Clinical Nutrition 39 (2020) 1587–1592

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Clinical utility of the modified Glasgow Prognostic Score to classify cachexia in patients with advanced cancer in palliative care

Geisiane Alves da Silva, Emanuelly Varea Maria Wiegert, Larissa Calixto-Lima, Livia Costa Oliveira*

Palliative Care Unit, National Cancer Institute José Alencar Gomes da Silva (INCA), Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 25 February 2019
Accepted 3 July 2019

Keywords:
Cachexia
Nutritional assessment
Inflammatory markers
Glasgow prognostic score
Advanced cancer
Palliative care

SUMMARY

Background & aims: It is a challenge in clinical practice to identify and classify cancer cachexia. Currently, it has been extensively discussed if the presence of alterations in inflammatory biomarkers implies the presence of cachexia. This study aimed to evaluate the clinical relevance of cachexia classification through modified Glasgow Prognostic Score (mGPS) in advanced cancer patients in palliative care.
Methods: Observational prospective cohort study conducted at a Palliative Care Unit in Brazil. Cachexia classification was performed according to mGPS (based on albumin and C-reactive protein) in four different stages: no cachexia (NCa), undernourished (Un), pre cachexia (PCa), and refractory cachexia (RCa). Logistic regression models were used to test the association between cachexia stages and clinical, nutritional and functional domains. Kaplan–Meier curve and Cox multivariate model were used to analyze overall survival (OS).
Results: A total of 1166 patients were included in the study. According to the cachexia framework 37.5% were NCa, 32.3% Un, 3.9% PCa and 26.4% RCa. Significant differences were observed among cachexia stages for most of the outcome measures. This classification was able to predict mortality in 90 days [Un (HR, 1.55; 95% CI, 1.25; 1.93); PCa (HR, 2.00; 95% CI, 1.34; 2.98); RCa (HR, 2.45; 95% CI, 1.34; 2.98)].
Conclusion: Cachexia stages were associated with significant differences in poor clinical outcomes and were also capable of predicting OS. This framework based on simple and objective criteria can be used as part of the routine to characterize the presence and stages of cachexia in advanced cancer patients.

1. Introduction

Cancer cachexia is a multifactorial syndrome driven by a complex combination that includes decreased food intake and impaired metabolism with modified catabolism and inflammation [1]. Advanced oncological disease exhibits an increased incidence of this disorder and their related clinical outcomes including weight loss (WL), altered body composition, decreased food intake, poor functional status, limited quality of life and reduced overall survival (OS) [2,3].

Due to its complex physiopathology, the challenge to diagnose and classify cancer cachexia in clinical practice still remains. Additionally, its prevalence is notably divergent according to the diagnostic criteria adopted [2,4,5]. Commonly routine standardized methods for cachexia diagnosis has centered on their consequences (e.g., WL, skeletal muscle depletion) and not on their causes [6].

The systemic inflammatory response has an important role as a key driver of energy imbalance and muscle wasting cancer cachexia [7]. Production of pro-inflammatory cytokines triggers a systemic inflammation and causes an acute phase response with increased C-reactive protein (CRP) and decreased albumin levels [8].

The most widely accepted index to characterize systemic inflammation is the modified Glasgow Prognostic score (mGPS) [9]. This score, that combines two simple clinical available biomarkers (CRP and albumin), has already been employed in a large number of different oncological patients and has also, previously, been shown to be associated with the prognosis in advanced cancer disease [10].

In 2014, Douglas and McMillan [10] published a review proposing the use of mGPS as an objective framework for the identification of cancer cachexia. However, its use specifically for the

* Corresponding author. 274, Visconde de Santa Isabel Street, Vila Isabel, 20560-120 Rio de Janeiro, RJ, Brazil.
E-mail addresses: alves.geisiane@hotmail.com (G.A. Silva), manuvarea@gmail.com (E.V.M. Wiegert), larissa_calixto@hotmail.com (L. Calixto-Lima), lillycostaoliveira@gmail.com (L.C. Oliveira).

https://doi.org/10.1016/j.clnu.2019.07.002
0261-5614/

diagnosis of this condition in advanced disease has not yet been elucidated. Hence, our aim in this study was to evaluate if an objective framework for classification of cancer cachexia can predict cachexia domains and OS in a cohort of cancer patients in palliative care.

2. Subjects and methods

This study presents results from a prospective cohort conducted in the Palliative Care Unit (PCU) at the National Cancer Institute José Alencar Gomes da Silva (INCA) in Brazil. The Ethical Committee of INCA (Protocol 1.407.458 of 2016) approved the study, and all the patients signed the consent form. The outpatients were evaluated at their first attendance care and inpatients within the first 48 h of the first hospitalization by trained researchers from June 2016 until May 2018. Age, sex, comorbidities, tumor type, metastasis, type of therapy, medical history and the date of death were collected from the patient medical records.

Eligible criteria were: age ≥20 years old, Karnofsky Performance Status (KPS) ≥30%, and ability to answer the necessary information and/or accompanied by someone capable of it.

2.1. Cachexia assessment

Cachexia was assessed using the mGPS framework in four different stages: no cachexia (NCa), undernourished (Un), pre cachexia (PCa) and refractory cachexia (RCa) according to Frame 1 [10].

2.2. Covariates

Weight was measured using a calibrated portable scale (Wiso Digital®) with an accuracy of 0.1 kg. For those patients who were unable to stand, it was used an in-bed scale system - Stryker®, model Go Bed II (Strayker Medical, USA). Height was measured using a tape stadiometer on the wall, however, when not possible, it had to be estimated through the Chumlea et al. [11] formulas. Body mass index (BMI) was calculated using weight (in kilograms) and height (in meters) and expressed in kg/m^2. Low BMI was diagnosed with a value < 20 kg/m^2 [4].

The skinfold thickness of triceps (TSF) was measured using a skinfold caliper Lange® (Cambridge Scientific Industries, USA). We also assessed arm circumference (AC) and mid-arm circumference (MAC) at the same point of TSF. Muscle mass was determined by anthropometry of mid upper-arm muscle area (MUAMA), calculated with the equation proposed by Heymsfield et al. [12]. Low muscle mass was characterized when MUAMA <32 cm^2 for male and <18 cm^2 for female [4].

Muscle strength was assessed through handgrip strength (HGS) using Jamar® hydraulic hand dynamometer (Baseline, Fabrication Enterprises, Inc, Elmsord, USA). Low muscle strength was defined when HGS <27 kg for male and <16 kg for female [13].

Frame 1
Cachexia framework.

mGPS	Biomarkers		Cachexia stage
	Albumin (g/dL)	CRP (mg/L)	
0	≥3.5	<10	No cachexia
0	<3.5	<10	Undernourished
1	≥3.5	≥10	Pre cachexia
2	<3.5	≥10	Refractory cachexia

Note: mGPS = modified Glasgow Prognostic Score; CRP= C – reactive protein.

All patients completed the validated Portuguese version of Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) (©FD Ottery, 2005, 2006, 2015), available by Ottery in Pt.Global.org, after permission for this use [14]. This tool consists of four boxes: Box 1 focuses on weight history (maximum score of 5), box 2 on food intake (maximum score of 4), box 3 on nutritional impact symptoms (maximum score of 24) and box 4 on functional status (maximum score of 3). The higher the score, the greater the nutritional risk.

Fatigue was evaluated using the Edmonton Symptom Assessment System, ranging from 0 (no symptoms) to 10 (worst possible symptoms) [15]. To define presence of fatigue, a value > 3 was used as cut-off point.

Laboratory profile included serum levels of albumin, CRP, complete blood cell count for leucocytes, neutrophils, lymphocytes, and platelets. The serum values were used to determine the neutrophil/lymphocyte and platelets/lymphocyte ratios (NLR and PLR, respectively). High NLR and PLR were defined as ≥5 and ≥ 300 respectively [16].

Cachexia syndrome classification according to the international consensus was also used to evaluate their association with the cachexia framework proposed. This classification system consists in the fulfillment of one of the three following criteria: WL >5% during the past 6 months; or BMI <20 kg/m^2 and ongoing WL >2%; or sarcopenia (reduced muscle mass) and ongoing WL >2% [4].

OS was assessed by using as baseline the date of inclusion in the study and the date of death or end of follow-up (May 2018) as the end of the study. For survival analysis, patients were dichotomized into survival ≤90 or >90 days.

2.3. Statistical analysis

Statistical analysis was processed using the Stata Data Analysis and Statistical Software 12.0. Kolmogorov–Smirnov test was performed to assess distribution of variables. Descriptive statistics are presented in percentages for the categorical variables and as mean with standard deviation (SD) or median with interquartile range (IQR) for the continuous variables. Differences between groups for continuous variables were tested by ANOVA followed by the Bonferroni post-hoc test.

The relationship between the variables and cachexia stages was explored by the performance of several logistic multiples regressions (one for each selected variable). The controls were: age ≥60 years, female gender, type of tumor, KPS 30 or 40% and current medical situation – inpatient *versus* outpatient.

As cachexia was categorized into four groups, 4 *dummy* variables (D1, D2, D3 and D4) were inserted into each of our regression equations. No cachexia group, represented by D1, were used as reference category. In each of the models, the odds ratio (OR) associated with D2, D3 and D4 were tested. If the estimator was determined to be "significant" according to its 95% confidence interval (CI), we interpreted that D2, D3 and/or D4 contributed to the explanatory power of the model and the nutritional status ratings for cachexia were independently related to the dependent variable to be compared.

Additionally, the Cox proportional hazard model was used to verify hazard ratios (HRs) of the cachexia stages that were able to predict OS. Kaplan–Meier curves were used to evaluate survival probability and the log-rank test to compare difference between the cachexia groups. A p value < 0.05 was considered statistically significant.

3. Results

A total of 1166 patients were included in this study. Patient characteristics are shown in Table 1. The mean age of the patients

was of 62 and the majority of them (57.1%) were female. Tumors of the gastrointestinal tract were the most prevalent among the patients and 80.4% of the sample presented metastatic disease.

According to cachexia classification, the majority of patients (37.3%) were NCa, followed by Un (32.3%) and RCa (26.4%). Only 3.9% were included in the PCa stage. A significant statistical difference was observed for all analyzed covariables according to cachexia groups, except to weight history score from PG-SGA SF (Box 1). Patients from the RCa group presented a more significant WL and nutritional impact symptoms, a higher PG-SGA SF score, and lower HGS when compared to other cachexia stages (Table 2).

As expected, it was observed a significant difference in the percentage of WL in all groups, both in the period of 1 month as in 6 months (NCa < Un < PCa < RCa) and the WL was significantly stronger in RCa patients (Fig. 1).

According to logistic regressions, the Un and RCa stages were able to identify significantly most of the differences related to the studied characteristics and the RCa group presented significant associations with all poor domains ($p < 0.01$), except for low MUAMA. The RCa patients have a greater risk of presenting the lowest BMI, highest WL, nutritional risk, more self-related symptoms, a poorer HGS, and the greatest biochemical disorders (Table 3).

Cachexia stages survival curves are described in Fig. 2. The median OS for all patients was of 39 days. There was a significant difference in OS between cachexia groups (77 *versus* 37 *versus* 31 *versus* 17 days, respectively; long-rank $p < 0.001$), except when compared Un and PCa group (long-rank p 0.345; data not show). When compared to NCa, the risk of death at 90 days was 1.5 times higher in the Un, 2.0 times in the PCa and 2.4 times in the RCa group ($p < 0.001$) (Table 3). Patients grouped in the RCa group had the highest probability to die during follow-up than the other groups studied.

Table 1
Characteristics of the advanced cancer patients treated at a Palliative Care Unit in the city of Rio de Janeiro, Brazil (n = 1166).

Variables	n (%)
Age (years)[a]	62 (±13.4)
Gender	
Female	666 (57.1)
Tumor Type	
GI Tract[b]	359 (30.8)
Gynecology[c]	196 (16.8)
Head and Neck[d]	155 (13.3)
Lung	125 (10.7)
Breast	118 (10.2)
Skin	57 (4.9)
Bones and soft tissues	39 (3.3)
Others[e]	117 (10.0)
Cancer Stage	
Local Advanced	174 (14.9)
Metastatic	992 (85.1)
Current Medical Situation	
Inpatient	218 (19.6)
Outpatient	898 (80.4)
Concurrent Treatment	
Surgery	463 (39.7)
Chemotherapy	701 (60.1)
Radiotherapy	508 (43.6)
KPS (%)	
30-40	576 (49.5)
50-60	406 (34.9)
≥70	181 (15.6)

Note: N = number of observations; % = frequency; GI = gastrointestinal; KPS= Karnofsky Performance Status.
[a] Mean/standard deviation.
[b] Upper and lower GI tract; cervix, uterus, endometrium, ovary and vulva.
[c] Cervix uterus endometriun ovary and, vulva.
[d] Oral and nasal cavity, pharynx, larynx, salivary glands, paranasal sinuses and eyes.
[e] Central nervous system, kidney and urinary tract, male reproductive system and hematologics.

4. Discussion

This is a pioneering study in which we demonstrated the clinical relevance of cachexia classification based on laboratory biomarkers in patients with advanced cancer in palliative care in a reference center in Brazil. Our results support that the stages of cachexia based on this simple and objective classification were associated with the main domains related to the cancer cachexia syndrome. Our findings confirm the hypothesis suggested by Douglas and McMillan [10] that mGPS can help in the assessment of cachexia progress.

In the present study, 36.2% of the sample had at least one altered criterion (albumin or CRP) and 26.4% fulfilled both laboratory altered criteria, named RCa. Bye et al. [17] using the mGPS framework in a group of patients with inoperable pancreatic cancer receiving palliative chemotherapy (n = 20) demonstrated a 65% prevalence of NCa, 5% of Un, 25% of PCa and 10% of RCa. The median survival rate reported by the authors was of 45.5 weeks. The disagreement between our reports should be justified by differences in the clinical profile, sample size, current medical situation and median OS. Gray and Axelsson [18] in a cohort study of patients enrolled in a specialized palliative home care found a prevalence of cachexia (define as CRP >10 mg/L and albumin <30 g/L) of 85% in the 0–30 days prior to death and 66% in the 31–60 days prior to death. In addition, these authors demonstrated that the majority of the sample (75%) had fulfilled the criteria within 0–120 days prior to death. Accordingly, the prevalence of cachexia seems to increase as death approaches.

Our results demonstrated that the cachexia framework allowed to capture alterations in clinical and functional features (nutritional risk, WL, symptoms, laboratory biomarkers, muscle mass, HGS, and performance status) according to the cachexia stage progression. Others have also related the elevated CRP with cachexia domains, like WL [7], skeletal muscle loss, strength impairment, physical function [19] and other symptoms [19,20].

Weight change is an important prognostic factor in advanced cancer. Furthermore, progressive WL is the most reported phenotype of cancer cachexia [4]. According to our results, RCa patients exhibited significantly higher WL than the NCa patients. Previous studies report inflammation as the major cause of WL in cancer patients and present the concentration of albumin and CRP as the best predictors of WL [21,22]. Takaioshi et al. [21] described increased WL rate as an independent predictor of poor OS and progression-free survival, and mGPS and CRP concentrations were significantly correlated with WL in this study. Likewise, Dean et al. [22] described that 34% of the WL observed was determined by elevated CRP concentration.

Irrespective of functionality markers, the RCa patients had poorer HGS, fatigue and functionality. Corroborating these findings, Wallengren et al. [2] evaluated different diagnostic criteria for cachexia in palliative cancer patients and demonstrated that elevated CRP and reduced albumin were associated with fatigue, low grip strength and short walking distance. Similarly, Kilgour et al. [23] showed that lower HGS percentiles were associated with reduced serum albumin values.

We also observed that the patients in advanced stages of cachexia exhibited higher nutritional impact symptoms burden. In a cohort of ovarian cancer patients it was shown that the highest mGPS values were associated with greater nausea, pain, dyspnea,

Table 2
Associations to characteristics studied according to cachexia stages.

Variables	N	No cachexia n = 435 (37.3%)	Undernourished n = 377 (32.3%)	Pre cachexia n = 46 (3.9%)	Refractory cachexia n = 308 (26.4%)	p-value	Total
Weight (kg)	903	61.8 (±16.1)	56.4 (±13.4)[a]	60.3 (±11.3)	55.3 (±14.6)[a]	**0.002**	58.6 (±15.1)
BMI (kg/m^2)	903	24.4 (±6.4)	22.3 (±5.3)[a]	23.9 (±4.5)	21.9 (±5.8)[a]	**0.002**	23.2 (±5.9)
WL 1 month (%)	714	3.8 (±5.2)	6.2 (±6.8)[a]	5.5 (±5.2)	8.7 (±8.3)[a,c]	**<0.001**	5.7 (±6.8)
WL 6 month (%)	867	9.5 (±9.5)	14.4 (±11.4)[a]	11.1 (±9.4)	16.8 (±11.6)[a,c]	**0.002**	13.0 (±11.1)
PG-SGA SF (score)	1163	12.8 (±6.9)	16.5 (±5.7)[a]	15.9 (±6.7)[a]	18.6 (±6.0)[a,b]	**0.001**	15.6 (±6.7)
Weight history (Box 1)	1163	1.8 (±1.7)	2.3 (±1.8)[a]	2.3 (±1.9)	2.5 (±1.8)[a]	0.622	2.2 (±1.8)
Food intake (Box 2)	1163	0.8 (±0.9)	1.0 (±1.0)[a]	1.1 (±1.1)	1.2 (±1.1)[a,b]	**0.005**	1.0 (±1.1)
Symptoms (Box 3)	1163	8.1 (±5.2)	10.5 (±4.8)[a]	10.0 (±5.4)	12.1 (±4.9)[a,b,c]	**0.017**	10.0 (±5.3)
Activity (Box 4)	1163	2.1 (±1.1)	2.7 (±0.7)[a]	2.4 (±0.9)	2.7 (±0.7)[a]	**<0.001**	2.5 (±0.9)
HGS	1117	22.5 (±10.5)	16.1 (±8.2)[a]	20.7 (±11.0)[b]	14.7 (±8.1)[a,c]	**<0.001**	18.3 (±9.8)
NLR	1163	5.8 (±5.4)	9.7 (±12.5)[a]	9.4 (±8.5)	13.6 (±13.0)[a,b]	**<0.001**	9.3 (±10.9)
PLR	1163	281.3 (±257.1)	373.2 (±332.5)[a]	398.0 (±284.2)	472.4 (±415.1)[a,b]	**<0.001**	366.0 (±338.5)

Note: N = number of observation; % = frequency; BMI = body mass index; WL = weight loss; PG-SGA SF= Patient-Generated Subjective Global Assessment Short Form; HGS = hand grip strength; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio.
The results was expressed as mean (±standard deviation). P-value refers to ANOVA. Bonferroni pairwise comparison were performed between groups.
Bold refers to p value that was statistically significant.
[a] Statistically different from No cachexia.
[b] Statistically different from Undernourished.
[c] Statistically different from pre cachexia.

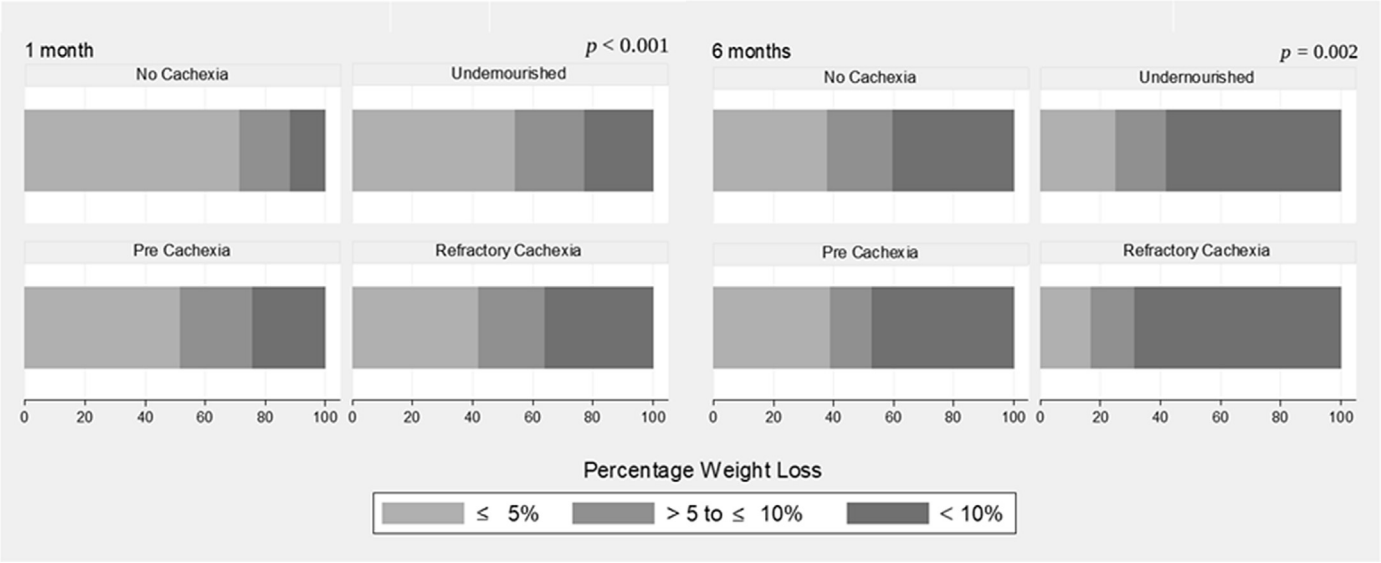

Fig. 1. Weight loss percentage during the past one and six months according to cachexia classification stages**. Notes:** P-value refers to ANOVA.

fatigue and anorexia [24]. Another study pointed that patients with higher CRP level (>10 mg/dL) presented a higher presence of symptoms and were 50% more likely to exhibit four or more symptoms [19]. In line with these studies, Vigano et al. [3] referred that patients in the RCa group presented the worst symptoms.

There was a strong association between elevated NLR and PLR and cachexia stages. In fact, NLR is an inflammation marker and increases with cancer progression [16]. Previous report, demonstrated that elevated NLR (≥5) and high CRP (≥10 mg/L) were independently associated with a poorer prognosis in advanced disease [25]. Our results suggest that NLR represents a sensible laboratory to associated with tumor related inflammation as well as PCR and albumin.

The NCa group had the best outcome measures, whereas patients in the RCa group had the poorest ones. According to the International Consensus on cachexia, RCa is characterized by a 3-month survival or less, an impossibility of reversion with conventional nutritional support, and an unresponsiveness to anticancer treatment [4]. Although International Consensus has already described cachexia in its different stages, it has not drawn any objective criteria to define RCa. In this context, our results suggest that a cachexia system framework can be useful in this regard, displacing us from a subjective definition of refractory cachexia.

In the present study, we observed that the RCa group presented the poor KPS when compared with the other groups. The PCa group did not presented a statistical difference when compared with RCa (data no show). Peformance status is a traditional prognostic tool used to advanced cancer patients. In the study of Laird et al. [26] the mGPS was similar to KPS in terms of prognostic power and according the authors when used together, performance status and mGPS improved prognostic accuracy.

It was also observed a lack of association of PCa and most of the covariates analyzed. This finding probably could be justified by the difficulty of classifying PCa stages using only CRP, once this marker can be easily altered by acute disorders. This suggests that in

Table 3
Regression models for cachexia classification stages according to outcomes.

Independent variables	N	Undernourish n = 377 (32.3%)		Pre cachexia n = 46 (3.9%)		Refractory cachexia n = 308 (26.4%)	
		OR (95% CI)[a]	p-value	OR (95% CI)[a]	p-value	OR (95% CI)[a]	p-value
Cachexia[d]	960	1.84 (1.23; 2.75)	**0.003**	1.51 (0.69; 3.32)	0.303	2.83 (1.73; 4.60)	**<0.001**
BMI < 20 kg/m^2	877	1.49 (1.04; 2.12)	**0.028**	0.89 (0.41; 1.97)	0.784	1.65 (1.11; 2.47)	**0.014**
WL >2%, 6 month	716	2.55 (1.59; 4.09)	**<0.001**	1.86 (0.73; 4.78)	0.195	2.30 (1.35; 3.91)	**<0.001**
WL >5%, 6 month	717	2.16 (1.43; 3.29)	**<0.001**	1.12 (0.50; 2.50)	0.776	2.71 (1.65; 4.43)	**<0.001**
Low MUAMA	1094	0.99 (0.73; 1.36)	0.995	1.38 (0.73; 2.61)	0.320	0.96 (0.68; 1.35)	0.825
Low HGS	1117	2.82 (1.24; 2.26)	**<0.001**	0.83 (0.14; 1.24)	0.424	4.35 (2.54; 8.14)	**<0.001**
PG-SGA SF (global score)							
≥9	1116	3.52 (2.55; 5.50)	**<0.001**	2.21 (0.94; 5.18)	0.067	4.11 (2.38; 7.10)	**<0.001**
≥18[b]	1116	1.41 (0.93; 1.80)	**0.035**	1.62 (0.84; 3.13)	0.151	2.53 (1.80; 3.55)	**<0.001**
Symptoms of nutritional impact[c]							
Hyporexia	1164	1.48 (1.10; 2.01)	**0.010**	1.50 (0.80; 2.80)	0.207	3.20 (2.25; 4.55)	**<0.001**
Nausea	1164	1.33 (0.98; 1.82)	0.063	1.78 (0.93; 3.39)	0.079	2.13 (1.52; 2.99)	**<0.001**
Intestinal Constipation	1164	1.30 (0.96; 1.74)	0.087	1.08 (0.58; 2.00)	0.797	1.75 (1.26; 2.44)	**<0.001**
Xerostomia	1164	1.47 (1.09; 1.98)	**0.012**	1.02 (0.55; 1.89)	0.954	2.00 (1.43; 2.80)	**<0.001**
Dysgeusia	1164	1.14 (0.84; 1.56)	0.388	1.44 (0.77; 2.72)	0.252	1.89 (1.36; 2.63)	**<0.001**
Fatigue[e]	1144	0.56 (0.07; 1.04)	**0.025**	0.32 (−0.69; 1.33)	0.529	1.06 (0.53; 1.59)	**<0.001**
NLR ≥ 5	1166	1.86 (1.37; 2.51)	**<0.001**	2.46 (1.26; 4.80)	**0.008**	4.84 (3.31; 7.09)	**<0.001**
PLR ≥ 300	1166	4.84 (1.26; 4.80)	**<0.001**	3.28 (1.75; 6.15)	**<0.001**	3.96 (2.82; 5.56)	**<0.001**
		HR (95% CI)[a]	**p-value**	**HR (95% CI)[a]**	**p-value**	**HR (95% CI)[a]**	**p-value**
90- days survival	866	1.55 (1.25; 1.93)	**<0.001**	2.00 (1.34; 2.98)	**0.001**	2.45 (1.34; 2.98)	**<0.001**

Note: OR = odds ratio; CI = confident interval; HR = hazard ratio; BMI = body mass index; MUAMA = mid-upper arm muscle area; PG-SGA SF= Patient-Generated Subjective Global Assessment Short Form; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; WL = weight loss; HGS = hand grip strength. Bold refers to p value that was statistically significant.

[a] Logistic and Cox regression adjusted for age ≥60 years, female gender, type of tumor, Karnofsky Performance Status 30 and 40%; current medical situation – in patient *versus* out patient.

[b] ROC curve of the PG-SGA SF score as a predictor of death in 90 days (cutoff: 18 points): AUC, 0.72; 95% IC, 0.68–0.76; p-value < 0.001.

[c] According PG-SGA SF.

[d] According Fearon et al., 2011.

[e] According Edmonton Symptom Assessment System.

chronically inflamed patients, albumin concentrations appear to improve accuracy to determine a diagnosis of cachexia. Additionally, we observed a lower prevalence of patients in PCa group (3.9%), which may reduce the statistical test accuracy.

Other studies failed to differentiate the PCa stage from the other stages [3,27]. Vigano et al. [3] proposed a cancer cachexia classification based on clinical features, however they were unsuccessful in distinguishing the pre-cachectic from the cachectic group. They justified that in the PCa group, there is a possibility of coexistence of patients with high cachexia risk and early stages of the syndrome. Thereby, we supposed, based on the dynamic nature of cancer cachexia that only cross-sectional observations of the inflammatory biomarkers should be insufficient to define PCa.

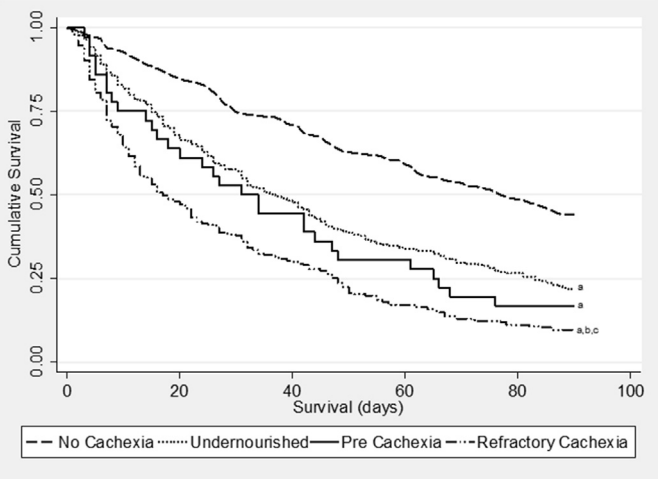

Fig. 2. Kaplan–Meier survival curves stratified according to cachexia classification stages. **Note:** [a]Statistically different from No cachexia; [b]Statistically different from Undernourished; [c]Statistically different from pre cachexia.

As would be expected, significant differences in the risk of death at 90-days were observed for all the cachexia stages. The cachexia classification system based on systemic inflammation criteria showed to be a better survival predictor when compared with another classification system based on clinical features [3,27]. As already discussed, Gray and Axelsson [18] reported a progressive increase in the prevalence of CRP >10 mg/dL and albumin <30 g/L when closer to death. In a study with inoperable pancreatic cancer patients, Bye et al. [17] showed that albumin decreased significantly from 43 mg/mL to 39 mg/mL (p = 0.01), whereas CRP increased from 5.8 mg/mL to 14.1 mg/mL. The median survival of this group was of 5.5 months.

The biggest limitation of this study was the evaluation of patients in a cross-sectional manner. Despite the fact that CRP was used as the most relevant biomarker for cachexia inflammation it is not specific for cancer, cachexia or for tumor activity, since it can be influenced by other factors such as infections. Moreover, although the mGPS framework clearly distinguishes NCa and RCa stages for all domains analyzed, it was unable to capture all stages of cachexia. Due to the lack of statistical discrimination between the PCa stage and almost all the outcomes examined, there is a need for further exploration, aiming a validation of this method with other clinical characteristics focusing on the benefits for cachectic advanced cancer patients.

5. Conclusion

Cachexia stages evaluated by mGPS were associated with poor clinical features and can predict OS. This classification system based on simple and objective criteria available in routine clinical practice

can be used to identify and characterize the presence and severity of cachexia in advanced cancer patients.

Conflict of interest

None declared.

CRediT authorship contribution statement

Geisiane Alves da Silva: Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization. **Emanuelly Varea Maria Wiegert:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization. **Larissa Calixto-Lima:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization. **Livia Costa Oliveira:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Mattox TW. Cancer cachexia: cause, diagnosis, and treatment. Nutr Clin Pract 2017;32:599–606. https://doi.org/10.1177/0884533617722986.
[2] Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer 2013;21:1569–77. https://doi.org/10.1007/s00520-012-1697-z.
[3] Vigano AAL, Morais JA, Ciutto L, Rosenthall L, Tomasso J, Khan S, et al. Use of routinely available clinical, nutritional, and functional criteria to classify cachexia in advanced cancer patients. Clin Nutr 2017;36:1378–90. https://doi.org/10.1016/j.clnu.2016.09.008.
[4] Fearon KC, Strasser F, Anker SD, Bosaeus I, Bruera E, Faisinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.
[5] Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006;83:1345–50. https://doi.org/10.1093/ajcn/83.6.1345.
[6] Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer cachexia: diagnosis, assessment, and treatment. Crit Rev Oncol Hematol 2018;127:91–104. https://doi.org/10.1016/j.critrevonc.2018.05.006.
[7] Lindenmann J, Fink-Neuboeck N, Koesslbacher M, Pichler M, Stojakovic T, Roller RE, et al. The influence of elevated levels of C-reactive protein and hypoalbuminemia on survival in patients with advanced inoperable esophageal cancer undergoing palliative treatment: CRP and albumin in esophageal cancer. J Surg Oncol 2014;110:645–50. https://doi.org/10.1002/jso.23711.
[8] Vanhoutte G, van de Wiel M, Wouters K, Sels M, Bartolomeeussen L, de Keersmaecker S, et al. Cachexia in cancer: what is in the definition? BMJ Open Gastroenterol 2016;3:e000097. https://doi.org/10.1136/bmjgast-2016-000097.
[9] McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer: nutrition Society and BAPEN Medical Symposium on 'Nutrition support in cancer therapy.'. Proc Nutr Soc 2008;67:257–62. https://doi.org/10.1017/S0029665108007131.
[10] Douglas E, McMillan DC. Towards a simple objective framework for the investigation and treatment of cancer cachexia: the Glasgow Prognostic Score. Cancer Treat Rev 2014;40:685–91. https://doi.org/10.1016/j.ctrv.2013.11.007.
[11] Chumlea WMC, Guo SS, Steinbaugh ML. Prediction of stature from knee height for black and white adults and children with application to mobility-impaired or handicapped persons. J Am Diet Assoc 1994;94:1385–91. https://doi.org/10.1016/0002-8223(94)92540-2.
[12] Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. Am J Clin Nutr 1982;36:680–90. https://doi.org/10.1093/ajcn/36.4.680.
[13] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing 2010;39:412–23. https://doi.org/10.1093/ageing/afq034.
[14] PG-SGA, AGS-PpeloD, Avaliação Global Subjetiva - Preenchida pelo Doente (PG-SGA). Traduzido, Adapt e validado para Popul Bras Scored Patient-Generated Subj Glob Assess PG-SGA (©FD Ottery, 2005, 2006, 2015). 2015. v.03.22.15.
[15] da Monteiro DR, de Almeida MA, Kruse MHL. Tradução e adaptação transcultural do instrumento Edmonton Symptom Assessment System para uso em cuidados paliativos. Rev Gaúcha Enferm 2013;(34):163–71. https://doi.org/10.1590/S1983-14472013000200021.
[16] Dolan RD, McSorley ST, Horgan PG, Laird B, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta-analysis. Crit Rev Oncol Hematol 2017;116:134–46. https://doi.org/10.1016/j.critrevonc.2017.06.002.
[17] Bye A, Wesseltoft-Rao N, Iversen PO, Skjegstad G, Holven KB, Ulven S, et al. Alterations in inflammatory biomarkers and energy intake in cancer cachexia: a prospective study in patients with inoperable pancreatic cancer. Med Oncol 2016;33:54. https://doi.org/10.1007/s12032-016-0768-2.
[18] Gray S, Axelsson B. The prevalence of deranged C-reactive protein and albumin in patients with incurable cancer approaching death. PLoS One 2018;13:e0193693. https://doi.org/10.1371/journal.pone.0193693.
[19] Amano K, Maeda I, Morita T, Baba M, Miura T, Hama T, et al. C-reactive protein, symptoms and activity of daily living in patients with advanced cancer receiving palliative care. J Cachexia Sarcopenia Muscle 2017;8:457–65. https://doi.org/10.1002/jcsm.12184.
[20] Laird BJ, McMillan DC, Fayers P, Fearon KCH, Kaasa S, Fallon MT, et al. The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. The Oncologist 2013;18:1050. https://doi.org/10.1634/theoncologist.2013-0120.
[21] Takayoshi K, Uchino K, Nakano M, Ikejiri K, Baba Eishi. Weight loss during initial chemotherapy predicts survival in patients with advanced gastric cancer. Nutr Cancer 2017;69:408–15. https://doi.org/10.1080/01635581.2017.1267774.
[22] Deans DAC, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. Br J Canc 2009;100:63–9. https://doi.org/10.1038/sj.bjc.6604828.
[23] Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. Support Care Cancer 2013;21:3261–70. https://doi.org/10.1007/s00520-013-1894-4.
[24] Roncolato FT, Berton-Rigaud D, O'Connell R, Lanceley A, Sehouli J, Buizen L, et al. Validation of the modified Glasgow prognostic score (mGPS) in recurrent ovarian cancer (ROC) – analysis of patients enrolled in the GCIG symptom benefit study (SBS). Gynecol Oncol 2018;148:36–41. https://doi.org/10.1016/j.ygyno.2017.10.019.
[25] Pinato DJ, Shiner RJ, Seckl MJ, Stebbing J, Sharma R, Mauri FA. Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. Br J Canc 2014;110:1930. https://doi.org/10.1038/bjc.2014.145. 5.
[26] Laird BJ, Kaasa S, McMillan DC, Fallon MT, Hjermstad MJ, Fayers P, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. Clin Cancer Res 2013;19:5456–64. https://doi.org/10.1158/1078-0432.CCR-13-1066.
[27] Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE. Validation of the consensus-definition for cancer cachexia and evaluation of a classification model–a study based on data from an international multicentre project (EPCRC-CSA). Ann Oncol 2014;25:1635–42. https://doi.org/10.1093/annonc/mdu086.