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Clinical Cancer Research

Imaging, Diagnosis, Prognosis

Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System

Barry J. Laird[1,6], Stein Kaasa[1,3], Donald C. McMillan[7], Marie T. Fallon[6], Marianne J. Hjermstad[1,5], Peter Fayers[1], and Pal Klepstad[1,4,2]

Abstract

Purpose: In advanced cancer, oncological treatment is influenced by performance status (PS); however, this has limitations. Biomarkers of systemic inflammation may have prognostic value in advanced cancer. The study compares key factors in prognosis (performance status, patient-reported outcomes; PRO) with an inflammation-based score (Glasgow Prognostic Score, mGPS). A new method of prognosis in advanced cancer (combining performance status and mGPS) is tested and then validated.

Experimental Design: Two international biobanks of patients with advanced cancer were analyzed. Key prognostic factors [performance status, PROs (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30), and mGPS (using C-reactive protein and albumin concentrations)] were examined. The relationship between these and survival was examined using Kaplan–Meier and Cox regression methods, in a test sample before independent validation.

Results: Data were available on 1,825 patients (test) and 631 patients (validation). Median survival ranged from 3.2 months (test) to 7.03 months (validation). On multivariate analysis, performance status (HR 1.62–2.77) and mGPS (HR 1.51–2.27) were independently associated with, and were the strongest predictors of survival ($P < 0.01$). Survival at 3 months varied from 82% (mGPS 0) to 39% (mGPS 2) and from 75% (performance status 0–1) to 14% (performance status 4). When used together, survival ranged from 88% (mGPS 0, PS 0–1) to 10% (mGPS 2, performance status 4), $P < 0.001$.

Conclusion: A systemic inflammation-based score, mGPS, and performance status predict survival in advanced cancer. The mGPS is similar to performance status in terms of prognostic power. Used together, performance status and mGPS act synergistically improving prognostic accuracy. This new method may be of considerable value in the management of patients with advanced cancer. *Clin Cancer Res; 19(19); 5456–64. ©2013 AACR.*

Introduction

"How long have I got?" is often asked by patients when they are diagnosed with advanced cancer, however, prognosis in this setting is challenging. The prognostic value of tumor stage and pathologic characteristics is well defined in early-stage cancer. However, its value for prognosis in advanced disease is much diminished with a ceiling level reached as patients with metastatic disease vary widely in terms of prognosis. Poor prediction of likely outcome may result in suboptimal care, whereas reliable prognostic information may help guide clinicians to decide the appropriate cancer treatment.

In advanced cancer, measures of performance status [e.g., Karnofsky (KPS) or Eastern Cooperative Oncology Group (ECOG)] are used to guide appropriate oncological treatment (1). Although performance status (PS) is established as a valid prognostic tool, classifying this accurately in the clinic can be challenging. Performance status is based primarily on physical activity, and this is derived from the information received from the patient and/or carers. Patients may report their physical activity inaccurately while estimation of performance status can also vary between health professionals. Although performance status is the gold standard prognostic measure, it may not correlate fully with actual physical activity and functional status, and concerns remain about the reproducibility of performance status measures (2, 3).

Authors' Affiliations: [1]European Palliative Care Research Centre; [2]Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology; Departments of [3]Oncology and [4]Anaesthesiology and Emergency Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim; [5]Department of Oncology, Regional Centre for Excellence in Palliative Care, Oslo University Hospital, Oslo, Norway; [6]University of Edinburgh, Edinburgh; and [7]University of Glasgow, Glasgow, United Kingdom

Corresponding Author: Barry J. Laird, Edinburgh Cancer Research Centre (CRUK), University of Edinburgh, Edinburgh, EH4 2XR. Phone: 44-131-777-3504; Fax: 44-131-777-3564; E-mail: barry.laird@ed.ac.uk

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Despite extensive efforts, few other reliable prognostic factors have been identified in patients with advanced cancer, which can be used to guide treatment and care plans. There remains a continuing and urgent need to identify reliable and routinely available prognostic factors in patients with advanced cancer.

On the basis of a systematic review of the literature, Maltoni and colleagues proposed that there was good evidence for the prognostic value of performance status, the clinical symptoms (appetite loss/cachexia, cognitive function and dyspnea), and an elevated C-reactive protein (CRP) concentration (4). The values of performance status (5, 6), appetite loss (5, 7), primary tumor site (5), and dyspnea (6) in prognosis, have been substantiated further. In addition, patient-reported outcomes (PRO) from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30; including aspects mentioned previously) have been shown to be of use in prognosis (8–10).

These prognostic parameters have been extensively studied and in some cases prognostic scoring systems have been developed (11). However, limitations of prognostic markers are acknowledged, such as subjective measures (symptoms, clinical prediction, performance status) or assessing multiple parameters. Therefore, these are not incorporated into routine clinical practice (4). Performance status remains the gold standard and the most widely used parameter in prognosis in advanced cancer.

To date, the role of biomarkers of systemic inflammation in cancer prognosis, has largely been ignored in clinical practice (12, 13). Systemic inflammation has been shown to predict survival, independent of tumor stage and pathologic characteristics, in patients with a variety of common solid tumors (14). There are various parameters that can be used to measure systemic inflammation and one method, termed the Glasgow Prognostic Score (mGPS), uses a combination of CRP and albumin (Table 1) (15). In the mGPS, CRP is used as a positive marker of systemic inflammation, whereas albumin is both a negative marker of inflammation and a measure of lean (muscle) tissue.

The mGPS has been examined in more than 60,000 patients with cancer (including homogenized groups, e.g., lung cancer), has been shown to have independent prognostic value, and is superior to other markers of the

Table 1. Patient demographics—test sample and validation sample

Parameter	Test sample ($n = 1825$) *n* (%)	Validation sample ($n = 631$) *n* (%)
Age (≤65/65- 74/≥74 years)	1,014/509/302 (56/28/16)	368/148/115 (58/24/18)
Sex (M/F)	931/894 (51/49)	237/294 (53/47)
Country[a]		
Switzerland	109 (6)	61 (10)
Germany	248 (14)	0 (0)
Denmark	12 (1)	0 (0)
Australia	0 (0)	11 (2)
United Kingdom	284 (16)	52 (18)
Iceland	150 (8)	0 (0)
Austria	0 (0)	80 (13)
Italy	348 (19)	0 (0)
Norway	541 (30)	426 (68)
Sweden	133 (7)	0 (0)
Canada	0 (0)	1 (1)
Primary cancer site		
Breast	244 (13)	88 (14)
Urological	124 (7)	43 (7)
Gynaecologic	138 (8)	14 (2)
Prostate	223 (12)	69 (11)
Gastrointestinal	387 (21)	183 (29)
Haematologic	107 (6)	23 (4)
Head and Neck	90 (5)	15 (2)
Pulmonary	310 (17)	117 (19)
Others	202 (11)	79 (13)
Place of care		
Inpatient	1,510 (83)	437 (69)
Outpatient	315 (17)	194 (31)

[a]Where $n = 0$, study not recruiting in that country.

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systemic inflammatory response in cancer prognosis (16). However, work to date using the mGPS has not reported on patients near the end of life, which is a complex group and difficult to stratify, thus the usefulness of the mGPS in this group of patients is not clear. Furthermore, a comparison with gold standard prognostic markers (such as performance status) has not been carried out.

In a single-centre pilot study, examining the mGPS in 100 patients with advanced cancer (median survival 8 weeks), the mGPS was reported to have independent prognostic value (17). However, this cohort was small and the clinical use of the mGPS in conjunction with existing prognostic markers, such as performance status, remains to be established.

The hypothesis of the present study is that the mGPS may have a role either alone or in combination, with other prognostic markers, such as performance status in advanced cancer. In turn, more accurate prognostic information may complement clinical impression and allow anticancer therapy to be given more appropriately in patients with advanced cancer.

The present study had three aims: First, to compare the prognostic value of established clinical factors (such as performance status, symptom measures) with the systemic inflammation-based mGPS. Second, to assess whether performance status in combination with mGPS is more powerful than either alone. Finally, to assess both of these aspects in a test sample before validation in an independent sample.

Materials and Methods

Study population

Analysis was undertaken on two international biobanks of adult cancer patients; termed test sample and validation sample.

The test sample was a prospective data collection of patients with cancer from 2005–2008 in multiple centers, across 8 European Countries (18). Eligible patients were 18 years of age or more, had a cancer diagnosis, and were taking strong opioids for cancer pain (in keeping with the primary purpose of the data collection).

The validation sample was a prospective data collection of patients with cancer from 2008–2009 as part of the European Palliative Care Research Collaborative–Computerized Symptom Assessment Study (19). Eligible patients were 18 years of age with either metastatic or locally advanced disease.

In both studies, a convenience sample of patients was recruited from across the following settings: oncology wards, palliative care units/hospices, surgical wards, and outpatient departments. Patients who could not communicate in the primary language at the study center were excluded. All patents provided written informed consent and ethical approval was given.

Procedure and assessment

In both studies, patient demographics and performance status, primary cancer site, and presence of metastases were recorded. Symptom and quality-of-life variables were recorded using the EORTC QLQ-C30 version 3 (20). All variables other than financial difficulties were used. Cachexia was assessed using body mass index (BMI) as a surrogate measure (BMI<20kg/m^2; ref. 21).

Biomarkers

CRP and albumin were used as biomarkers of the inflammatory response and were taken by venous blood sampling at entry points to both studies. The limit of detection of CRP was less than 5mg/L, all samples (CRP and albumin) were analyzed at a central laboratory. The mGPS was calculated as follows:

- CRP $\leq$ 10mg/L = 0
- CRP > 10mg/L = 1
- CRP > 10mg/L and albumin < 35 g/L = 2

These cutoffs are based on previous studies examining the mGPS and not derived from the present analysis (16).

Statistical analysis

BMI and mGPS were grouped using the thresholds described above. EORTC QLQ-C30 scores were analyzed as discrete categories representing underlying continuous constructs (22). KPS was transformed as described by Ma and colleagues into ECOG performance status groupings, to simplify analysis and interpretation (23).

All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout.

The survival time, defined as the number of months from study entry until death, or censored if alive at follow-up date, was calculated. Survival curves were plotted using Kaplan–Meier methods and the log-rank test applied. Survival analysis was carried out using Cox proportional hazards model, and HRs were calculated. To allow for possible nonlinearity, performance status and mGPS were analyzed using dummy indicators to represent different categories of these two variables.

Multivariate survival analysis was conducted using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding P value had to be >0.10. Stratification by primary cancer site was undertaken in the survival analysis.

All analyses were done on the test sample before being undertaken on the validation sample. All analyses were conducted in SPSS Version 18.0 (SPSS Inc).

Results

Data were available on 1,825 patients in the test sample and 631 patients in the validation sample, across a total of 11 countries. Patient demographics are shown in Table 1. All patients had cancer with the most common primary cancer types being gastrointestinal, pulmonary cancer, and breast cancer.

Test sample: 1,524 patients (84%) had metastatic disease at study entry and 281(15.4%) were on active treatment

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(chemotherapy). The median age was 63 years (Interquartile range (IQR) 54–71) and 931 patients were male (51%). The median performance status (ECOG) was 2.0 (IQR 2–3). The minimum and median follow-up for survivors was 4.9 months and 30.5 months, respectively. At the time of cessation of data collection, 224 patients were alive and 1,601 had died. The median survival was 3.2 months (1.0–10.6).

Validation sample: All patients had metastatic or locally advanced cancer at study entry and 458 (72.6%) were on active treatment. The median age was 64 years (IQR 56–71) and 237 patients were male (53%). The median performance status (ECOG) was 2 (IQR (1–2). The minimum and median follow-up for survivors was 10.1 months and 14.7 months, respectively. At the time of cessation of data collection, 160 patients were alive and 471 had died. The median survival was 7.03 months (IQR 2.5–7.33).

The relationship between clinicopathological factors and survival is shown in Table 2.

Test sample

On univariate survival analysis, age ($P < 0.001$), cognitive function ($P < 0.001$), dyspnea ($P < 0.001$), appetite loss ($P = 0.002$), quality of life ($P < 0.001$), physical function ($P < 0.001$), role function ($P < 0.001$), fatigue ($P < 0.001$), BMI ($P = 0.007$), performance status (all $P < 0.01$) and mGPS ($P < 0.001$) were significantly associated with survival. No other EORTC QLQ-C30 variables were associated with survival. On multivariate survival analysis, the most highly predictive factors were performance status (HR 1.76–2.77, all $P < 0.001$) and mGPS (HR 1.62–2.05, all $P < 0.001$), and only dyspnea (HR 1.03, $P = 0.003$) added significant prognostic information about survival.

Validation sample

On univariate survival analysis, quality of life ($P = 0.043$), physical function ($P = 0.005$), emotional function ($P = 0.042$), pain ($P = 0.012$), BMI ($P = 0.015$), performance status (all $P < 0.001$), and mGPS (all $P < 0.001$) were significantly associated with survival. No other EORTC QLQ-C30 variables were associated with survival. On multivariate survival analysis, the most highly predictive factors were performance status (HR 1.62, $P = 0.001$) and mGPS (HR 1.51–2.27, all $P < 0.01$), and only quality of life (HR 0.99, $P = 0.015$), physical function (HR 0.99, $P < 0.01$),

Table 2. The relationship between clinicopathological factors and survival in patients with advanced cancer—test sample ($n = 1,825$) and validation sample ($n = 631$)

	Test sample					Validation sample				
		Univariate[b]		Multivariate[b]			Univariate[b]		Multivariate[b]	
	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≤65/65–74/≥74)	1,014/509/302	1.13 (1.05–1.21)	0.001			368/148/115	1.01 (0.88–1.14)	0.987		
Sex (male/female)	931/894	0.93 (0.82–1.06)	0.270			337/294	0.91 (0.73–1.14)	0.417		
Symptoms (EORTC QLQ-C30)[a]										
Cognitive function	1,529	0.96 (0.93–0.98)	<0.001			631	0.99 (0.99–1.00)	0.067		
Dyspnea	1,528	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.04)	0.002	631	1.01 (0.99–1.04)	0.565		
Appetite loss	1,531	1.02 (1.01–1.04)	0.002			631	1.00 (0.99–1.04)	0.836		
Quality of life	1,513	0.94(0.92–0.97)	<0.001			631	0.99 (0.99–1.00)	0.043	0.99 (0.99–0.99)	0.011
Physical functioning	1,533	0.89 (0.87–0.91)	<0.001			631	1.00 (0.99–1.03)	0.005	0.99 (0.98–1.00)	<0.001
Role functioning	1,525	0.93 (0.91–0.96)	<0.001			631	1.00 (0.99–1.03)	0.443		
Emotional functioning	1,528	0.98 (0.96–1.01)	0.157			631	1.06 (1.00–1.10)	0.042		
Social functioning	1,524	0.99 (0.97–1.01)	0.235			631	1.01 (1.01–1.05)	0.512		
Fatigue	1,531	1.05 (1.03–1.07)	<0.001			631	1.00 (0.99–1.04)	0.533		
Nausea and vomiting	1,537	1.01 (0.99–1.03)	0.237			631	1.04 (1.00–1.08)	0.118		
Pain	1,535	1.01 (0.99–1.03)	0.314			631	1.05 (1.01–1.08)	0.012	1.04 (1.00–1.09)	0.028
Insomnia	1,530	0.99 (0.98–1.01)	0.453			631	1.00 (0.99–1.02)	0.387		
Constipation	1,524	1.00 (0.98–1.01)	0.654			631	1.00 (0.99–1.00)	0.636		
Diarrhea	1,521	0.99 (0.97–1.01)	0.373			631	1.00 (0.99–1.00)	0.056		
BMI (<20/≥20)[c]	376/1403	0.84 (0.74–0.95)	0.007			104/527	0.73 (0.57–0.94)	0.015	0.76 (0.60–0.98)	0.031
Performance status (ECOG grouping)[d]										
P1 (ECOG 2)	713	1.21 (1.05–1.40)	0.007			262	1.58 (1.27–1.97)	<0.001		
P2 (ECOG 3)	549	1.98 (1.71–2.29)	<0.001	1.76 (1.50–2.06)	<0.001	83	3.74 (2.78–5.02)	<0.001	2.12 (1.48–3.04)	<0.001
P3 (ECOG 4)	179	3.61 (2.97–4.39)	<0.001	2.77 (2.17–3.52)	<0.001	13	3.75 (2.03–6.91)	<0.001		
mGPS[d]										
G1 (mGPS 1)	544	1.55 (1.32–1.84)	<0.001	1.62 (1.35–1.93)	<0.001	168	1.76 (1.39–2.22)	<0.001	1.58 (1.25–2.01)	<0.001
G_2 (mGPS 2)	1,004	2.01 (1.71–2.35)	<0.001	2.05 (1.72–2.44)	<0.001	177	2.41 (1.90–3.05)	<0.001	2.06 (1.62–2.63)	<0.001

[a]EORTC QLQ-C30 scores available on approximately 1,500 patients in test sample.

[b]HR expressed as per 10 unit change.

[c]BMI available on 1,779 patients in test sample.

[d]Using indicator variables.

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emotional function (HR 1.05, $P = 0.02$), pain (HR 1.05, $P = 0.004$), and diarrhea (HR 0.99, $P = 0.048$) added prognostic information about survival.

Performance status and mGPS independently predicted survival and were the strongest predictors of survival in the test sample. This was confirmed in the validation sample. Furthermore, performance status and mGPS were consistently similar across both datasets. EORTC PROs were not consistent prognostic factors across both datasets.

The relationship between mGPS, performance status, and survival in the test sample is shown in Fig. 1. Increasing mGPS was significantly associated with poorer survival ($P < 0.001$). Worsening performance status was associated with poorer survival ($P < 0.001$). These findings were supported in the validation sample (Fig. 2). Increasing mGPS was significantly associated with poorer survival ($P < 0.001$). Worsening performance status was associated with poorer survival ($P < 0.001$).

The relationship between the mGPS, performance status, and survival at 3 months in the test sample is shown in Table 3. Survival at 3 months varied from 82% (mGPS 0) to 39% (mGPS 2) and from 75% (PS 0–1) to 15% (PS 4). When used in combination, survival ranged from 88% (mGPS 0, PS 0–1) to 10% (mGPS 2, PS 4), $P < 0.001$. In all patients, using 3-month mortality as an endpoint, the area under the receiver operator curve was for mGPS: 0.667 (95% CI, 0.64–0.69; $P < 0.001$) and PS: 0.703 (95% CI, 0.68–0.73; $P < 0.001$).

The relationship between the mGPS, performance status, and survival at 3 months is confirmed in the validation sample, shown in Table 4. Survival at 3 months varied from 87% (mGPS 0) to 46% (mGPS 2) and from 88% (PS 0–1) to 23% (PS 4). When used in combination, survival ranged from 93% (mGPS 0, PS 0–1) to 18% (mGPS 2, PS 3), $P < 0.001$. In all patients, using 3-month mortality as an endpoint, the area under the receiver operator curve was for mGPS: 0.720 (95% CI, 0.67–0.77; $P < 0.001$) and PS: 0.717 (95% CI, 0.67–0.76; $P < 0.001$).

Discussion

The results of the present study show that perfomance status and the systemic inflammation-based score, the mGPS, are strong prognostic factors in advanced cancer. The mGPS independently predicts survival in patients with advanced cancer and this supports our pilot work examining the mGPS. Of particular interest, however, is that the mGPS performed similarly to performance status, in terms of survival prediction (based on HRs). Furthermore, the the use of the mGPS in isolation, and an approach combining mGPS and performance status, have been tested and validated, in two large independent datasets. These findings may have an impact in oncological practice.

Performance status has been shown to be an independent prognostic factor in patients with advanced cancer and remains the gold standard; a finding supported by the present study (5). The KPS was the first commonly used tool of this type, and more recently the ECOG performance status tool was developed and is very similar, but simpler, for quantifying the functional status of patients with cancer (1). However, one of the challenges when using performance status as a prognostic measure, is that it is subjective and may not be reproducible (2, 3). It is also difficult to categorize accurately in the busy clinical setting, relying heavily on patient-reported information.

In comparison, a prognostic tool such as the mGPS is more reproducible. If several clinicians were asked to rate performance status on a patient, there would be a degree of variability (2). When presented with CRP and albumin and asked to calculate an mGPS, there would be consensus.

The results of the present study place the mGPS in a favorable light. It is simple to calculate, inexpensive, standardized worldwide, and has been validated in primary operable cancer and now in advanced disease. It has been

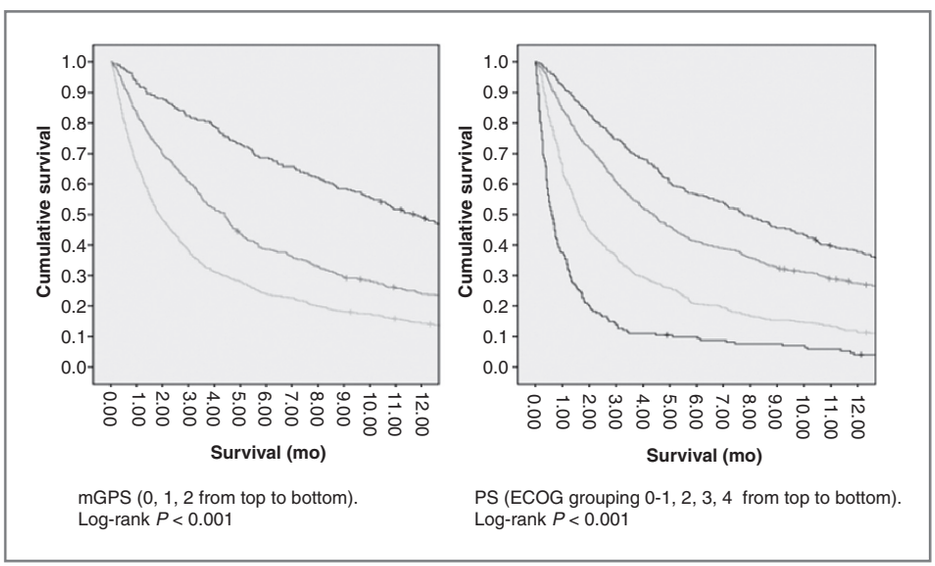

Figure 1. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Test sample ($n = 1,825$). Both mGPS and performance status predict survival $P < 0.001$.

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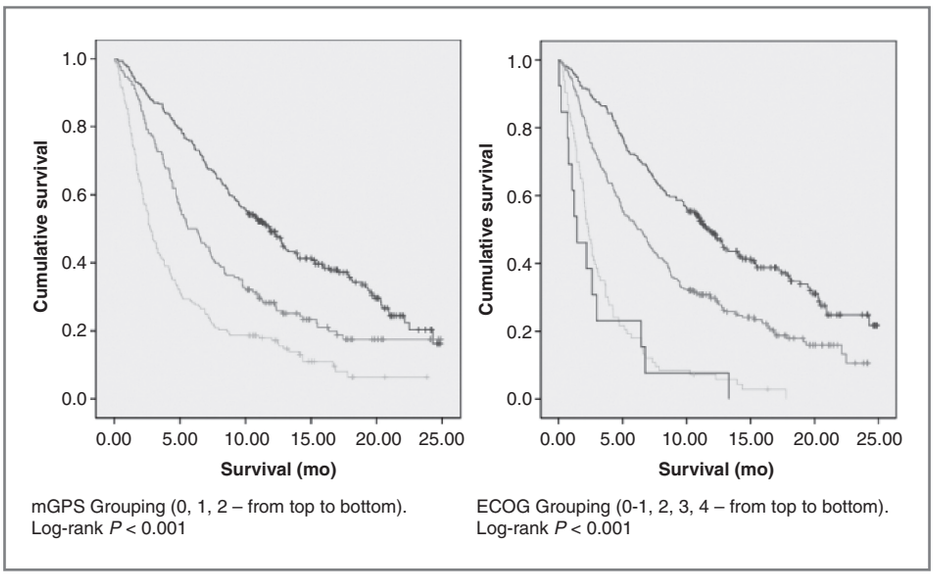

Figure 2. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Validation sample ($n = 631$). Both mGPS and performance status predict survival $P < 0.001$.

compared with other markers of the systemic inflammatory response [neutrophil lymphocyte ratio (24), platelet lymphocyte ratio (25), prognostic index (26)] and is a more powerful prognostic marker (27). Chechlinska and colleagues have proposed that "the systemic inflammatory response in patients with cancer frequently relates to clinical values and as such has prognostic value" but this is often overlooked (28). The present study addresses this by showing the usefulness of the mGPS as a marker of the systemic inflammatory response in cancer and prognosis. Furthermore, the findings support that the mGPS has independent prognostic value in a variety of clinical scenarios (including patients on chemotherapy) and is unlikely to be affected by this as few patients change their systemic inflammatory response status before or after treatment (29, 30).

The present study's findings are insufficient to support that performance status as a prognostic marker is superceded by the mGPS. Furthermore, biochemical markers should never dictate patient care with the adage of "treating the patient, not the results" never being more appropriate than in prognosis. However, performance status in combination with an objective score (such as the mGPS) is of interest and is more appropriate for clinical use, than isolated biomarkers. The present study shows that the mGPS can be used with performance status, and improves the accuracy of survival prediction of performance status alone as the combination effectively predicts survival at 3 months ranging from 88% to 10%. Therefore, this easy to obtain combination (mGPS-PS) may be a simple procedure that can be used to predict outcome in patients with advanced cancer.

Prognosis in cancer is an essential and currently unmet need; a crude artform based mostly on clinicians' intuition/experiences, which are often erroneous, optimistic, informal, and subjective (6). Improved prognostic accuracy may have several benefits in advanced cancer.

First, chemotherapy or radiotherapy is becoming increasingly commonplace late in the disease trajectory in advanced cancer: one study showed that 18.5% of patients were still receving chemotherapy within 2 weeks of death (31). However, the decision as to give such treatments is often challenging and is often made after careful discussion about possible risks and benefits with the patient, taking into consideration the likely prognosis. Clinician-predicted

Table 3. The relationship between the mGPS and performance status and the survival rate at 3 months in patients with advanced cancer ($n = 1825$)—test sample

Performance status (ECOG grouping)	mGPS 0 ($n = 277$)	mGPS 1 ($n = 544$)	mGPS 2 ($n = 1,004$)	mGPS 0–2 ($n = 1,825$)
0–1 ($n = 384$)	88 (3)% ($n = 102$)	78 (4)% ($n = 131$)	63 (4)% ($n = 151$)	75 (2)%
2 ($n = 713$)	84 (3)% ($n = 122$)	66 (3)% ($n = 243$)	49 (3)% ($n = 348$)	61 (2)%
3 ($n = 549$)	65 (7)% ($n = 49$)	43 (4)% ($n = 138$)	30 (2)% ($n = 362$)	36 (2)%
4 ($n = 179$)	($n = 4$)	28 (8)% ($n = 32$)	10 (2)% ($n = 143$)	15 (3)%
0–4 ($n = 1825$)	82 (2)%	61 (2)%	39 (2)%	52 (1)%

NOTE: Survival rate (SE)% at 3 months, not calculated if $n < 10$.

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Table 4. The relationship between the mGPS and performance status and the survival rate at 3 months in patients with advanced cancer ($n = 631$)—validation sample.

Performance status (ECOG grouping)	mGPS 0 ($n = 286$)	mGPS 1 ($n = 168$)	mGPS 2 ($n = 177$)	mGPS 0–2 ($n = 631$)
0-1 ($n = 273$)	93 (2)% ($n = 151$)	89 (4) ($n = 75$)	66 (7)% ($n = 47$)	88 (2)%
2 ($n = 262$)	87 (3)% ($n = 103$)	68 (5)% ($n = 79$)	52 (6)% ($n = 80$)	71 (3)%
3 ($n = 83$)	63 (9)% ($n = 27$)	58 (14)% ($n = 12$)	18 (6)% ($n = 44$)	39 (5)%
4 ($n = 13$)	($n = 5$)	($n = 2$)	($n = 6$)	23 (12)%
0–4 ($n = 631$)	87 (2)%	77 (3)%	46 (4)%	73 (2)%

NOTE: Survival rate (SE)% at 3 months, not calculated in $n < 10$.

survival remains suboptimal with one study of approximately 1,500 advanced patients showing that only one in four estimates of life expectancy by clinicians was accurate (32). Furthermore, patients prefer a realistic and individualized approach about prognosis in cancer to enable them to make decisions about having treatment (33, 34). The findings of the present study provide additional information to enable clinicians and patients to make a more informed choice about the appropriateness of chemotherapy or radiotherapy in advanced disease. This may translate to anticancer therapy being directed toward those in whom it is likely to benefit versus those in whom no benefit and/or potential harm is likely.

Second, place of care in advanced cancer is challenging. Improved prognostic accuracy may assist clinicians as to the most appropriate place of care (specialist palliative care unit or cancer centre) and also as to the purpose of that admission (e.g., end-of-life care). The decision to treat potentially life-limiting conditions near the end of life (e.g., lower respiratory tract infection) may also be influence by improved prognostic accuracy.

Finally, the concept of a good death is usually one where a patient dies free from distressing symptoms and once all goodbyes and personal affairs have been addressed (35, 36). An accurate knowledge of prognosis may aid this and also help health professionals in their discussion with patients.

Limitations

A limitation is that no direct comparison was conducted with other prognosis systems, and further studies to clarify differences between prognosis systems in patients with advanced cancer are required. Another important consideration is that there is evidence that tumor cells produce proinflammatory/inflammatory cytokines and that tumor burden is associated with an increased release of such cytokines. Therefore, it may be postulated that tumor burden relates to the proinflammatory state and may affect biomarkers of inflammation. However, it is also recognized that resection of the primary tumor does not significantly alter systemic inflammatory response status (16, 29, 30). This would suggest that the primary defect is in the dysregulation of the immune cell and inflammatory responses in the patient with cancer, supporting the role of inflammatory biomarkers in prognostication.

Future Work

In the present study, it was clear from both the test and validation datasets that performance status and the mGPS were correlated and therefore are likely to capture some of the same elements that determine survival. Future work should develop the objective mGPS such that it may displace the subjective performance status in the prediction of survival in patients with advanced cancer. If this was achieved it would represent a paradigm shift in the clinical management of these difficult to treat patients. The present study represents a major step forward in this goal.

Conclusion

The present study shows that the mGPS predicts survival in advanced cancer independently and performs well compared with performance status in terms of prognostic power. These findings highlight a potential role for the mGPS (objective measure) in combination with performance status (subjective measure), with these acting synergistically, predicting survival effectively. This new approach would also enable measures of systemic inflammation to be a part of the routine, clinical prediction of survival in patients with advanced cancer (7, 8). A prognostic tool combining mGPS and performance status could guide clinicians in the appropriate cancer treatment for their patients, and further work examining this in practice would be of interest.

These findings extend previous observations in other disease states such as cardiovascular disease that has established the independent prognostic value of inflammatory biomarkers in patient risk stratification.

Disclosure of Potential Conflicts of Interest

P. Klepstad has a honoraria from speakers' bureau from Ferrer Pharma, Mundipharma, and Pharma and is a consultant/advisory board member of Orion Pharma. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: B.J. Laird, D.C. McMillan, M.T. Fallon, M.J. Hjermstad, P. Klepstad

Development of methodology: B.J. Laird, M.T. Fallon, M.J. Hjermstad, P. Klepstad

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P. Klepstad
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.J. Laird, D.C. McMillan, P. Fayers, P. Klepstad
Writing, review, and/or revision of the manuscript: B.J. Laird, S. Kaasa, D.C. McMillan, M.T. Fallon, M.J. Hjermstad, P. Fayers, P. Klepstad
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.J. Laird, M.J. Hjermstad, P. Klepstad
Study supervision: B.J. Laird, M.T. Fallon, M.J. Hjermstad

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Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System

Barry J. Laird, Stein Kaasa, Donald C. McMillan, et al.

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