Inflammation and performance status

Title: Inflammation and performance status: the cornerstones of prognosis in advanced cancer

Running title: Prognosis' cornerstones in advanced cancer

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Abstract

Background: In advanced cancer, although performance status (PS), systemic inflammatory response and nutritional status are known to have prognostic value, geographical variations and sociodemographic indexes may also impact survival. This study compares validated prognostic factors in two international cohorts and establishes a prognostic framework for treatment.

Methods: Two international biobanks of patients (n=1.518) with advanced cancer were analyzed. Prognostic factors (Eastern Cooperative Oncology Group Performance Status [ECOG-PS], body mass index [BMI] and modified Glasgow Prognostic Score [mGPS]) were assessed. The relationship between these and survival was examined using Kaplan–Meier and Cox regression methods.

Results: According to multivariate analysis, in the European cohort the most highly predictive factors were BMI <20 kg/m^2 (hazard ratio [HR] 1.644), BMI 20-21.9 kg/m^2 (HR 1.347), ECOG-PS (HR 1.597–11.992) and mGPS (HR 1.843–2.365). In the Brazilian cohort, the most highly predictive factors were ECOG-PS (HR 1.678–8.938) and mGPS (HR 2.103–2.837). Considering gastrointestinal cancers in particular (n=551), the survival rate at 3 months in both cohorts together ranged from 93% (mGPS 0, PS 0–1) to 0% (mGPS 2, PS 4), and from 81% (mGPS 0, BMI >28 kg/m^2) to 44% (mGPS 2, BMI <20 kg/m^2).

Conclusion: The established prognostic factors that were compared had similar prognostic capacity in both cohorts. A high ECOG-PS and a high mGPS as outlined in the ECOG-PS/mGPS framework were consistently associated with poorer survival of patients with advanced cancer in the prospective European and Brazilian cohorts.

Keywords: Advanced cancer, Inflammation, Performance status, Prognosis, Survival analysis.

Key message: This article compared prognostic factors in international cohorts of patients with advanced cancer and established a prognostic framework for treatment. A high ECOG-PS and mGPS were consistently associated with poorer survival and the ECOG-PS/mGPS framework proposed can be incorporated into the routine assessment due to its simplicity and clinical utility.

Introduction

The management of patients with advanced cancer should include a prognostic assessment as a fundamental component to guide appropriate care and optimal therapies to improve quality of life and survival [1, 2].

In this context, performance status (PS) in patients with advanced cancer is established using routine prognostic tools such as Karnofsky (KPS) or Eastern Cooperative Oncology Group (ECOG) [2]. However, PS is a subjective assessment as it is primarily based on daily living activities, and this depends on the information giving by the patient and carers [2].

Simmons and colleagues, following a systematic review [1], carried out a prospective comparison of validated prognostic factors and identified that, in addition to PS, the modified Glasgow Prognostic Score (mGPS), a method used to measure systemic inflammation that uses a combination of C-reactive protein (CRP) and albumin, had independent prognostic value [3,4].

Another study showed that the mGPS predicts survival in advanced cancer independently and performs well compared with PS in terms of prognostic power. Yet, these findings highlighted that the combination of mGPS (objective measure) and PS (subjective measure), synergistically, effectively predicted survival [2].

A multi-center observational study with prospective follow-up of 414 incurable cachectic cancer patients showed that mGPS, PS and tumor spread were significantly associated with 3 and 6-month survival [5]. Recently, two systematic reviews provided consistent evidence that the presence of a systemic inflammatory response as evidenced by the mGPS is associated with the loss of lean tissue, anorexia, weakness and fatigue and poor survival in patients with advanced cancer [6, 7].

Given the above, it is important to extend these data to different populations and in different geographic locations. Knowing that several external factors, such as geographical variations and sociodemographic indexes may impact the survival of patients with advanced cancer [8,9], one hypothesis of this study is that even in international and multicentric samples, physical function, systemic inflammation, and nutrition remain strong prognostic factors.

In this way, the present study had two aims: Firstly, to compare established prognostic factors, such as performance status, systemic inflammatory response, and body mass index in two international cohorts of patients with advanced cancer. Secondly, to establish a prognostic framework for treatment in this cohort.

Materials and Methods

Study population

Analysis was undertaken on two international biobanks of adult cancer patients: the European cohort and the Brazilian cohort.

The European cohort was a prospective data collection of patients across sites in the United Kingdom and Ireland between 2011 and 2016 [10, 11] whereas the Brazilian cohort included patients from Brazil (Barretos Cancer Hospital, Barretos-SP) over three years (2011–2014). In both cohorts, eligible adult patients with advanced cancer (defined as locally advanced or with histological, cytological, or radiological evidence of metastasis), across all cancer subtypes, who provided a venous blood sample and with a recorded ECOG-PS were assessed for inclusion. In the European cohort, patients who were undergoing active anticancer therapy or not, in either an inpatient or outpatient

setting were included. In the Brazilian cohort, patients who attended the Palliative Care Outpatient Clinic for their first consultation, regardless of whether or not they were undergoing palliative antineoplastic treatment, were included.

All patients provided written informed consent. The study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee (West of Scotland Ethics Committee UK: 18/WS/0001 [18/01/2018]; Cork Research Ethics Committee Ireland: ECM 4 [g] [03/03/2015]; Ethics Committee of the Barretos Cancer Hospital [HCB433/2011 and HCB783/2014]). The study also conformed to the STROBE guidelines for cohort studies [12].

Procedure and assessment

General demographic data and clinicopathological characteristics were recorded for each patient. Primary cancer site was grouped as lung, breast, gynecological, gastrointestinal, urological, hematological, skin and soft tissue, neurological, head and neck, unknown primary, and other. Then, these groups of mentioned tumor sites were categorized into hormone-dependent (breast, gynecologic and urological) and hormone-independent (lung, gastrointestinal, hematological, skin and soft tissue, neurological, head and neck, unknown primary, and others). ECOG-PS was determined by a clinician or clinical researcher at the institute the patient was receiving treatment. Patients were categorized according to their ECOG-PS into five grades (grades 0–4) and then grouped as 0-1/2/3/4, as previously described [10]. Patients were categorized according to BMI as previously described (<20.0, 20.0 to 21.9, 22.0 to 24.9, 25.0 to 27.9, and >=28.0 kg/m^2) [13]. The systemic inflammatory response was analyzed using CRP and albumin. The biomarkers were taken by venous blood sampling at entry points in both studies and all

samples were analyzed at a central laboratory. The mGPS was calculated and grouped as follows [14]: mGPS 0 (CRP <= 10mg/L), mGPS 1 (CRP > 10mg/L) and mGPS 2 (CRP > 10mg/L and albumin < 35 g/L) [14].

Statistical analysis

The survival time, defined as the number of months from study entry until death, or censored if alive at the follow-up date, was calculated. Survival curves were plotted using Kaplan–Meier methods and the log-rank test was applied. Survival analysis was carried out using Cox proportional hazards model, and hazard ratios (HR) were calculated. 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. The Chi-square test was used for comparisons of categorical variables. All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout. Two-sided P-values less than 0.05 were considered significant. All analyzes were conducted in SPSS Version 20 (SPSS Inc).

Results

European cohort

The clinicopathological characteristics from 1,027 European cohort patients are shown in Table 1. The median age was 65.87 years (interquartile range [IQR] 56.93–73.57) and 524 patients were male (51%). The majority of patients had either BMI >= 28

kg/m^2 (29%, n=279) or BMI 22-24.9 kg/m^2 (24%, n=223). The majority of patients had either gastrointestinal (40%, n=411) or lung (26%, n=266) tumors as primary cancer sites. The median ECOG-PS was 1 (IQR 1–2). 43% of the patients had mGPS 0 and 40% of the patients had mGPS 2. At the time of cessation of data collection, 317 patients were alive (31%) and 710 (69%) had died. The median survival was 7.3 months (IQR 3.3 – 16.7).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular (n=411), their clinicopathological characteristics are shown in Table 2. The median age was 66.44 years (IQR 57.02–74.41) and 253 patients were male (62%). The majority of patients had either BMI >= 28 kg/m^2 (27%, n=102) or BMI 22-24.9 kg/m^2 (27%, n=105). The median ECOG-PS was 1 (IQR 1–2). 46% of the patients had mGPS 0 and 41% of the patients had mGPS 2. At the time of cessation of data collection, 96 patients were alive (23%) and 315 (77%) had died. The median survival was 7.7 months (IQR 3.4 – 16.8).

The relationship between clinicopathological characteristics and survival in patients with advanced cancer is shown in Table 3. On univariate survival analysis, age >74 (P = 0.048), BMI 20-21.9 kg/m^2 (P = 0.006), primary tumor site (P < 0.001), ECOG-PS (all P < 0.001) and mGPS (P < 0.001) were significantly associated with survival. Age (65-74) and sex were not associated with survival. On multivariate survival analysis, the most highly predictive factors were BMI <20 kg/m^2 (HR 1.644, P=0.001), BMI 20-21.9 kg/m^2 (HR 1.347, P=0.044), ECOG-PS (HR 1.597–11.992, all P < 0.001) and mGPS (HR 1.843–2.365, all P < 0.001).

When further stratification of the sample was carried out for gastrointestinal cancers in particular, the relationship between their clinicopathological characteristics and survival is shown in Table 4. On univariate survival analysis, ECOG-PS (all P <

0.001) and mGPS 1 and 2 (P=0.004 and P < 0.001, respectively) were significantly associated with survival. Age, sex and BMI were not associated with survival. On multivariate survival analysis, the most highly predictive factors were ECOG-PS (HR 1.911–19.518, all P < 0.001) and mGPS 1 and 2 (HR 1.736–2.270, P = 0.004 and P < 0.001, respectively).

Brazilian cohort

The clinicopathological characteristics of 491 patients in the Brazilian cohort are shown in Table 1. The median age was 60 years (IQR 52–69) and 271 patients were female (55%). The majority of patients had either BMI >= 28 kg/m^2 (25%, n=120) or BMI < 20 kg/m^2 (24%, n=114). The majority of patients had either gastrointestinal (29%, n=140) or breast (21%, n=102) tumors as primary cancer sites. The median ECOG-PS was 2 (IQR 1-2). 80% of the patients had mGPS 0 and 13% of the patients had mGPS 2. At the time of cessation of data collection, 38 (8%) patients were alive and 453 (92%) had died. The median survival was 4.6 months (IQR 2 – 10.7).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular (n=140), their clinicopathological characteristics are shown in Table 2. The median age was 63 years (IQR 57.2–68.9) and 80 patients were male (57%). The majority of patients had either BMI < 20 kg/m^2 (36%, n=49) or BMI 20-21.9 kg/m^2 (19%, n=26). The median ECOG-PS was 2 (IQR 1–2). 76% of the patients had mGPS 0 and 15% of the patients had mGPS 2. At the time of cessation of data collection, 10 patients were alive (7%) and 130 (93%) had died. The median survival was 4.15 months (IQR 2.0 – 9.2).

The relationship between clinicopathological characteristics and survival in patients with advanced cancer is shown in Table 3. According to univariate survival analysis, sex (P = 0.001), BMI <20 kg/m^2 (P = 0.001), BMI 22-24.9 kg/m^2 (P = 0.006), primary tumor site (P = 0.002), ECOG-PS (all P < 0.01) and mGPS (P < 0.001) were significantly associated with survival. Age was not associated with survival. According to multivariate survival analysis, the most highly predictive factors were ECOG-PS (HR 1.678–8.938, all P < 0.001) and mGPS (HR 2.103–2.837, all P < 0.001).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular, the relationship between their clinicopathological characteristics and survival is shown in Table 4. According to univariate survival analysis, ECOG-PS (all P < 0.001) and mGPS 2 (P < 0.001) were significantly associated with survival. Age, sex and BMI were not associated with survival. According to multivariate survival analysis, the most highly predictive factors were ECOG-PS (HR 2.380–14.081, all P < 0.001) and mGPS (HR 2.147–2.208, P = 0.015 and P = 0.003, respectively).

Considering the relationship between mGPS, performance status, BMI and survival in the European cohort, increasing mGPS was significantly associated with poorer survival (P <0.001). Also, worsening performance status and BMI 20-21.9 kg/m^2 were associated with poorer survival (P < 0.001 and P = 0.02, respectively) (Figure 1). These findings were similar in the Brazilian cohort (Figure 2). Increasing mGPS, worsening performance status and BMI <20 kg/m^2 were significantly associated with poorer survival (P < 0.001, P < 0.001 and P = 0.006, respectively).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular, the relationship between mGPS, performance status, BMI and survival rate at 3 months in both cohorts together is shown in Table 5. When mGPS and ECOG-PS were used in combination, survival at 3 months ranged from 93% (mGPS 0,

ECOG-PS 0–1) to 0% (mGPS 2, ECOG-PS 4). When mGPS and BMI were used in combination, survival at 3 months ranged from 81% (mGPS 0, BMI >28 kg/m^2) to 44% (mGPS 2, BMI < 20 kg/m^2).

Discussion

The results of the present study show that performance status and mGPS, which independently predicted survival, were the strongest predictors of survival in the European and Brazilian cohorts. Furthermore, although there was considerable variation in case mix between the cohorts, these prognostic factors had similar Hazard Ratios across both datasets (in particular mGPS). Although an objective marker of nutritional status, BMI did not show consistent prognostic value.

The results of the present study are consistent with the observations of Dolan and co-workers who found that ECOG-PS and mGPS remained independently associated with overall survival in 730 patients with advanced cancer [11]. In addition, Simmons and colleagues showed that ECOG-PS, mGPS, and neutrophil count were independent predictors of survival of 478 patients with advanced cancer at 1 and 3 months [3]. These results are consistent with a systematic review and meta-analysis of the systemic inflammatory response in predicting outcomes that showed a significant association between elevated mGPS and overall survival in thirty six studies of patients with advanced inoperable cancer [15].

When further stratification of the results was carried out for gastrointestinal cancers, in particular, similar results were obtained by univariate and multivariate analysis in both the European and Brazilian cohorts, suggesting that ECOG-PS and mGPS could be independent prognostic factors in different cancer types and remain strong when

used in combination. Therefore, the present study highlights the ECOG-PS/mGPS prognostic framework for patients with advanced cancer in both cohorts and its use should be considered as part of routine assessment.

The present study shows that BMI had a modest impact on the survival prediction of patients in both cohorts. Similarly, Fearon and co-workers found that weight loss alone did not identify the full effect of cachexia on physical function and was not a prognostic variable. In this way, the authors proposed a three-factor profile assessment to identify patients at risk of adverse outcomes: weight loss, reduced food intake and systemic inflammation [16]. Also, a prospective study concluded that some extra factors gain importance in the survival prediction of patients with cancer cachexia, such as chronic inflammation, anemia, protein depletion, reduced food intake, fatigue, decreased muscle strength and lean tissue depletion [17]. It is important to consider that Cederholm and co-workers proposed the Global Leadership Initiative on Malnutrition (GLIM) criteria that defined cancer cachexia as a chronic disease related to malnutrition and inflammation. The three phenotypic criteria identified were involuntary weight loss, low BMI and low muscle mass, and the tumor etiologic criteria were reduced food intake or assimilation and inflammation or disease burden [18]. Given this, an international and multi-cohort analysis of almost 13,000 patients reported that weight loss is largely determined by dietary intake and systemic inflammation measured by CRP [19]. Also, in the context of GLIM phenotypic criteria, a consistent association between the systemic inflammatory response and low muscle mass has been reported in a recent systematic review [6].

In daily practice, oncologists often have to decide whether to maintain or stop anticancer treatments for patients with advanced cancers. In this complex task, they need to take into account the risks and potential benefits of anticancer therapy and the beliefs,

desires and treatment goals of the patients [20]. Moreover, estimating the prognosis is a cornerstone in this decision-making process. The performance status assessment, usually performed by the ECOG-PS, is essential for the oncologist to map the patient's clinical conditions while estimating at the same time the treatment risks and the patient's prognosis. We believe that the addition of mGPS to the ECOG-PS should improve the ability to assess the patient in these situations. The patient with ECOG-PS 2, for example, is in a borderline condition to continue with chemotherapy. In these cases, if the mGPS is 2, the prescription of chemotherapy is very unfavorable. Further studies need to prospectively evaluate the impact of the ECOG-PS/mGPS framework in the real-world decision-making process.

The present study had limitations. It is subject to sample bias and the majority of patients were undergoing palliative care and it may be assumed that there was a high symptom burden which has been an indicator of a shorter prognosis. Also, there was heterogeneity in the primary cancer types. However, the prognostic value was consistent across tumor types. Finally, in the present study, weight loss (WL) data was not reliably recorded in most patients and therefore the BMI/WL grade was not assessed. Nevertheless, these data may be readily tested in other prospective datasets.

In summary, the established prognostic factors compared had similar prognostic capacity in both cohorts. A high ECOG-PS and a high mGPS, as outlined in the ECOG-PS/mGPS framework, were consistently associated with poorer survival of patients with advanced cancer in the prospective European and Brazilian cohorts. It can be readily incorporated into the routine assessment of patients due to its simplicity and clinical utility.

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Authors' contributions

Conceptualization, design and methodology (B.M.M.R., R.D.D., C.E.P., J.M., D.C.M, Y.C.P.M., B.J.L.), data curation (B.M.M.R., R.D.D., C.E.P., J.M., B.S.R.P., D.D.P, D.C.M, Y.C.P.M., B.J.L.), formal analysis (B.M.M.R., R.D.D., C.E.P., J.M., D.C.M, Y.C.P.M., B.J.L.), funding acquisition (B.M.M.R., R.D.D., C.E.P., D.C.M, Y.C.P.M., B.J.L.), project administration (B.M.M.R., R.D.D., C.E.P., D.C.M, Y.C.P.M., B.J.L.), supervision (R.D.D., C.E.P., D.C.M, Y.C.P.M., B.J.L.), writing: original draft (B.M.M.R., C.E.P., D.C.M, Y.C.P.M., B.J.L.), review and editing (B.M.M.R., R.D.D., C.E.P., J.M., B.S.R.P., D.D.P, D.C.M, Y.C.P.M., B.J.L.).

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All patients provided written informed consent. The study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee (West of Scotland Ethics Committee UK: 18/WS/0001 (18/01/2018); Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015); Ethics Committee of the Barretos Cancer Hospital (HCB433/2011 and HCB783/2014))

Data availability

The datasets that formed the basis of this article are contained in the University of Glasgow's MVLS institute (Scotland) and Barretos Cancer Hospital (Brazil). They contain patient sensitive information and therefore cannot be made available on a public repository.

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Figures legends

Figure 1 – Kaplan–Meier curves examining the relationship between performance status (ECOG grouping) and survival, mGPS and survival, and BMI and survival. European cohort (n = 1.027).

Figure 2 – Kaplan–Meier curves examining the relationship between performance status (ECOG grouping) and survival, mGPS and survival, and BMI and survival. Brazilian cohort (n = 491).

Table 1. Clinicopathological characteristics of patients with advanced cancer – European cohort (n=1027) and Brazilian cohort (n=491).

Parameter	European cohort (*n* = 1027) *n* (%)	Brazilian Cohort (n = 491) *n* (%)	P - value[a]
Age			<0.001
<65 years	483 (47)	301 (61)	
65-74 years	300 (29)	116 (24)	
74 years	244 (24)	74 (15)	
Sex			0.023
Male	524 (51)	220 (45)	
Female	503 (49)	271 (55)	
BMI[b]			<0.001
< 20.0 kg/m^2	122 (13)	114 (24)	
20 - 21.9 kg/m^2	123 (13)	64 (13)	
22 - 24.9 kg/m^2	223 (24)	95 (20)	
25 - 27.9 kg/m^2	202 (21)	85 (18)	
>= 28.0 kg/m^2	279 (29)	120 (25)	
Primary cancer site			<0.001
Lung	266 (26)	68 (14)	
Breast	91 (9)	102 (21)	
Gynecological	64 (6)	49 (10)	
Gastrointestinal	411 (40)	140 (29)	
Urological	69 (7)	55 (11)	
Hematological	43 (4)	0 (0)	
Skin and soft tissue	40 (4)	20 (4)	
Neurological	10 (1)	4 (1)	
Head and neck	0 (0)	40 (8)	
Unknown primary	12 (1)	11 (2)	
Others	21 (2)	2 (0)	
ECOG[c]			<0.001
0/1	575 (59)	186 (38)	
2	292 (30)	188 (38)	
3	96 (10)	93 (19)	
4	16 (1)	23 (5)	
mGPS[d]			<0.001
0	353 (43)	367 (80)	
1	139 (17)	31 (7)	
2	329 (40)	59 (13)	
Status			
Alive	317 (31)	38 (8)	<0.001
Dead	710 (69)	453 (92)	

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

[a] P value from $\chi 2$ analysis.

[b]BMI available on 949 patients in the European cohort and 478 patients in the Brazilian cohort.

[c]ECOG available on 979 patients in the European cohort and 490 patients in the Brazilian cohort.

[d]mGPS available on 821 patients in the European cohort and 457 patients in the Brazilian cohort.

Table 2. Clinicopathological characteristics of patients with gastrointestinal cancers – European cohort (n=411) and Brazilian cohort (n=140).

Parameter	European cohort (*n* = 411) *n* (%)	Brazilian Cohort (n = 140) *n* (%)	P - value[a]
Age			0.023
<65 years	187 (45)	78 (56)	
65-74 years	118 (29)	41 (29)	
74 years	106 (26)	21 (15)	
Sex			0,356
Male	253 (62)	80 (57)	
Female	158 (38)	60 (43)	
BMI[b]			<0.001
< 20.0 kg/m^2	46 (12)	49 (36)	
20 - 21.9 kg/m^2	51 (13)	26 (19)	
22 - 24.9 kg/m^2	105 (27)	21 (15)	
25 - 27.9 kg/m^2	79 (21)	18 (13)	
>= 28.0 kg/m^2	102 (27)	24 (17)	
ECOG[c]			<0.001
0/1	246 (61)	57 (41)	
2	111 (28)	53 (38)	
3	36 (9)	26 (19)	
4	8 (2)	4 (3)	
mGPS[d]			<0.001
0	159 (46)	101 (76)	
1	45 (13)	12 (9)	
2	145 (41)	20 (15)	
Status			<0.001
Alive	96 (23)	10 (7)	
Dead	315 (77)	130 (93)	

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

[a] P value from $\chi 2$ analysis.

[b]BMI available on 383 patients in the European cohort and 138 patients in the Brazilian cohort.

[c]ECOG available on 401 patients in the European cohort.

[d]mGPS available on 349 patients in the European cohort and 133 patients in the Brazilian cohort.

Table 3. The relationship between clinicopathological factors and survival in patients with advanced cancer – European cohort (n=1027) and Brazilian cohort (n=491).

	European cohort					Brazilian cohort				
		Univariate[a]		Multivariate[a]			Univariate[a]		Multivariate[a]	
	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age										
<65	483	1.000 (Ref.)				301	1.000 (Ref.)			
65-74	300	1.100 (0.926-1.307)	0.276			116	1.181 (0.946-1.475)	0.143		
>74	244	1.209 (1.002-1.459)	0.048			74	1.138 (0.872-1.486)	0.340		
Sex										
Female	503	1.000 (Ref.)				271	1.000 (Ref.)			
Male	524	1.135 (0.980-1.315)	0.092			220	1.357 (1.126-1.635)	0.001		
BMI										
<20.0	122	1.287 (0.994 – 1.667)	0.055	1.644 (1.219 – 2.216)	0.001	114	1.585 (1.209 – 2.078)	0.001	1.253 (0.926 – 1.697)	0.144
20.0 – 21.9	123	1.411 (1.104 – 1.802)	0.006	1.347 (1.007 – 1.802)	0.044	64	1.306 (0.951 – 1.794)	0.099	1.159 (0.823 – 1.632)	0.398
22.0 – 24.9	223	0.993 (0.802 – 1.230)	0.948	1.142 (0.890 – 1.466)	0.296	95	1.483 (1.120 – 1.962)	0.006	1.282 (0.955 – 1.722)	0.099
25.0 – 27.9	202	0.873 (0.698 – 1.093)	0.873	1.059 (0.814 – 1.377)	0.671	85	1.130 (0.842 – 1.518)	0.416	1.224 (0.897 – 1.670)	0.203
>=28	279	1.000 (Ref.)		1.000 (Ref.)		120	1.000 (Ref.)		1.000 (Ref.)	
Primary tumor site										
HD	224	1.000 (Ref.)				206	1.000 (Ref.)			
HI	803	1.421 (1.181 – 1.708)	<0.001	1.187 (0.921 – 1.530)	0.184	285	1.354 (1.121 – 1.635)	0.002	1.216 (0.976 – 1.514)	0.081
Performance status										
ECOG 0/1	575	1.000 (Ref.)		1.000 (Ref.)		186	1.000 (Ref.)		1.000 (Ref.)	
ECOG 2	292	2.015 (1.696-2.395)	<0.001	1.597 (1.308 – 1.950)	<0.001	188	1.756 (1.416-2.176)	<0.001	1.678 (1.337 – 2.105)	<0.001
ECOG 3	96	3.830 (3.001-4.887)	<0.001	2.469 (1.804 – 3.312)	<0.001	93	2.826 (2.171-3.678)	<0.001	2.449 (1.822 – 3.292)	<0.001
ECOG 4	16	22.699 (13.471-38.247)	<0.001	11.992 (6.346 – 22.663)	<0.001	23	10.344 (6.545-16.348)	<0.001	8.938 (5.426–14.722)	<0.001
mGPS										
mGPS 0	353	1.000 (Ref.)		1.000 (Ref.)		367	1.000 (Ref.)		1.000 (Ref.)	
mGPS 1	139	2.014 (1.577-2.573)	<0.001	1.843 (1.403 – 2.422)	<0.001	31	1.987 (1.370-2.880)	<0.001	2.103 (1.437 – 3.078)	<0.001
mGPS 2	329	2.849 (2.362-3.435)	<0.001	2.365 (1.928 – 2.900)	<0.001	59	3.761 (2.819-5.017)	<0.001	2.837 (2.083 – 3.864)	<0.001

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; HD, hormone-dependent; HI, hormone-independent.
[a] HR expressed as per 10 unit change.

Table 4. The relationship between clinicopathological factors and survival in patients with gastrointestinal cancers – European cohort (n=411) and Brazilian cohort (n=140).

	European cohort					Brazilian cohort				
		Univariate[a]		Multivariate[a]			Univariate[a]		Multivariate[a]	
	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age										
<65	187	1.000 (Ref.)				78	1.000 (Ref.)			
65-74	118	0.953 (0.732-1.240)	0.720			41	1.261 (0.849-1.874)	0.250		
>74	106	1.198 (0.909-1.579)	0.200			21	0.879 (0.530-1.460)	0.619		
Sex										
Female	158	1.000 (Ref.)				60	1.000 (Ref.)			
Male	253	0.936 (0.747-1.174)	0.570			80	1.123 (0.792-1.591)	0.515		
BMI										
<20.0	46	1.104 (0.732 – 1.667)	0.637			49	1.153 (0.701 – 1.896)	0.575		
20.0 – 21.9	51	1.107 (0.753 – 1.626)	0.606			26	0.760 (0.430 – 1.343)	0.344		
22.0 – 24.9	105	0.959 (0.702 – 1.309)	0.790			21	1.036 (0.571 – 1.880)	0.907		
25.0 – 27.9	79	0.922 (0.661 – 1.287)	0.632			18	0.781 (0.413 – 1.479)	0.449		
>=28	102	1.000 (Ref.)				24	1.000 (Ref.)			
Performance status										
ECOG 0/1	246	1.000 (Ref.)		1.000 (Ref.)		57	1.000 (Ref.)		1.000 (Ref.)	
ECOG 2	111	2.074 (1.603-2.682)	<0.001	1.911 (1.455 – 2.514)	<0.001	53	2.338 (1.538-3.554)	<0.001	2.380 (1.542 – 3.672)	<0.001
ECOG 3	36	2.734 (1.840-4.062)	<0.001	2.012 (1.326 – 3.052)	0.001	26	2.491 (1.530-4.054)	<0.001	2.568 (1.516 – 4.350)	<0.001
ECOG 4	8	32.567 (15.040-70.521)	<0.001	19.518 (8.914 – 42.735)	<0.001	4	14.983 (5.114-43.896)	<0.001	14.081 (4.654–42.604)	<0.001
mGPS										
mGPS 0	159	1.000 (Ref.)		1.000 (Ref.)		101	1.000 (Ref.)		1.000 (Ref.)	
mGPS 1	45	1.758 (1.204-2.569)	0.004	1.736 (1.187 – 2.538)	0.004	12	1.741 (0.950-3.192)	0.073	2.147 (1.158 – 3.980)	0.015
mGPS 2	145	2.529 (1.951-3.279)	<0.001	2.270 (1.737 – 2.968)	<0.001	20	2.611 (1.577-4.323)	<0.001	2.208 (1.300 – 3.749)	0.003

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

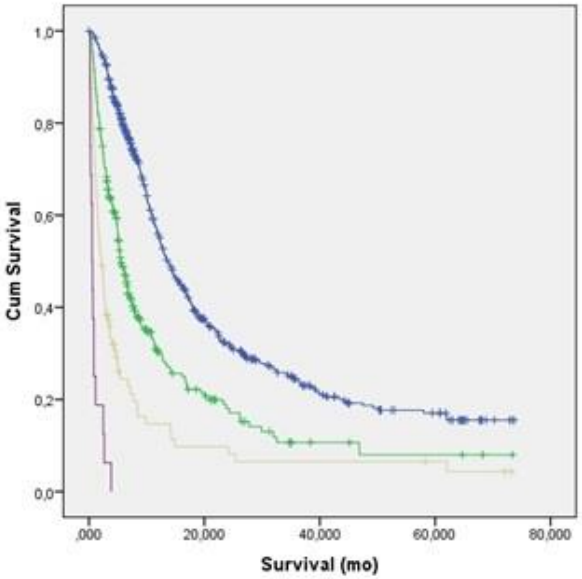
[a] HR expressed as per 10 unit change.

Table 5 – The relationship between the mGPS, performance status and BMI and the survival rate at 3 months in patients with gastrointestinal cancers – European cohort and Brazilian cohort (n=551)

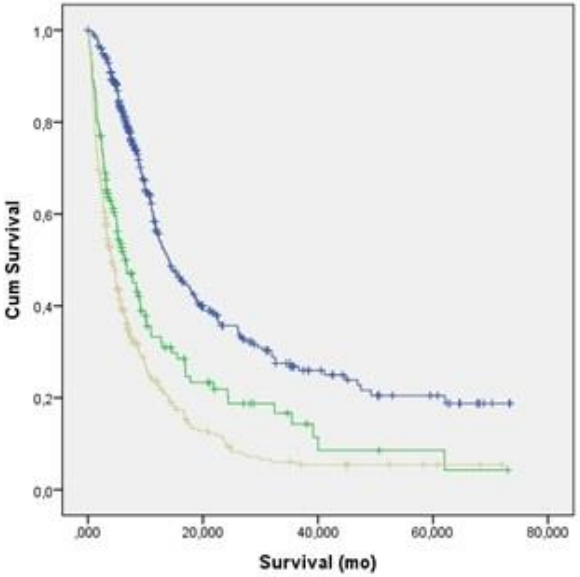
Performance status (ECOG grouping)	**mGPS 0 (n=260)**	**mGPS 1 (n=57)**	**mGPS 2 (n=165)**	***P-Value***	**mGPS 0-2 (n=482)**
0-1 (n = 303)	93% (n=147)	83% (n=25)	85% (n=56)	0.724	90% (n=228)
2 (n = 164)	74% (n=59)	62% (n=13)	46% (n=25)	<0.001	63% (n=97)
3 (n = 62)	65% (n=13)	(n=1)	31% (n=11)	<0.001	42% (n=25)
4 (n = 12)	(n=0)	(n=0)	(n=0)		(n=0)
P-Value	0.071	<0.001	<0.001		
0-4 (n = 541)	84% (n=219)	68% (n=39)	65% (n=92)		73% (n=350)
Body mass index (BMI grouping)	**mGPS 0 (n=260)**	**mGPS 1 (n=57)**	**mGPS 2 (n=165)**	***P-Value***	**mGPS 0-2 (n=482)**
>=28 (n=126)	81% (n=38)	93% (n=13)	63% (n=27)	0.002	75% (n=78)
25.0 – 27.9 (n=97)	89% (n=47)	(n=8)	79% (n=15)	<0.001	80% (n=70)
22.0 – 24.9 (n=126)	87% (n=47)	(n=7)	64% (n=29)	<0.001	75% (n=83)
20.0 – 21.9 (n=77)	90% (n=38)	(n=5)	(n=8)	<0.001	80% (n=51)
<20 (n=95)	77% (n=43)	(n=1)	44% (n=12)	<0.001	64% (n=56)
P-Value	0.753	0.023	<0.001		
<20 - >28 (n=521)	85% (n=213)	68% (n=34)	61% (n=91)		75% (n=338)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.
NOTE: Survival rate (SE)% at 3 months, not calculated if n < 10.

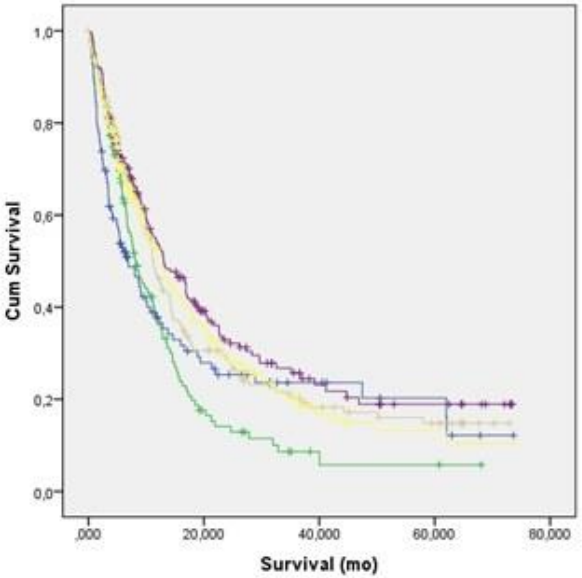
Figure 1 – Kaplan–Meier curves examining the relationship between performance status (ECOG grouping) and survival, mGPS and survival, and BMI and survival. European cohort (n = 1.027).



PS (ECOG grouping 0-1, 2, 3, 4 from top bottom).
Log- rank P < 0.001

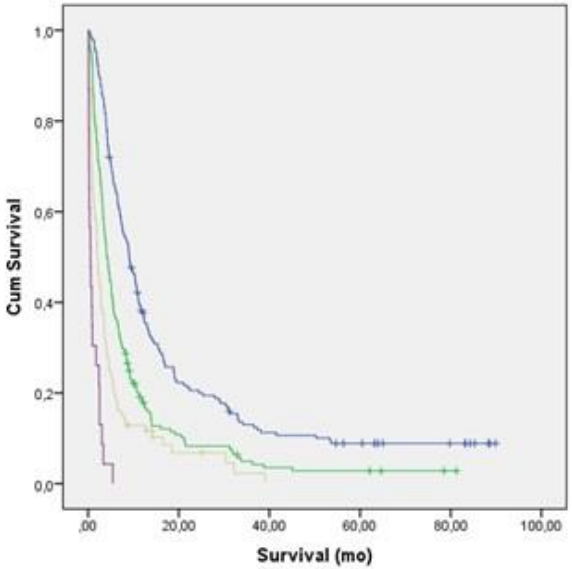


mGPS (0, 1, 2 from top bottom).
Log- rank P < 0.001

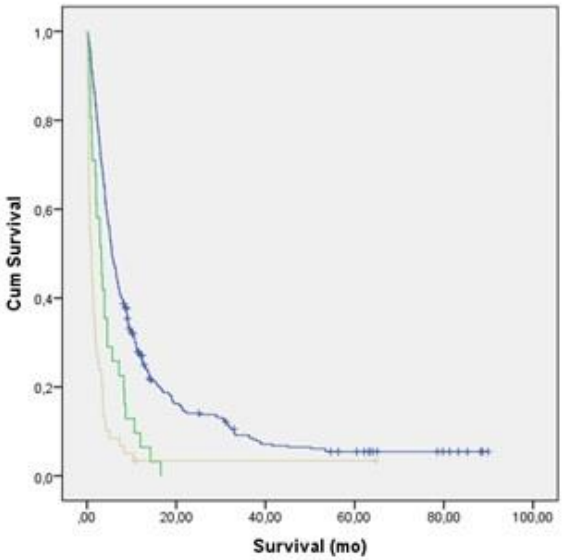


BMI (<20 blue, 20-21.9 green, 22-24.9 gray, 25-27.9 purple, >28 yellow).
Log- rank P = 0.02

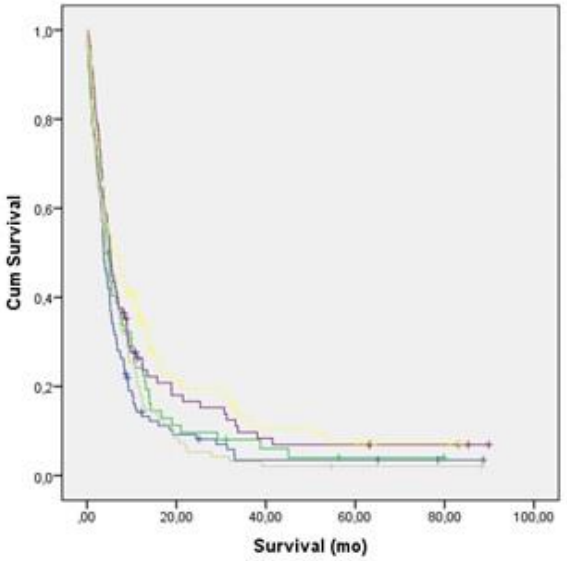
Figure 2 – Kaplan–Meier curves examining the relationship between performance status (ECOG grouping) and survival, mGPS and survival, and BMI and survival. Brazilian cohort (n = 491).



PS (ECOG grouping 0-1, 2, 3, 4 from top bottom).
Log- rank P < 0.001



mGPS (0, 1, 2 from top bottom).
Log- rank P < 0.001



BMI (<20 blue, 20-21.9 green, 22-24.9 gray, 25-27.9 purple, >28 yellow).
Log- rank P = 0.006