EUROPEAN JOURNAL OF CANCER 47 (2011) 2633–2641

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A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study

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ARTICLE INFO

Article history:
Available online 1 July 2011

Keywords:
C-reactive protein
Albumin
Neutrophil
Lymphocyte
Platelet
Neoplasia
Prognosis
Survival analysis

ABSTRACT

Introduction: Components of the systemic inflammatory response, combined to form inflammation-based prognostic scores (modified Glasgow Prognostic Score (mGPS), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Prognostic Index (PI), Prognostic Nutritional Index (PNI)) have been associated with cancer specific survival. The aim of the present study was to compare the prognostic value of these scores.

Methods: Patients ($n = 27{,}031$) who had an incidental blood sample taken between 2000 and 2007 for C-reactive protein, albumin, white cell, neutrophil, lymphocyte and platelet counts, as well as a diagnosis of cancer (Scottish Cancer Registry) were identified. Of this group 8759 patients who had been sampled within two years following their cancer diagnosis were studied.

Results: On follow up, there were 5163 deaths of which 4417 (86%) were cancer deaths. The median time from blood sampling to diagnosis was 1.7 months. An elevated mGPS, NLR, PLR, PI and PNI were predictive of a reduced cancer specific survival independent of age, sex and deprivation and tumour site (all $p < 0.001$). The area under the receiver operator curves was greatest for mGPS and PI. Specifically, in colorectal cancer, an elevated mGPS and PI were predictive of a reduced cancer specific survival independent of age, sex, deprivation and tumour stage (both $p < 0.001$).

Conclusion: The results of the present study show that systemic inflammation-based scores, in particular the mGPS and PI, have prognostic value in cancer independent of tumour site. Based on the present results and the existing validation literature, the mGPS should be included in the routine assessment of all patients with cancer.

1. Introduction

Cancer incidence is increasing in the United Kingdom as well as on a global basis.[1] Over 1 in 3 people in the UK will develop cancer during their lifetime with around 150,000 people dying each year as a consequence.[2,3] Such a burden of disease accounts for a significant proportion of annual healthcare spending in the UK, US and worldwide.[1,4]

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.03.028

Although it is recognised that the development of cancer has a genetic basis, there is increasing evidence that the host inflammatory response plays an important role in the development and progression of cancer.[5–9] In particular the systemic inflammatory response, as evidence by C-reactive protein, plays an important role in the progression of a variety of common solid tumours.[10] The measurement of the systemic inflammatory response has been subsequently refined using a selective combination of C-reactive protein and albumin (termed the modified Glasgow Prognostic Score, mGPS) and has been shown to have prognostic value, independent of tumour stage, in lung, gastrointestinal and renal cancers.[11,12]

It is also of interest that other haematological components of the systemic inflammatory response have been combined to form inflammation-based prognostic scores that have been associated with survival in patients with cancer (Table 1). The Neutrophil Lymphocyte Ratio (NLR), a combination of circulating neutrophil and lymphocyte counts,[13] has been associated with survival in lung[14,15] and ovarian[16] cancers. The Platelet Lymphocyte Ratio (PLR), a combination of circulating platelet and lymphocyte counts, has been associated this survival in patients with pancreatic cancer.[17] The combination of C-reactive protein and white cell count in a Prognostic Index (PI) has been associated with survival in patients with lung cancer.[18] Finally, Onodera's Prognostic Nutritional Index (PNI) has also been associated with survival in patients with pancreatic,[19] gastric[20] and oesophageal cancer.[21]

More recently it has been shown that, in a large cohort study (Glasgow Inflammation Outcome Study) that the mGPS is elevated in patients with cancer[22] and predictive of survival across all tumour sites studied independent of age, sex and deprivation.[23] Therefore, it is of considerable interest to compare the prognostic value of the mGPS, NLR, PLR, PI and PNI across different tumour sites.

The aim of the present study was to compare the prognostic value of the mGPS, NLR, PLR, PI and PNI adjusted for age, sex, deprivation and tumour site in the Glasgow Inflammation Outcome Study. We hypothesised that these systemic inflammation-based prognostic scores at the time of diagnosis would all predict cancer survival.

Table 1 – Systemic inflammation-based prognostic scores.

The modified Glasgow Prognostic Score	Score
C-reactive protein $\leqslant$ 10 mg/l and albumin $\geqslant$ 35 g/l	0
C-reactive protein $\leqslant$ 10 mg/l and albumin < 35 g/l	0
C-reactive protein > 10 mg/l	1
C-reactive protein > 10 mg/l and albumin < 35 g/l	2
Neutrophil Lymphocyte Ratio	
Neutrophil count:lymphocyte count < 5:1	0
Neutrophil count:lymphocyte count $\geqslant$ 5:1	1
Platelet Lymphocyte Ratio	
Platelet count:lymphocyte count < 150:1	0
Platelet count:lymphocyte count 150–300:1	1
Platelet count:lymphocyte count > 300:1	2
Prognostic Index	
C-reactive protein $\leqslant$ 10 mg/l and white cell count $\leqslant 11 \times 10^9$/l	0
C-reactive protein $\leqslant$ 10 mg/l and white cell count $> 11 \times 10^9$/l	1
C-reactive protein > 10 mg/l and white cell count $\leqslant 11 \times 10^9$/l	1
C-reactive protein > 10 mg/l and white cell count $> 11 \times 10^9$/l	2
Prognostic Nutritional Index	
Albumin (g/L) + 5 × total lymphocyte count × 10^9/l $\geqslant$ 45	0
Albumin (g/L) + 5 × total lymphocyte count × 10^9/l < 45	1

2. Materials and methods

2.1. Study design

From a cohort previously described,[22] cancer patients in North Glasgow, who had a single blood sample taken for C-reactive protein, albumin, calcium, white cell, neutrophil, lymphocyte and platelet counts were included. Briefly, patients who were sampled incidentally between the 1st January 2000 and the 31st December 2007 were considered and if more than one set of measurements were available for a given patient, only the initial set was used. Cancer diagnosis was established through linkage with the Scottish Cancer Registry using exact matches of patients' forename, surname and date of birth followed by a Soundex phonetic matching algorithm if initial exact matching was unsuccessful. At the time of data collection, the Scottish Cancer Registry held complete pathological and clinical cancer diagnosis records from the 1st of January 1980 until 31st December 2007 and mortality follow up until 30th June 2009. In those who had died, patients whose primary cause of death matched their primary cancer diagnosis were classed under cancer specific deaths. All other deaths were classed as non-cancer specific deaths. Staging information on tumours was extracted where available.

Only patients with blood samples taken within two years following their cancer diagnosis were included. Also, only patients who had complete Cancer Registry follow up were included in the study. Patients were excluded if they were under 16, did not have a complete set of identifying details (name, date of birth and hospital number) or did not have haematological variables available.

Cancers were coded in accordance with the International Classification of Disease 10 and broadly grouped according to tumour site; breast, bladder, gynaecological, prostate, gastroesophageal, haematological, renal, colorectal, head and neck, hepatopancreaticobiliary and pulmonary cancer. These groups were listed in order of the magnitude of their inflammatory status as shown previously.[22] Patients with multiple malignancies, metastatic disease or cancer of an unknown origin were excluded.

The study was approved by the Research Ethics Committee, North Glasgow NHS Trust.

2.2. Methods

Patients with routine laboratory measurements of C-reactive protein, albumin, calcium, white cell, neutrophil, lymphocyte and platelet counts were obtained by systematically search-

ing the North Glasgow biochemical database system. The limit of detection of C-reactive protein was a concentration of less than 5 mg/L. The mGPS, NLR, PLR, PI and PNI were constructed as described in Table 1.

International Classification of Disease 10 codes were used to identify the site of cancer diagnosis. These include breast (C50), bladder (C67), gynaecological (C51–58), prostate (C61), gastroesophageal (C15–16), haematological (C81–96), renal (C64–65), colorectal (C18–20), head and neck (C00–14, C30–32), hepatopancreaticobiliary (C22–25) and pulmonary (C33, C34, C45) cancer.

Deprivation was measured using the Scottish Index of Multiple Deprivation (SIMD) 2006 and in this study was presented with the least deprived being scored as 1 to the most deprived scoring 5. The SIMD 2006 classification of deprivation is based on an individual's postcode and is derived from the measurements of 37 indicators across seven domains including income, employment, education, housing, health, crime and geographical access. The SIMD 2006 is the recommended method for measuring deprivation in Scotland by the Information Services Division (ISD) on behalf of NHS Scotland and the Scottish Government Department of Health.[24]

2.3. Statistics

Survival, overall and cancer specific, was calculated from the time of cancer diagnosis to death. Cancer groups with less than 150 cancer specific deaths were excluded to ensure statistical power. Analysis was carried on all cancer patients as well as on a sub-group of patients who had a diagnosis of cancer made within 2 months following their blood sample. This was carried out in order to examine the relationships between the mGPS, NLR, PLR, PI, PNI and survival in all patients with a recently diagnosed malignancy (patients sampled within 2 years following a diagnosis of cancer) and those at the time of diagnosis (patients sampled within 2 months following a diagnosis of cancer).

The mGPS, NLR, PLR, PI and PNI proportionality assumptions were explored using log–log plots and were found to be satisfactory. Kaplan–Meier estimator was used to analyse

Table 2 – The relationship between patient characteristics, tumour site, inflammatory-based prognostic scores and survival.

			Patients $n = 8759$ (%)	Five year overall survival % (n of deaths) $n = 5163$	p-Value	Five year cancer specific survival % (n of deaths) $n = 4417$	p-Value
Age	⩽65 years		4237 (48)	52 (1977)	<0.001	55 (1808)	<0.001
	65–74 years		2620 (30)	33 (1703)		41 (1439)	
	⩾75 years		1902 (22)	21 (1483)		31 (1170)	
Sex	Male		4115 (47)	29 (2844)	<0.001	36 (2432)	<0.001
	Female		4644 (53)	49 (2319)		55 (1985)	
SIMD 2006	1 (least deprived)		1278 (15)	51 (609)	<0.001	57 (523)	<0.001
	2		1138 (13)	48 (579)		54 (495)	
	3		1391 (16)	43 (779)		48 (683)	
	4		1786 (20)	37 (1110)		44 (940)	
	5 (most deprived)		3166 (36)	33 (2086)		40 (1776)	
Tumour site	Breast		1853 (21)	79 (361)	<0.001	85 (263)	<0.001
	Bladder		437 (5)	48 (226)		63 (149)	
	Gynaecological		460 (5)	45 (248)		51 (217)	
	Prostate		456 (5)	53 (206)		64 (153)	
	Gastroesophageal		874 (10)	12 (754)		15 (697)	
	Haematological		817 (10)	48 (418)		57 (320)	
	Renal		400 (5)	38 (242)		44 (214)	
	Colorectal		996 (11)	39 (583)		45 (493)	
	Head and neck		555 (7)	34 (344)		51 (239)	
	Hepatopancreaticobiliary		474 (5)	7 (430)		8 (410)	
	Pulmonary		1437 (16)	5 (1351)		7 (1262)	
Inflammation based prognostic scores	mGPS	0	3673 (42)	61 (1349)	<0.001	68 (1083)	<0.001
		1	2436 (28)	32 (1640)		39 (1425)	
		2	2650 (30)	16 (2174)		22 (1909)	
	NLR	0	5151 (59)	51 (2401)	<0.001	58 (2021)	<0.001
		1	3608 (41)	23 (2762)		29 (2396)	
	PLR	0	2734 (31)	52 (1253)	<0.001	60 (996)	<0.001
		1	3522 (40)	42 (1993)		48 (1716)	
		2	2503 (29)	23 (1917)		28 (1705)	
	PI	0	3084 (35)	64 (1042)	<0.001	70 (832)	<0.001
		1	3460 (40)	31 (2303)		38 (1994)	
		2	2215 (25)	17 (1818)		23 (1591)	
	PNI	0	4342 (50)	57 (1806)	<0.001	63 (1487)	<0.001
		1	4417 (50)	21 (3357)		27 (2930)	

the relationship between patient characteristics, mGPS, NLR, PLR, PI and PNI, tumour site and overall and cancer specific survival (Table 2, Figs. 1 and 2). Cox proportional hazards model multivariate regression analysis (stratified by tumour site) was used to correct for age, sex and deprivation and determine the relationship between patient characteristics, mGPS, NLR, PLR, PI and PNR and survival (Tables 3 and 4). To determine whether one of the independently significant variables was more predictive than the other, the area under the receiver operating characteristic (ROC) curve was calculated. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

From the Glasgow Inflammation Outcome Study of 223,303 patients originally described,[22] 27,031 patients were identified as having a diagnosis of cancer Scottish Cancer Registry and a blood sample for C-reactive protein, albumin, white cell, neutrophil, lymphocyte and platelet counts taken between January 2000 and December 2007. Within this identified group there were 8759 patients who had been sampled within two years following a diagnosis of cancer and were included in the present study. The majority, 6857 (78%), were under 75 years of age. There were 4644 (53%) females and 4115 (47%) males. Fifteen per cent of patients lived in affluent areas (least deprived quintile of the Scottish population) and 36% in deprived areas (most deprived quintile of the Scottish population). The minimum follow-up from cancer diagnosis was 18 months and the maximum 115 months (median 51 months for survivors).

The relationship between patient characteristics, tumour site, inflammatory-based prognostic scores and survival is shown in Table 2 and Fig. 1. In total 8759 patients were studied. On follow up, there were 5163 deaths of which 4417 (86%) were cancer deaths. The median time from diagnosis to blood sampling was 1.7 months, suggesting that most scores reflect status at diagnosis rather that at a later stage. Increasing age, male gender and increasing deprivation were associated with reduced 5 year overall and cancer specific survival (all $p < 0.001$). An elevated mGPS, NLR, PLR, PI and PNI were also associated with a reduced 5 year overall and cancer specific survival (all $p < 0.001$). When this analysis was repeated on a subgroup of patients ($n = 4674$) who were sampled within two months following their cancer diagnosis (median time to diagnosis 0.5 months) the above proportions remained similar and the associations significant (all $p < 0.001$). The relationship between the mGPS, NLR, PLR, PI and PNI and cancer specific survival in individual tumour groups is shown in Fig. 2. All were predictive of cancer specific survival in bladder, breast, colorectal, gastroesophageal, gynaecological, prostate, pulmonary and renal cancer (all $p < 0.001$). Additionally, the mGPS, NLR, PI and PNI were predictive of cancer specific haematological, head and neck and hepatopancreaticobiliary cancer survival (all $p < 0.001$).

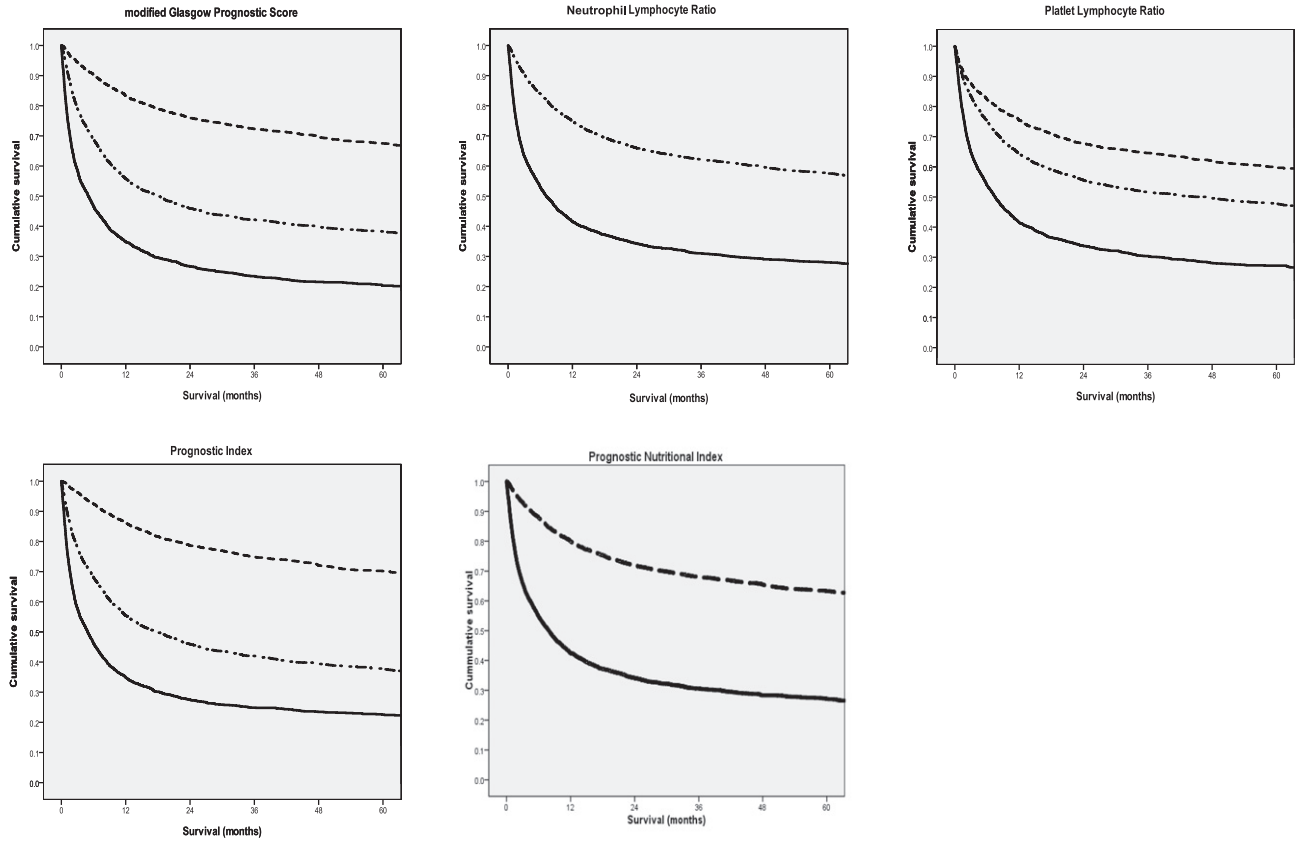

Fig. 1 – The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), NLR (0-top, large dash line; 1-bottom, solid line), PLR (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PI (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PNI (0-top, large dash line; 1-bottom, solid line) and cancer specific survival in all patients (all $p<0.001$).

Fig. 2 – The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), NLR (0-top, large dash line; 1-bottom, solid line), PLR (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PI (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line) and PNI (0-top, large dash line; 1-bottom, solid line) and cancer specific survival in individual tumour groups (all $p < 0.001$).

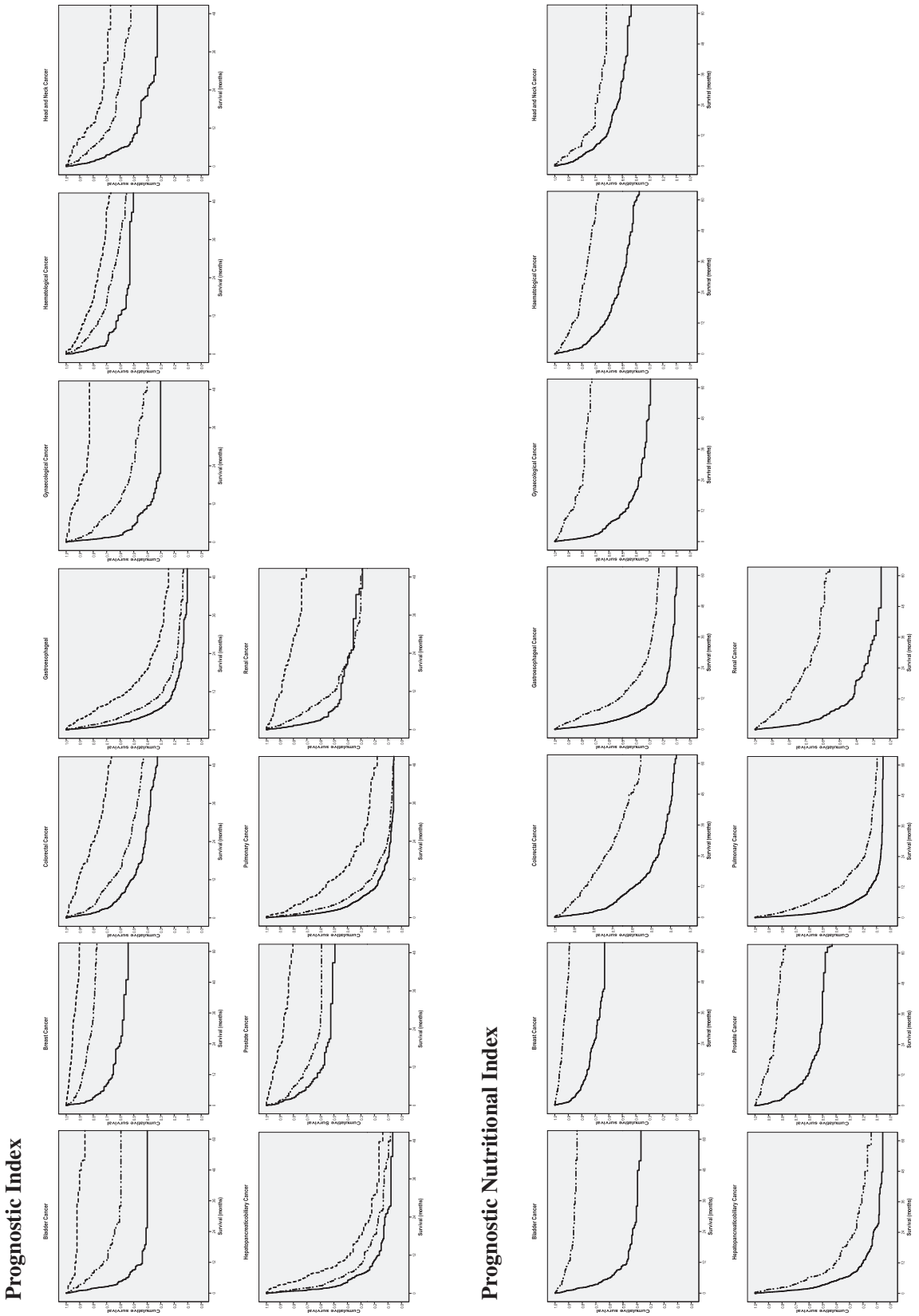

Fig 2. *(continued)*

The relationship between inflammation-based prognostic scores and survival, adjusted for age, sex and deprivation and stratified by tumour site is shown in Table 3. On survival analysis of all patients ($n = 8759$), a raised mGPS, NLR, PLR, PI

Table 3 – The relationship between inflammation-based prognostic scores and survival. Adjusted for age, sex, deprivation and stratified by tumour site.

		Overall survival		Cancer specific survival	
		HR	*p*-Value	HR	*p*-Value
All patients (n = 8759)					
mGPS	0	1	<0.001	1	<0.001
	1	1.74	<0.001	1.85	<0.001
	2	2.91	<0.001	3.06	<0.001
NLR	0	1	<0.001	1	<0.001
	1	1.93	<0.001	1.97	<0.001
PLR	0	1	<0.001	1	<0.001
	1	1.22	<0.001	1.31	<0.001
	2	1.89	<0.001	2.08	<0.001
PI	0	1	<0.001	1	<0.001
	1	2.03	<0.001	2.15	<0.001
	2	2.87	<0.001	3.03	<0.001
PNI	0	1	<0.001	1	<0.001
	1	2.24	<0.001	2.34	<0.001
Patients sampled within two months following cancer diagnosis (n = 4674)					
mGPS	0	1	<0.001	1	<0.001
	1	1.65	<0.001	1.74	<0.001
	2	2.35	<0.001	2.44	<0.001
NLR	0	1	<0.001	1	<0.001
	1	1.76	<0.001	1.77	<0.001
PLR	0	1	<0.001	1	<0.001
	1	1.19	<0.001	1.24	<0.001
	2	1.71	<0.001	1.82	<0.001
PI	0	1	<0.001	1	<0.001
	1	1.78	<0.001	1.87	<0.001
	2	2.44	<0.001	2.51	<0.001
PNI	0	1	<0.001	1	<0.001
	1	1.98	<0.001	2.01	<0.001

Table 4 – The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis. Adjusted for age, sex, deprivation and Dukes stage.

n = 374		Overall survival		Cancer specific survival	
		HR	*p*-Value	HR	*p*-Value
mGPS	0	1	<0.001	1	<0.001
	1	1.81	0.004	1.91	<0.001
	2	2.30	<0.001	2.51	<0.001
NLR	0	1	0.102	1	0.146
	1	1.27	0.102	1.25	0.146
PLR	0	1	0.786	1	0.560
	1	1.16	0.487	1.30	0.281
	2	1.13	0.596	1.23	0.403
PI	0	1	<0.001	1	<0.001
	1	1.69	0.012	1.92	<0.001
	2	2.83	<0.001	3.07	<0.001
PNI	0	1	0.059	1	0.095
	1	1.33	0.059	1.31	0.095

and PNI were associated with reduced overall and cancer specific survival independent of age, sex and deprivation (all $p < 0.001$). When this analysis was repeated on a subgroup of patients ($n = 4674$) who were sampled within two months following their cancer diagnosis the above proportions remained similar and the associations significant (all $p < 0.001$).

In all patients, using overall mortality at as an end-point, the area under the receiver operator curve was for the mGPS 0.718 (95% CI, 0.707–0.729, $p < 0.001$); NLR 0.650 (95% CI, 0.638–0.661, $p < 0.001$); PLR 0.632 (95% CI, 0.620–0.644, $p < 0.001$); PI 0.715 (95% CI, 0.704–0.726, $p < 0.001$) and PNI 0.678 (95% CI, 0.666–0.689, $p < 0.001$). Using cancer-specific mortality at as an end-point, the area under the receiver operator curve was for the mGPS 0.698 (95% CI, 0.687–0.709, $p < 0.001$); NLR 0.632 (95% CI, 0.620–0.643, $p < 0.001$); PLR 0.632 (95% CI, 0.620–0.644, $p < 0.001$); PI 0.694 (95% CI, 0.682–0.705, $p < 0.001$) and PNI 0.660 (95% CI, 0.649–0.672, $p < 0.001$).

When this analysis was repeated on a subgroup of patients ($n = 4674$) who were sampled within two months following their cancer diagnosis, using overall mortality as an end-point, the area under the receiver operator curve was for the mGPS 0.730 (95% CI, 0.715–0.745, $p < 0.001$); NLR 0.657 (95% CI, 0.641–0.672, $p < 0.001$); PLR 0.644 (95% CI, 0.628–0.660, $p < 0.001$); PI 0.724 (95% CI, 0.724–0.753, $p < 0.001$) and PNI 0.692 (95% CI, 0.677–0.708, $p < 0.001$). Using cancer-specific mortality as an end-point, the area under the receiver operator curve was for the mGPS 0.712 (95% CI, 0.697–0.727, $p < 0.001$); NLR 0.640 (95% CI, 0.624–0.656, $p < 0.001$); PLR 0.638 (95% CI, 0.622–0.654, $p < 0.001$); PI 0.719 (95% CI, 0.704–0.733, $p < 0.001$) and PNI 0.673 (95% CI, 0.658–0.689, $p < 0.001$).

In the present cohort only a limited number of patients had staging information available from the Scottish Cancer Registry. Of those patients sampled within two months following cancer diagnosis, tumour staging was available in 470 (35%) patients with breast cancer, 374 (75%) patients with colorectal cancer and 108 (12%) patients with pulmonary cancer. All other cancer groups had no staging available. Therefore, only in colorectal cancer was staging available in over 50% of patients. In this group there were 31 Dukes A, 113 Dukes B, 113 Dukes C and 117 Dukes D with 227 dying of their cancer on follow-up. The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis adjusted for age, sex, deprivation and Dukes stage is shown in Table 4. Given the small numbers of Dukes A, Dukes A and B were grouped together. On survival analysis ($n = 374$), only a raised mGPS and PI were associated with reduced overall and cancer specific survival independent of age, sex, deprivation and Dukes stage (all $p < 0.001$).

As mGPS and PI both contain C-reactive protein, the prognostic value of a low albumin (<35 g/l) or high white cell count ($>11 \times 10^9$/l), independent of each other was of interest. On Cox-regression multivariate survival analysis of the same group of patients ($n = 374$), both a high white cell count (HR 1.57, $p = 0.011$) and low albumin (HR 1.59, $p = 0.004$) were predictive of cancer specific survival independent of age, sex, deprivation and Dukes stage.

4. Discussion

The results of the present study show clearly that systemic inflammation-based prognostic scores, whether it be the mGPS, NLR, PLR, PI or PNI, predict cancer specific outcome in most cancers. Moreover, those scores based on C-reactive protein, an acute phase protein, (mGPS and PI) were superior, in terms of differentiating good from poor prognostic groups in a variety of tumour sites, to those based on components of the circulating white cell count (NLR, PLR) or in combination with albumin (PNI). Therefore, any further development of prognostic scores, based on the systemic inflammatory-response, should currently include the prototypical acute phase protein[25], C-reactive protein. Also, based on the present results and the existing validation literature,[12] the mGPS should be included in the routine assessment of all patients with cancer.

In the present study, it was of interest that the combination of C-reactive protein and albumin (mGPS) had similar prognostic value to that of C-reactive protein and white cell count (PI). Although few patients had a low albumin (5%) or a high white cell count (3%) in the presence of a normal C-reactive protein concentration ($\leqslant$10 mg/l), both a low albumin concentration and a high white cell count, both had prognostic value independent of C-reactive protein. These results would suggest that a white cell count, rather than the NLR or PLR, may be a useful addition to the comprehensively validated mGPS.

It was also of interest that a nutritional index previously shown to have prognostic value (PNI) and used extensively in Japan[19–21] behaved, in terms of prognostic value, very similar to the systemic inflammation-based prognostic scores (mGPS, NLR, PLR and PI). The present results therefore add further weight to the proposal that the systemic inflammatory response is a major factor in the relationship between nutritional decline and poor outcome in patients with cancer.[11,12]

Taken together, the results of the present study highlight the importance of systemic inflammation in the poor outcome in patients with cancer. Therefore, we believe that the present results provide good evidence of systemic inflammation acting as a 'common soil'[26] promoting the fatal progression in most, if not all, cancers. If this proves to be the case then moderation of the systemic inflammatory response will become, in the future, as important a therapeutic target as the tumour itself.

In this context it is of interest that Chechlinskam, Kowalewska and co-workers[27] have proposed that 'systemic inflammation is a confounding factor in the interpretation of the biomarker profile of cancer patients' and 'to assess the independent predictive value of a biomarker, it should be validated against its expression in inflammatory conditions, and examined in the context of unspecific parameters of systemic inflammation'. Also, they have concluded that if this is not done 'we will end up using advanced technologies to assess inflammatory reactions in cancer patients', an opinion shared by the authors of the present study.

In summary, the results of the present study show that systemic inflammation-based scores mGPS, NLR, PLR, PI and PNI have prognostic value in a variety of cancers. However, in terms of differentiating good from poor prognostic groups in a variety of tumour sites and the existing validated literature, the mGPS is superior. A measurement of systemic inflammation, in particular the mGPS, should be included in the routine assessment of all patients with cancer.

Conflict of interest statement

None declared.

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