for KPS was expressed as the total area under the KPS curve from study entry until death, divided by the total number of days represented (KPS AUC per day), thereby reflecting average but not actual daily scores.

To compare mean KPS AUC per day and categorical variables (sex, location, cancer stage and analgesics), two-tailed Student's *t*-tests or analysis of variance (ANOVA) tests were used. Pearson's correlations were used for age and the EORTC QLQ-C15-PAL scales and items. Candidate

Table 1. Data collected at each assessment visit.

Collected by healthcare providers	Self-reported patient measures

• Patient location: inpatient, day care/outpatient, home
• Karnofsky Performance Status (KPS): 0%–100%; 100 is 'perfect' health and 0 is dead
• Analgesic use (yes/no), for non-opioid analgesics, opioids and co-analgesics
  ○ Co-analgesics were defined as drugs that are not designed to manage pain per se, but which has effects that can help reduce the pain, for example, antidepressants and anticonvulsants
  ○ Non-opioid analgesics included paracetamol and non-steroidal anti-inflammatory drugs.
• C-reactive protein (CRP)
	The palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–15 (EORTC QLQ-C15-PAL).[16] Item scored from 1 'not at all' to 4 'very much' and was transformed to a 0–100 scale
	• Functional items: high score means a good function or quality of life
	  ○ Physical functioning
	  ○ Emotional functioning
	  ○ Global quality of life
	• Symptom items: high score indicates more severe symptoms
	  ○ Fatigue
	  ○ Nausea/vomiting
	  ○ Pain
	  ○ Dyspnoea
	  ○ Sleep disturbances
	  ○ Appetite loss
	  ○ Constipation

predictors were chosen if there was a plausible biological and knowledge-based rationale between cause and outcome (e.g. have a relationship between cause and outcome based on existing knowledge). Univariable and multivariable regression models were used to explore further the relationships between KPS AUC per day with β (standard error (SE)), as well as the *p*-value for each predictor presented. Candidate predictors associated at the $p < 0.2$ level at univariable analysis, and/or with a plausible biological rationale, were included in the multivariable model in this exploratory analysis. A subgroup analysis of participants with CRP data ($n = 240$) was performed. All analyses were undertaken on STATA SE (StataCorp 2015, Stata Statistical Software: Release14; StataCorp LP, College Station, TX).

Ethical approval

Ethical approval was obtained at each European Palliative Care Cancer Symptom study recruiting site. The Regional Research Ethics Committee in Medicine, Central Norway, evaluated and accepted the project on 26 November 2010. The study was performed according to the Declaration of Helsinki. No further ethical approval was necessary for this secondary analysis of anonymised data (http://www.hra.nhs.uk).

Results

Patient characteristics

At baseline, 1739 patients were included (65.8 years (SD = 12.4 years), range = 21–97 years; men 50%). Baseline characteristics are shown in Table 2. At baseline, the mean KPS score was available for 1724 patients. The mean KPS score at baseline was 67.0 (16.5), and 719 (42%) had a performance status <70%. The last recorded KPS values showed a mean KPS of 62.8 (18.2) and 895/1730 (52%) had performance status below 70%.

During the study, 1090 patients died (25 with no documented date of death). The characteristics of these patients are shown in Table 2. AUC was calculated for 1052 patients, where baseline KPS was recorded. The mean KPS AUC per day was 41.1 (14.1) and data were normally distributed. Mean KPS AUC per day was lower for those with baseline KPS <70% (33.3 (11.9)) than those scoring ⩾70% (49.0 (11.6), $p < 0.001$). Similarly, mean KPS AUC per day at their last study visit was lower for those with KPS <70% (36.5 (13.0)) than those scoring ⩾70% (49.0 (12.3), $p < 0.001$).

Table 3 shows a univariable analysis of baseline characteristics and mean (SD) KPS AUC per day. Increasing age was associated with lower KPS AUC per day ($r = -0.153$, $p < 0.01$). The mean KPS AUC per day was lower for those who were an inpatient and used any opioid, non-opioid analgesic and co-analgesic at baseline. However, higher mean KPS AUC per day was seen in those with metastatic/disseminated disease at baseline compared to local/locally advanced.

Table 4 shows the correlations between EORTC QLQ-C15-PAL items and KPS AUC per day; the strongest correlation was for physical functioning ($r = 0.539$). Except nausea/vomiting, more severe symptoms were correlated with lower KPS AUC per day.

Table 5 shows the univariable and multivariable analyses. Older age ($p = 0.004$), opioids ($p < 0.001$), co-analgesics ($p = 0.023$), lower levels of physical functioning ($p < 0.001$) and more severe appetite loss ($p = 0.009$) at baseline remained as independent explanatory factors for reduced KPS AUC over time. Together these factors explained 34.8% (R^2 of final model) of the relationship, indicating that other variables are important.

Table 2. Descriptive characteristics at baseline.

		Total Mean (SD), min–max, *n* (%)	Patients with CRP at baseline Mean (SD), min–max, *n* (%)	Patients who died Mean (SD), min–max, *n* (%)
Age (years)		65.8 (12.4), 21–97 *n* = 1739	67.3 (12.1) *n* = 240	66.6 (12.5), 23–97 *n* = 1052
Sex	Female	871 (50%)	101 (42%)	478 (45%)
	Male	866 (50%)	139 (58%)	574 (55%)
	Missing	2	0	0
Stage	Metastatic/ disseminated	1437 (84%)	219 (91%)	887 (84%)
	Local/locally advanced	284 (16%)	21 (9%)	163 (16%)
	Missing	18	0	2
Location of care	Inpatient	365 (21%)	105 (44%)	275 (27%)
	Day care	1026 (61%)	92 (38%)	595 (58%)
	Home	300 (18%)	36 (15%)	154 (15%)
	Missing	48	7	28
Non-opioid analgesics	Yes	808 (47%)	103 (43%)	552 (53%)
	No	896 (53%)	134 (57%)	486 (47%)
	Missing	35	3	14
Opioids	Yes	1012 (59%)	136 (58%)	677 (65%)
	No	694 (41%)	99 (42%)	361 (35%)
	Missing	33	5	14
Co-analgesics	Yes	410 (24%)	41 (17%)	257 (25%)
	No	1279 (76%)	194 (83%)	768 (75%)
	Missing	50	5	27
CRP		55.0 (77.7), 0–379, *n* = 240	55.0 (77.7), 0–379, *n* = 240	65.8 (77.9), 1–379, *n* = 185
KPS		67.0 (16.5), 10–100, *n* = 1724	63.9 (18.7), 20–100, *n* = 239	63.8 (16.2), 10–100, *n* = 1052
EORTC QLQ-C15-PAL				
Physical functioning		64.8 (29.2), 0–100, *n* = 1698	56.1 (30.5), 0–100, *n* = 232	59.7 (29.6), 0–100, *n* = 1021
Emotional functioning		68.7 (23.9), 0–100, *n* = 1695	70.3 (26.2), 0–100, *n* = 232	69.5 (24.0), 0–100, n = 1019
Global quality of life		51.5 (26.3), 0–100, *n* = 1682	48.4 (27.2), 0–100, *n* = 229	49.5 (26.1), 0–100, *n* = 1009
Fatigue		50.0 (28.7), 0–100, *n* = 1700	53.6 (31.4), 0–100, *n* = 232	52.2 (28.6), 0–100, *n* = 1022
Nausea/vomiting		17.4 (27.4), 0–100, *n* = 1699	21.3 (29.6), 0–100, *n* = 232	18.6 (28.0), 0–100, *n* = 1021
Pain		38.3 (31.1), 0–100, *n* = 1700	43.6 (34.2), 0–100, *n* = 232	40.9 (31.5), 0–100, *n* = 1022
Dyspnoea		23.3 (28.9), 0–100, *n* = 1694	28.1 (31.0), 0–100, *n* = 231	26.7 (30.8), 0–100, *n* = 1018
Sleep disturbances		31.3 (28.9), 0–100, *n* = 1693	34.2 (33.8), 0–100, *n* = 231	30.8 (32.3), 0–100, *n* = 1019
Appetite loss		33.8 (34.8), 0–100, *n* = 1698	42.0 (37.3), 0–100, *n* = 232	36.8 (35.3), 0–100, *n* = 1021
Constipation		27.5 (31.8), 0–100, *n* = 1688	32.5 (34.7), 0–100, *n* = 228	30.0 (33.3), 0–100, *n* = 1012

SD: standard deviation; CRP: C-reactive protein; KPS: Karnofsky Performance Status; EORTC QLQ-C15-PAL: The Palliative Care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.

CRP subgroup analysis

In the subgroup analysis, the baseline characteristics of participants with CRP data (*n* = 240) are shown in Table 2. These patients were slightly older and there was a higher proportion male, with metastatic/disseminated disease, inpatient and lower KPS, compared to the whole sample. Only CRP and physical function were associated with change in KPS: lower physical functioning (β (SE) = 0.15 (0.04), $p < 0.001$) and CRP (β (SE) = −0.03 (0.01), $p = 0.040$). Opioids ($p = 0.114$), co-analgesics ($p = 0.187$) and severe appetite loss ($p = 0.078$) were not significant. The R^2 value of this model was 34.0%.

Discussion

Summary of main findings

These data indicate that older age (β (SE) = −0.09 (0.32), $p = 0.004$); opioids use (β (SE) = −3.63 (0.89), $p < 0.001$); co-analgesics use (β (SE) = −2.04 (0.90), $p = 0.023$); poorer physical function, where a high score means a good physical function (β (SE) = 0.19 (0.03), $p < 0.001$); and appetite loss at baseline, where a high score indicates more severe symptoms (β (SE) = −0.03 (0.01), $p = 0.009$) were independent predictors of worse KPS over time in patients with advanced cancer. A CRP subgroup analysis showed

Table 3. Karnofsky Performance Status area under the curve per day by baseline characteristics.

Baseline characteristics		Mean (SD)	*N*	*p*-Value
Sex	Female	41.4 (13.6)	478	0.434
	Male	40.8 (14.6)	574	
Stage	Local/locally advanced	38.9 (13.1)	163	**0.036**
	Metastatic/disseminated	41.5 (14.3)	887	
Location of care	Inpatient	33.4 (12.9)	275	**<0.001**
	Day care	46.0 (12.4)	595	
	Home	35.9 (14.6)	154	
Non-opioid analgesics	Yes	41.1 (13.5)	552	**0.045**
	No	41.3 (14.8)	486	
Opioids	Yes	38.9 (13.4)	677	**<0.001**
	No	45.4 (14.6)	361	
Co-analgesics	Yes	39.1 (12.9)	257	**0.004**
	No	42.0 (14.5)	768	

SD: standard deviation.
The total number of participants included for each characteristic is variable due to missing data.
p-Values that reached statistical significance are in bold.

Table 4. Correlations between EORTC QLQ-C15-PAL items and Karnofsky Performance Status area under the curve per day.

EORTC QLQ-C15-PAL	Correlation	*N*	*p*-Value
Physical functioning	0.539	1021	**<0.001**
Emotional functioning	0.216	1019	**<0.001**
Global quality of life	0.242	1009	**<0.001**
Fatigue	−0.315	1022	**<0.001**
Nausea/vomiting	−0.031	1021	0.326
Pain	−0.209	1022	**<0.001**
Dyspnoea	−0.151	1018	**<0.001**
Sleep disturbances	−0.076	1019	**0.015**
Appetite loss	−0.255	1021	**<0.001**
Constipation	−0.177	1012	**<0.001**

EORTC QLQ-C15-PAL: The Palliative Care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.
p-Values that reached significance are in bold.

that this inflammatory marker was statistically significant at explaining worse performance. In this model, only CRP and physical function remained significantly associated with deteriorating KPS. In both models, two-thirds of the variability was unexplained. KPS incorporates a much broader construct than physical function alone, also consisting of mental and behavioural approaches and social support.

The only statistically significant symptom remaining in the final model in the whole dataset was loss of appetite. This is consistent with the findings of the CRP sub-analysis. In a Japanese secondary data analysis, increased CRP was associated with more physician-rated symptoms (fatigue, anorexia and weight loss dyspnoea) and poorer activities of daily living were observed in advanced cancer patients receiving palliative care.[14] Although this study primarily looked for associations with KPS, there are similarities in the findings, notably the association of CRP with cancer-cachexia symptoms and ability to perform everyday tasks. Inflammation could act as a uniting pathophysiological process for analgesics, poorer physical function and loss of appetite. Inflammatory cancers are more painful.[18,19] Inflammatory cytokines mediate cancer cachexia with accompanying anorexia and loss of skeletal muscle mass with reduction in physical function and worse prognosis.[20,21] Inflammation leading to fatigue decreases exercise capacity and movement, exacerbating skeletal muscle loss.[22] There is a need to detect cancer-related cachexia early, and have a multimodal approach, to maintain function for as long as possible.[23]

Implications for practice

This study was an exploratory analysis to indicate patients at risk of deterioration in performance status, and targets for intervention to ameliorate this decline. These data suggest that attention to the inflammatory state with accompanying anorexia cachexia, including regular weight measurement and appetite assessment and nutritional status, is important in this context.

Limitations

This was a large European prospective cohort study; as it was an observational study, only associations (not causation) can be determined. Although consecutive patients were recruited, those with cognitive impairment were excluded. Some of the statistical associations had small effect sizes and are unlikely to be clinically relevant, as reported in a previous study.[8] Pro-inflammatory cytokines, acute infections and acute medical conditions influence CRP levels. The associations found in the subgroup analysis need to be examined in a larger group.

Table 5. Regression for Karnofsky Performance Status area under the curve per day.

	Univariable		Multivariable	
	β (SE)	*p*-Value	β (SE)	*p*-Value
Age	–0.17 (0.03)	<0.001	–0.09 (0.32)	**0.004**
Sex (female)	0.69 (0.87)	0.434	0.64 (0.75)	0.393
Stage (local/locally advanced)	–2.52 (1.2)	0.036	–1.17 (1.04)	0.260
Location of care				
Inpatient	–2.51 (0.30)	0.053	1.02 (1.23)	0.409
Day care	10.07 (1.16)	<0.001	5.10 (1.14)	<**0.001**
Home	Reference		Reference	
Non-opioid (yes)	–0.19 (0.88)	0.832	1.03 (0.76)	0.180
Opioid (yes)	–6.48 (0.90)	<0.001	–3.63 (0.89)	<**0.001**
Co-analgesic (yes)	–2.89 (1.01)	0.004	–2.04 (0.90)	**0.023**
EORTC QLQ-C15-PAL				
Physical functioning	0.25 (0.01)	<0.001	0.19 (0.03)	<**0.001**
Emotional functioning	0.13 (0.02)	<0.001	0.01 (0.02)	0.906
Global quality of life	0.13 (0.02)	<0.001	0.01 (0.02)	0.434
Fatigue	–0.15 (0.01)	<0.001	–0.01 (0.02)	0.428
Nausea/vomiting	–0.02 (0.02)	0.326		
Pain	–0.10 (0.01)	<0.001	0.01 (0.02)	0.951
Dyspnoea	–0.07 (0.01)	<0.001	–0.01 (0.01)	0.870
Sleep disturbances	–0.03 (0.01)	0.015	0.02 (0.01)	0.170
Appetite loss	–0.10 (0.01)	<0.001	–0.03 (0.01)	**0.009**
Constipation	–0.07 (0.01)	<0.001	–0.01 (0.01)	0.724

SE: standard error; EORTC QLQ-C15-PAL: The Palliative Care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.
p-Values that reached statistical significance in the multivariable analysis are in bold.

Conclusion

This secondary data analysis of the European Palliative Care Cancer Symptom study data set of adults with advanced, incurable cancer showed an association of lower average daily KPS with opioids, co-analgesics, lower levels of physical functioning at baseline and appetite loss. A CRP subanalysis indicated that systemic inflammation has a role in performance status and may be a useful therapeutic target to help patients maintain function. Interventions targeting physical function, appetite and inflammation, such as those used for cachexia management, may help maintain KPS in people with advanced cancer. Further research assessing this association and the impact of managing systemic inflammation on clinical outcomes is needed.

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