

Prognostic value of GLIM criteria including systemic inflammation in patients with advanced cancer

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Abstract

An assessment of systemic inflammation and nutritional status may form the basis of a framework to examine the prognostic value of cachexia in patients with advanced cancer. The objective of the study was to examine the prognostic value of GLIM criteria, including body mass index (BMI), weight loss (WL) and systemic inflammation (mGPS), in advanced cancer patients. Three criteria were examined in a combined cohort of patients with advanced cancer and their relationship with survival was examined using Cox regression methods. Data were available on 1303 patients. Considering BMI and the mGPS, the 3-month survival rate varied from 74% (BMI >28 kg/m²) to 61% (BMI <20 kg/m²) and from 84% (mGPS 0) to 60% (mGPS 2). Considering WL and the mGPS, the 3-month survival rate varied from 81% (WL ±2.4%) to 47% (WL ≥15%) and from 93% (mGPS 0) to 60% (mGPS 2). Considering BMI/WL grade and mGPS, the 3-month survival rate varied from 86% (BMI/WL grade 0) to 59% (BMI/WL grade 4) and from 93% (mGPS 0) to 63% (mGPS 2). When these criteria were combined, they better predicted survival. On multivariate survival analysis, the most highly predictive factors were BMI/WL grade 3 (HR 1.454, P=0.004), BMI/WL grade 4 (HR 2.285, P<0.001) and mGPS 1 and 2 (HR 1.889, HR 2.545, all P < 0.001). In summary, a high BMI/WL grade and a high mGPS as outlined in the BMI/WL grade/mGPS framework were consistently associated with poorer survival of patients with advanced cancer. It can be readily incorporated into the routine assessment of patients.

Keywords: Advanced cancer; Systemic inflammatory response; Body composition; Malnutrition; Cachexia; Prognosis.

Introduction

Cancer cachexia (CC) is considered a complex multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass, with or without loss of fat mass⁽¹⁾. Considered to affect up to half of patients with advanced cancer, contemporary evidence suggests it is responsible for approximately 20% of cancer-related deaths⁽²⁾. Furthermore, it is negatively associated with response to anti-cancer therapy⁽³⁾, physical function, survival and quality of life in patients with advanced cancer^(4,5). Thus, cachexia has been recognised for a long time as an adverse effect of cancer, and its clinical management is currently both limited and complex^(4,6). The Global Leadership Initiative on Malnutrition (GLIM) consensus defines cachexia as a chronic disease-related malnutrition associated with inflammation. It was agreed that diagnosis required one of three recognised phenotypic diagnostic criteria (low body mass index, non-volitional weight loss, and reduced muscle mass) and one aetiologic criterion (reduced food intake/assimilation and disease burden/inflammation secondary to acute disease/injury or chronic disease)⁽⁷⁾. However, the frameworks for the clinical application of the GLIM criteria require validation. Considering body mass index (BMI) and weight loss (WL), two phenotypic criteria proposed by GLIM, Martin and colleagues suggested that their BMI-adjusted WL grading system was useful to predict survival, as it was independent of cancer site, stage, and performance status, and strongly discriminates survival differences⁽⁸⁾. In another study by the same group analyzing a cohort of almost 5,000 patients, they showed that weight loss is largely determined by dietary intake and systemic inflammation⁽⁹⁾. Of these two GLIM aetiologic criteria, the authors concluded that impairment in food intake and elevated C-reactive protein (CRP) levels may improve the diagnosis and classification of cancer-associated cachexia⁽⁹⁾. Based on the present evidence, an assessment of systemic inflammation may provide a framework for examining the prognostic value of cachexia in patients with advanced cancer. Indeed, previous inflammation-based frameworks, combining modified Glasgow Prognostic Score (mGPS) and performance status, have been shown to have complimentary prognostic value in patients with advanced cancer⁽¹⁰⁾.

Therefore, the aim of the present study was to examine the prognostic value of the GLIM criteria, including BMI, weight loss and systemic inflammation, in patients with advanced cancer.

Material and Methods

Study population

Analysis was undertaken on a combined European and Brazilian cohort of adult patients with advanced cancer. The combined cohort was a prospective data collection of patients with advanced cancer across sites in the United Kingdom and Ireland between 2011 and 2016^(11,12), and from Brazil between 2011 and 2014. 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 were assessed for inclusion. Patients who were undergoing active anticancer therapy or not, in either an inpatient or outpatient setting were included. The study had ethics committee approval and all patients signed a consent-to-participate form in compliance with the Declaration of Helsinki^(11,12) and Resolution 466/12 of the Brazilian National Health Council. Furthermore, the study also conformed to the STROBE guidelines for cohort studies⁽¹³⁾.

Procedure and assessment

General demographic data and clinicopathological characteristics were recorded for each patient. Tumor site was grouped as lung, breast, gynecological, gastrointestinal, urological, hematological, melanoma, neurological, unknown primary and other. The systemic inflammatory response was analyzed using CRP and albumin and the mGPS was calculated as previously described and grouped as 0/1/2⁽¹⁴⁾. The biomarkers were taken by venous blood sampling at entry points and an autoanalyzer was used to measure CRP (mg/L) and albumin (g/L) concentrations according to routine clinical laboratory protocols.

Patients were also categorized according to BMI (<20.0, 20.0 to 21.9, 22.0 to 24.9, 25.0 to 27.9 and ≥ 28.0 kg/m²); WL (+- 2.4%, 2.5% to 5.9%, 6.0% to 10.9%, 11.0% to 14.9% and $\geq 15\%$) and BMI/WL grade (0, 1, 2, 3 and 4) as previously described by Martin and co-authors⁽⁸⁾. This study with 8,160 oncologic patients developed a robust grading system incorporating the independent prognostic significance of both BMI and weight loss and %WL was calculated as follows: [(current weight in kg – previous weight in kg)/previous weight in kg] X 100.

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 analysis was carried out using Cox proportional hazards model, and HRs 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 analyses were conducted in SPSS Version 20 (SPSS Inc).

Results

Data were available on 1303 patients in the combined European and Brazilian cohort. Patient's clinicopathological characteristics are shown in Table 1. The median age was 64.75 years (interquartile range (IQR) 55.54–72.70) and 667 patients were female (51%). The majority of patients had either gastrointestinal (37%, $n=487$) or lung (23%, $n=305$) tumors as a primary cancer site. The liver was the most common metastatic site (39%, $n=506$), followed by lung (31%, $n=409$) and bone (31%, $n=405$). The majority of patients had either BMI $\geq 28\text{kg/m}^2$ (29%, $n=353$) or BMI 22 – 24.9kg/m^2 (22%, $n=274$). 62% of the patients had weight stable and 35% had BMI/WL grade 0. 52% of the patients had mGPS 0 and 34% of the patients had mGPS 2. At the time of cessation of data collection, 344 patients were alive (26%) and 959 (74%) had died. The median survival was 6.6 months (IQR 3.0 – 14.6).

In Table 2, the 3-month survival rates were compared based on mGPS and BMI classifications. Regarding BMI, regardless of mGPS, the 3-month survival rates were similar and range from 78% (BMI 20-21.9) to 61% (BMI < 20). Considering the mGPS alone, the 3-month survival rate ranges from 84% (mGPS 0) to 60% (mGPS 2). Considering the combination of these two parameters, the 3-month survival rates range from 93% (mGPS 1 and BMI 20-21.9) to 43% (mGPS 2 and BMI < 20). Notably, the 3-month survival rate in the worst prognosis subgroup (BMI < 20) is 76% when mGPS is 0 and 43% when mGPS is 2.

In Table 3, the 3-month survival rate is described based on mGPS and WL classifications. Regarding the WL categories, the 3-month survival rates decreased as weight loss increased, ranging from 47% in cases of WL $\geq 15.0\%$ to 81% when weight was

considered stable ($\pm 2.4\%$). When considering mGPS alone, the 3-month survival rate was higher when mGPS was 0 (93%), compared to mGPS 1 (67%) and 2 (60%). Considering the combination of these two parameters, the 3-month survival rate ranges from 95% (weight stable and mGPS 0) to 28% (WL $\geq 15.0\%$ and mGPS 2). So, integrating the two prognostic tools enhances the precision of prognosis prediction, particularly in cases of stable WL, where the mGPS categories distinguished patients with 3-month survival rates of 95% (mGPS 0), 71% (mGPS 1), and 66% (mGPS 2). Specifically, in the subgroup with the poorest prognosis (WL $\geq 15.0\%$), the 3-month survival rate is 87% when the mGPS is 0 and drops to 28% when the mGPS is 2.

The 3-month survival rates were also compared based on mGPS and BMI/WL grade (Table 4). Individually, the higher the BMI/WL grade, the worse the prognosis; with 3-month survival rates of 86% and 87% for BMI/WL grades 0 and 1, respectively, and 59% for BMI/WL grade 4. When considering mGPS alone, the 3-month survival rate was higher with an mGPS of 0 (93%) compared to mGPS 1 (71%) and mGPS 2 (63%). Combining the two prognostic tools enhances the accuracy of prognosis differentiation. In all evaluated categories, the combination of the two prognostic tools effectively distinguished patients with different outcomes. Notably, in patients with BMI/WL grade 4, the 3-month survival rates were 86% and 38% when mGPS was 0 and 2, respectively.

The relationship between objective clinicopathological factors and survival in patients with advanced cancer is shown in Table 5. On univariate survival analysis, lung, hematological and breast as primary cancer sites (HR 1.334 and $P=0.001$, HR 0.284 and $P<0.001$, HR 0.693 and $P=0.001$, respectively), mGPS (HR 1.543-2.175, all $P<0.001$) and BMI/WL grade 1, 2, 3 and 4 (HR 1.300 and $P=0.014$, HR 1.405 and $P=0.011$, HR 1.745 and $P<0.001$, HR 2.307 and $P<0.001$, respectively) were significantly associated with survival. Age and sex were not associated with survival. On multivariate survival analysis, the most highly predictive factors were BMI/WL grade 3 (HR 1.454, $P=0.004$), BMI/WL grade 4 (HR 2.285, $P<0.001$) and mGPS (HR 1.887–2.545, all $P<0.001$).

Discussion

The results of the present study show that BMI, WL and the mGPS, which are phenotypic and aetiologic criteria proposed by GLIM, were significantly and independently associated with survival in patients with advanced cancer (European and Brazilian cohorts

combined). Furthermore, when these phenotypic and aetiologic criteria were combined, they provided an enhanced prediction of survival.

The results of the present study are consistent with the findings of Martin and co-workers, who demonstrated that BMI and WL predicted survival independently of conventional prognostic factors. When used in combination as a BMI/WL grading system, it provided a severity grade related to the risk of shortened survival⁽⁸⁾. Indeed, a prospective study with patients with advanced cancer showed that BMI/WL grade remained independently associated with overall survival. Additionally, in patients with a BMI/WL grade 0/1, both performance status and mGPS also remained independently associated with overall survival⁽⁸⁾. In this study, the mGPS predicted survival in patients for whom the GLIM criteria were considered normal. These results have several implications, particularly, that the systemic inflammatory response (SIR) precedes the development of malnutrition and should be the basis of the application of GLIM criteria in clinical practice. A recent review highlighted that systemic inflammation has progressively moved to the forefront of the definition and diagnosis of cancer cachexia. The authors consider cancer cachexia as primarily a SIR syndrome and, in this way, there are a number of potential implications for daily clinical practice⁽¹⁵⁾. Furthermore, a recent article compared prognostic factors in patients with advanced cancer found that a high performance status score and mGPS were consistently associated with poorer survival⁽¹⁶⁾.

Furthermore, contemporary evidence suggests that systemic inflammation is a determinant of body composition, symptom burden, physical function, and outcomes in patients with advanced cancer^(9,10,13,17,18). A phase III trial with advanced gastric and esophagogastric junction cancer patients showed that the mGPS was correlated with sarcopenia and dominated the prognostic role of baseline body composition parameters in these patients. The authors support a model where tumor-mediated inflammatory response, as measured by mGPS, represents a well-validated strong negative prognostic factor, which is related to sarcopenia. Whereas, a direct causal path from sarcopenia to survival is lacking⁽¹⁹⁾. Considering that patients with advanced cancer who are systemically inflamed but with no evidence of weight loss are pre-cachectic⁽²⁰⁾, cancer cachexia may be considered a disease-related inflammation with malnutrition. For instance, Wallengren and coworkers reported that patients with advanced cancer and CRP level greater than 10 mg/L exhibited lower muscle mass at baseline and longitudinally⁽²¹⁾. In addition, Malietzis et al. reported that, in patients with operable colorectal cancer (CCR), a neutrophil lymphocyte ratio (NLR) greater than 3

was associated with lower muscle mass⁽²²⁾. Another study with 650 operable CCR patients showed that sarcopenia (SMI) and myosteatorsis (SMD) were associated with the presence of a systemic inflammatory (in particular the mGPS) and had independent prognostic value⁽¹⁸⁾. Given the above, the assessment of systemic inflammation, in addition to nutritional status, should be considered as an essential component of the routine clinical and nutritional evaluation. In this context and based on the results of our study, it is suggested that the tool used to assess systemic inflammation in GLIM would be the mGPS.

Relevant studies and systematic reviews with meta-analyses on GLIM criteria and prognosis in cancer patients have been published, and highlight the relevance of the applicability of GLIM in cancer patients and the differences in the data set. Zhang and coworkers conducted a retrospective cohort analysis with almost 1,500 cancer patients, reported that the GLIM criteria can be used in elderly cancer patients not only to assess malnutrition, but also to predict survival outcome⁽²³⁾. A systematic review of 21 cohort studies published after 2018 showed that GLIM defined malnutrition consistently predictive of worse clinical outcomes in cancer patients. Notably, the predictive capacity of GLIM for survival was not affected by different measures of muscle mass reduction. However, variation in the assessment of etiological criteria has resulted in variation in the predictive ability of the GLIM diagnosis for survival⁽²⁴⁾. Matsui and coauthors conducted a systematic review and random-effects meta-analysis studies that included cancer patients receiving any type of treatment, with nutritional status assessed using GLIM criteria. The study highlighted that GLIM-defined malnutrition may worsen overall survival and increase the risk of postoperative complications in patients with cancer undergoing treatment⁽²⁵⁾.

The present study had limitations that should be considered. Given its cross-sectional design, heterogenous population, and observational nature, it is subject to sample bias. However, a large cohort of well characterised patients was examined, and the prognostic value of GLIM criteria was consistent across tumor types. The prognostic roles of BMI, WL, and BMI/WL were evaluated alongside mGPS. Our findings indicate that mGPS improves prognostic prediction when used in conjunction with weight loss measures. One limitation of the study is that the accuracy of these measures was not compared directly. Nevertheless, we believe that BMI/WL should be used in combination with mGPS, particularly because these variables were significant in the multivariate survival analysis.

In summary, a high BMI/WL grade and a high mGPS, as outlined in the BMI/WL grade/mGPS framework, were consistently associated with poorer survival outcomes of

patients with advanced cancer in the combined prospective European and Brazilian combined cohort. This framework can be readily incorporated into routine patient assessments of due to its simplicity and clinical utility.

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Competing interests

The authors declare no potential conflicts of interest.

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Authors' Contributions:

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

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)).

Availability of data and materials

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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Table 1. Clinicopathological characteristics of patients with advanced cancer – combined European and Brazilian cohort (n=1303)

Parameter	<i>n</i>	%
Age		
<65 years	658	50
65-74 years	362	28
74 years	283	22
Sex		
Male	636	49
Female	667	51
Primary cancer site		
Lung	305	23
Breast	156	12
Gynecological	91	7
Gastrointestinal	487	37
Urological	94	7
Haematological	43	3
Melanoma	50	4
Neurological	12	1
Unknown primary	19	2
Others	46	4
Metastatic sites		
Lung	409	31
Liver	506	39
Bone	405	31
Non-regional Lymph nodes	392	30
Peritoneum	175	13
Central Nervous System	76	6
Adrenal	59	4
Gynecological organs	17	1
Renal	11	1
Spleen	8	1
Not applicable	39	3
BMI ^a categories		
< 20.0 kg/m ²	188	15
20 - 21.9 kg/m ²	156	13
22 - 24.9 kg/m ²	274	23
25 - 27.9 kg/m ²	244	20
≥ 28.0 kg/m ²	353	29
WL ^b categories		
±2.4% (weight stable)	617	62
2.5–5.9%	142	14

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6.0–10.9%	119	12
11.0–14.9%	51	5
≥15.0%	68	7
BMI/WL grade ^c		
0	333	35
1	216	23
2	110	12
3	180	19
4	98	11
mGPS ^d		
0	564	52
1	153	14
2	372	34
Status		
Alive	344	26
Dead	959	74

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; WL, weight loss; BMI, body mass index.

^a BMI available on 1215 patients.

^b WL available on 997 patients.

^c BMI/WL grade available on 937 patients. BMI/WL grades calculated based on Martin *et al*⁽⁸⁾.

^d mGPS available on 1089 patients.

Table 2 – The relationship between body mass index (BMI) and the mGPS and the survival rate at 3 months in patients with advanced cancer – European cohort and Brazilian cohort (n=1.303)

Body mass index^a	mGPS 0 (n=564)	mGPS 1 (n=153)	mGPS 2 (n=372)	<i>P-Value</i>^b	mGPS 0-2 (n=1089)
>28 (n=353)	82% (n=122)	79% (n=34)	60% (n=56)	<0.001	74% (n=212)
25.0 – 27.9 (n=244)	88% (n=108)	56% (n=14)	74% (n=40)	<0.001	80% (n=162)
22.0 – 24.9 (n=274)	83% (n=93)	67% (n=22)	65% (n=55)	<0.001	74% (n=170)
20.0 – 21.9 (n=156)	90% (n=61)	93% (n=14)	54% (n=24)	<0.001	78% (n=99)
<20 (n=188)	76% (n=68)	(n=5)	43% (n=26)	<0.001	61% (n=99)
<i>P-Value</i> ^b	<0.001	<0.001	<0.001		
<20 - >28 (n=1215)	84% (n=452)	69% (n=89)	60% (n=201)		74% (n=742)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score.

^a BMI grouping based on Martin *et al*⁽⁸⁾.

^b P value from χ^2 analysis.

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

Table 3 – The relationship between weight lost (WL) and the mGPS and the survival rate at 3 months in patients with advanced cancer – European cohort and Brazilian cohort (n=1.303)

Weight loss^a	mGPS 0 (n=564)	mGPS 1 (n=153)	mGPS 2 (n=372)	<i>P-Value</i>^b	mGPS 0-2 (n=1089)
±2.4%(weight stable)(n=617)	95% (n=218)	71% (n=58)	66% (n=111)	<0.001	81% (n=387)
2.5–5.9% (n=142)	95% (n=53)	61% (n=11)	65% (n=26)	<0.001	79% (n=90)
6.0–10.9% (n=119)	91% (n=30)	59% (n=10)	63% (n=31)	0.002	72% (n=71)
11.0–14.9% (n=51)	(n=9)	(n=5)	53% (n=10)	0.416	60% (n=24)
≥15.0% (n=68)	87% (n=13)	(n=6)	28% (n=12)	0.249	47% (n=31)
<i>P-Value</i> ^b	<0.001	<0.001	<0.001		
±2.4% - ≥15.0% (n=997)	93% (n=323)	67% (n=90)	60% (n=190)		75% (n=603)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score.

^a WL grouping based on Martin *et al*⁽⁸⁾.

^b P value from χ^2 analysis.

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

Table 4 – The relationship between BMI/WL grade and the mGPS and the survival rate at 3 months in patients with advanced cancer – combined European and Brazilian cohort (n=1.303)

BMI/WL grade^a	mGPS^b 0 (n=564)	mGPS 1 (n=153)	mGPS 2 (n=372)	<i>P-Value</i>^b	mGPS 0-2 (n=1089)
0 (n=333)	93% (n=128)	73% (n=24)	78% (n=63)	<0.001	86% (n=215)
1 (n=216)	97% (n=72)	90% (n=26)	73% (n=44)	<0.001	87% (n=142)
2 (n=110)	93% (n=41)	(n=8)	61% (n=19)	<0.001	75% (n=68)
3 (n=180)	90% (n=45)	60% (n=15)	56% (n=43)	<0.001	68% (n=103)
4 (n=98)	86% (n=25)	(n=7)	38% (n=18)	0.007	59% (n=50)
<i>P-Value</i> ^b	<0.001	<0.001	<0.001		
0-4 (n=937)	93% (n=311)	71% (n=80)	63% (n=187)		78% (n=578)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; BMI, body mass index; WL, weight loss.

^a BMI/WL grades calculated based on Martin *et al*⁽⁸⁾.

^b P value from χ^2 analysis.

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

Table 5. The relationship between objective clinicopathological factors and survival in patients with advanced cancer – combined European and Brazilian cohort (n=1.303)

	Patients (N)	Univariate ^a		Multivariate ^a	
		HR (95% CI)	P	HR (95% CI)	P
Age					
<65	658	1.000 (Ref.)			
65-74	362	1.074 (0.926 – 1.246)	0.345		
>74	283	1.090 (0.923 – 1.287)	0.308		
Sex					
Male	636	1.000 (Ref.)			
Female	667	0.891 (0.785 – 1.012)	0.075		
Primary cancer site					
Gastrointestinal	487	1.000 (Ref.)		1.000 (Ref.)	
Lung	305	1.334 (1.130 – 1.574)	0.001	1.110 (0.896 – 1.376)	0.338
Neurological	12	1.010 (0.478 – 2.134)	0.979	2.472 (0.910 – 6.714)	0.076
Urological	94	0.932 (0.727 – 1.196)	0.580	0.823 (0.566 – 1.196)	0.307
Gynecological	91	0.846 (0.654 – 1.096)	0.205	1.376 (0.913 – 2.073)	0.127
Melanoma	50	0.838 (0.581 – 1.209)	0.345	0.814 (0.454 – 1.459)	0.490
Haematological	43	0.284 (0.175 – 0.463)	<0.001	0.267 (0.145 – 0.490)	<0.001
Breast	156	0.693 (0.557 – 0.864)	0.001	0.564 (0.344 – 0.926)	0.024
Unknown primary	19	1.530 (0.912 – 2.564)	0.107	1.668 (0.782 – 3.559)	0.186
Others	46	1.134 (0.806 – 1.596)	0.470	0.809 (0.415 – 1.579)	0.534
BMI/WL grade ^b					
0	333	1.000 (Ref.)		1.000 (Ref.)	
1	216	1.300 (1.055 – 1.601)	0.014	1.126 (0.880 – 1.441)	0.345

2	110	1.405 (1.082 – 1.824)	0.011	1.257 (0.930 – 1.698)	0.137
3	180	1.745 (1.398 – 2.177)	<0.001	1.454 (1.128 – 1.875)	0.004
4	98	2.307 (1.773 – 3.001)	<0.001	2.285 (1.703 – 3.067)	<0.001
mGPS					
mGPS 0	564	1.000 (Ref.)		1.000 (Ref.)	
mGPS 1	153	1.543 (1.249 – 1.906)	<0.001	1.887 (1.439 – 2.475)	<0.001
mGPS 2	372	2.175 (1.870 – 2.530)	<0.001	2.545 (2.084 – 3.109)	<0.001

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; BMI, body mass index; WL, weight lost.

^a HR expressed as per 10 unit change.

^b BMI/WL grades calculated based on Martin *et al*⁽⁸⁾.