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Prognostic factors in inpatients with advanced cancer at a palliative care unit

Fatores prognósticos em pacientes internados com câncer avançado em uma unidade de cuidados paliativos

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ABSTRACT

Objectives: This study aims to identify prognostic factors and their discriminatory ability in inpatients with advanced cancer at a palliative care unit (PCU). **Material and Methods:** Observational, prospective cohort study involving advanced cancer patients (October 2019 to May 2021) of their first admission to a PCU. Sociodemographic, clinical, functional, nutritional, and laboratory variables were evaluated. The outcome was death within 30 days. Kaplan-Meier curves, log-rank test, and Cox proportional hazard model were used to assess prognostic value. The C-statistic was used to test the predictive accuracy of the variables. **Results:** Among 136 patients, 77 (56.6%) died within 30 days and the median overall survival was 10 (interquartile range: 6-14) days. The variables of 30-day mortality were tumor in the gastrointestinal tract (GIT) (hazard ratio [HR]: 1.61, 95% confidence interval [CI]: 1.11-2.82), impaired functionality (HR: 1.73, 95%CI: 1.09-3.00), nutritional risk (HR: 4.58, 95%CI: 1.62-12.92), and albumin <3g/dL (HR: 1.88, 95%CI: 1.05-3.34). However, albumin presented acceptable discrimination, with a C-statistic value of 0.75. **Conclusion:** Inpatients with advanced cancer in the GIT, impaired functionality, reduced serum albumin, and at nutritional risk have a worse prognosis. Albumin concentration has better discriminatory ability than the other factors identified.

Keywords: Neoplasms; Palliative care; Prognosis; Hospitalization; Mortality.

RESUMO

Objetivos: Este estudo tem como objetivo identificar fatores prognósticos e sua capacidade discriminatória em pacientes com câncer avançado internados em uma unidade de cuidados paliativos (UCP). **Material e Métodos:** Estudo observacional de coorte prospectivo envolvendo pacientes com câncer avançado (outubro de 2019 a maio de 2021) de sua primeira admissão em uma UCP. Foram avaliadas variáveis sociodemográficas, clínicas, funcionais, nutricionais e laboratoriais. O desfecho foi a morte em 30 dias. Curvas de Kaplan-Meier, teste de log-rank e modelo de risco proporcional de Cox foram usados para avaliar o valor prognóstico. A estatística-C foi utilizada para testar a acurácia preditiva das variáveis. **Resultados:** Entre 136 pacientes, 77 (56,6%) morreram em 30 dias e a sobrevida global mediana foi de 10 (intervalo interquartil: 6-14) dias. As variáveis de mortalidade em 30 dias foram tumor no trato gastrointestinal (TGI) (taxa de risco [HR]: 1,61, intervalo de confiança de 95% [IC]: 1,11-2,82), funcionalidade prejudicada (HR: 1,73, IC95%: 1,09 -3,00), risco nutricional (HR: 4,58, IC95%: 1,62-12,92) e albumina <3g/dL (HR: 1,88, IC95%: 1,05-3,34). No entanto, a albumina apresentou discriminação aceitável, com valor da estatística-C de 0,75. **Conclusão:** Pacientes internados com câncer avançado no TGI, funcionalidade prejudicada, albumina sérica reduzida e em risco nutricional apresentam pior prognóstico. A concentração de albumina tem melhor capacidade discriminatória do que os outros fatores identificados.

Palavras-chave: Neoplasias; Cuidado paliativo; Prognóstico; Hospitalização; Mortalidade.

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INTRODUCTION

In countries where access to health is poor, most individuals with cancer arrive at health services when it is already at an advanced stage[1]. Data from a specialized palliative care unit (PCU) in Brazil, indicate that most patients entered the institution with advanced cancer and did not meet the eligibility criteria to receive curative treatment[2].

In this context, clinical decisions related to procedures or surgeries, nutrition, artificial hydration, etc., draw on the results of a prognostic assessment[3]. As a large part of this group of individuals experience reduced survival[4], especially in a hospital setting, it is essential for an adequate prognosis to be made to ensure adequate care planning[5], with a view to optimizing treatment strategies, minimizing the risk of undertreatment or approaches that are futile and/or disproportionate to the progression of the disease[6].

Thus, the use of good discrimination prognostic factors is essential for inpatients, since a shorter survival time and higher mortality rates are observed in the hospital setting. Therefore, this study aims to identify prognostic factors and their discriminatory capacity for advanced cancer patients hospitalized at the PCU of a specialized cancer hospital.

MATERIAL AND METHODS

This clinical, observational, prospective cohort study was conducted with patients admitted to the PCU in Brazil. The focus of treatment in the PCU is symptom control and promotion of quality of life and death. It begins when antitumor treatment is interrupted due to ineffective response and/or serious side effects, so none of the patients in the cohort were receiving any curative cancer treatment. The study was approved by the Ethics Committee of INCA (3,550,658) and the participants were included in the research after agreeing and signing the free and informed consent term.

Patients were continuously enrolled from October 2019 to May 2021, evaluated by trained researchers within 72 hours of the first hospital admission, and monitored until the outcome of their hospital stay. Eligibility criteria for the study were: having advanced malignant neoplasm regardless of location, age ≥20 years, Karnofsky Performance Status (KPS) ≥30%, and being able to provide the required information. The KPS is a percentage scale that classifies the individual as to their ability to perform normal daily activities, active work, self-care, and need for regular medical care due to greater evidence of disease (100%: full function; 0%: death)[7].

Independent variables

The following variables were obtained from the electronic medical records: sociodemographic (age [<60 vs. ≥60 years] and sex [male vs. female]); clinical (diagnosis [gynecological cancer vs. breast vs. gastrointestinal tract (GIT) vs. lung vs. head and neck vs. connective bone tissue vs. others] and distant metastasis [no vs. yes]), functionality (KPS [30% vs. ≥40%]), nutritional (overall score of the patient-generated global subjective assessment short-form [PG-SGA SF©] <9 vs. ≥9). For laboratory characteristics, it was considering these cutoff: albumin (<3 vs. ≥3g/dL), C-reactive protein (CRP, <5 vs. ≥5mg/L), C-reactive protein albumin ratio (CAR, <2 vs. ≥2), and the modified Glasgow Prognostic Score (mGPS, 0 vs. 1+2).

After permission, the translated Portuguese version of the PG-SGA SF©, available at pt-global.org (©FD Ottery, 2005, 2006, 2015) was used. The instrument, comprising the first four domains of the complete tool, was administered by trained researchers in order to assess: (1) change in body weight (score from 0 to 5); (2) food intake (score from 0 to 4); (3) presence of symptoms of nutritional impact (score from 0 to 24); (4) functional capacity (score from 0 to 3). At the end of the evaluation, a numerical score was generated based on the sum of each of the items in the questionnaire, ranging from 0 to 36. The higher the score, the worse the nutritional status, with 9 being the cutoff point for classification of nutritional risk[8,9]. As directed by the tool, patients with cutoff ≥9 points need an urgent interventional nutrition to control symptoms.

Outcome

The outcome evaluated was death within 30 days, based on information collected from the medical records.

Statistical analysis

Statistical analysis was performed using Stata 13.0 (Stata Corp., College Station, Texas, USA); *p*-values<0.05 were considered statistically significant.

Descriptive statistics were presented as percentages (number of observations/frequency, %) and the death rate between groups was compared using the chi-square test for proportions. The log-rank test was used to compare survival differences between the groups and Kaplan Meier curves were constructed to assess the probability of survival for selected variables (log-rank *p*-value<0.050).

In addition, Cox proportional regression analyses were used to identify prognostic factors, with the hazard ratio (HR) and confidence interval (95%CI) as measures of effect. The variables considered in the multivariate analysis were the ones for which $p \leq 0.20$ in the univariate analysis, and were removed one by one, in descending order of *p*-value. Only those with $p < 0.050$ were retained in the final model.

The agreement statistic (C-statistic) was used to assess the discrimination of the factors associated with the dependent variables. A C-statistic of 0.5 indicates that the model predicts the outcome as well as chance (equal numbers of true and false positives), 0.7 to <0.8 indicates acceptable discrimination, 0.8 to <0.9 indicates excellent discrimination, 0.9 to <1.0 is remarkable discrimination, and 1.0 is perfect prediction[10].

RESULTS

A total of 136 patients were included in the study. Most of them were older (≥60 years: 55.2%), female (68.4%), with gynecological as the primary site of malignancy (23.5%), and had distant metastasis (83.1%). In general, they had low functionality (KPS 30%: 59.6%), nutritional risk (PG-SGA SF© ≥9 points: 83.1%), and exacerbated systemic inflammation (albumin <3g/dL: 59.6%, CRP ≥5mg/L: 80.4%, CAR ≥2: 70.9%, mGPS 1+2: 56.4%) (Table 1).

Among the patients evaluated, 77 (56.6%) died within 30 days and the median overall survival was 10 (interquartile range [IQR]: 6-14) days. Death rates were higher in patients with gynecological and GIT tumors (p=0.001), KPS=30% (p=0.030), PG-SGA SF© ≥9 points (p=0.005), albumin <3g/dL (p=0.001), and CAR ≥2 (p=0.051) at admission (Table 1). The survival medians were statistically lower in these same groups (Table 1 and Figure 1).

Table 1. General characteristics and median survival of inpatients with advanced cancer (n=136).

Variables	Total	Death inpantiens			Survival (days)		
		No (n=59; 43.4%)	Yes (n= 77; 56.6%)	p[a]	Median	IQR	p[b]
Age (years)							
<60	61 (44.8%)	28 (45.9%)	33 (54.1%)	0.593	14	8-23	0.327
≥60	75 (55.2%)	31 (41.3%)	44 (58.7%)		13	7-20	
Gender							
Male	43 (31.6%)	20 (46.5%)	23 (53.5%)	0.617	13	7-22	0.935
Female	93 (68.4%)	39 (41.9%)	54 (58.1%)		14	8-21	
Tumor type							
Gynecological	32 (23.5%)	8 (25.0%)	24 (75.0%)	0.001	12	7-19	0.056
Breast	30 (22.0%)	22 (73.3%)	8 (26.7%)		16	14-19	
GIT	27 (19.9%)	7 (25.9%)	20 (74.1%)		9	6-15	
Lung	12 (8.8%)	6 (50.0%)	6 (50.0%)		12	7-18	
HN	10 (7.3%)	3 (30.0%)	7 (70.0%)		13	11-19	
CBT	9 (6.6%)	3 (33.3%)	6 (66.7%)		11	5-22	
Others[c]	16 (11.9%)	10 (62.5%)	6 (37.5%)		21	13-21	
Distant metastasis							
No	23 (16.9%)	8 (34.8%)	15 (65.2%)	0.361	13	6-14	0.244
Yes	113 (83.1%)	51 (45.1%)	62 (54.9%)		14	8-22	
KPS (%)							
30%	81 (59.6%)	29 (35.8%)	52 (64.2%)	0.030	11	6-19	0.025
≥40%	55 (40.4%)	30 (54.5%)	25 (45.5%)		15	11-22	
PG-SGA SF© (points)							
<9	23 (16.9%)	16 (69.6%)	7 (30.4%)	0.005	22	14-27	0.002
≥9	113 (83.1%)	43 (38.0%)	70 (62.0%)		12	7-18	
Albumin (g/dL)							
<3	65 (59.6%)	21 (32.3%)	44 (67.7%)	0.001	11	6-18	0.006
≥3	44 (40.4%)	28 (63.6%)	16 (36.4%)		17	11-24	
CRP (mg/L)							
<5	20 (19.6%)	12 (60.0%)	8 (40.0%)	0.135	20	7-27	0.127
≥5	82 (80.4%)	34 (41.5%)	48 (58.5%)		14	8-21	
mGPS							
0	44 (43.6%)	23 (52.3%)	21 (47.7%)	0.170	17	8-24	0.252
1+2	57 (56.4%)	22 (38.6%)	35 (61.4%)		14	8-22	
CAR							
<2	23 (29.1%)	15 (65.2%)	8 (34.8%)	0.051	21	8-24	0.017
≥2	56 (70.9%)	23 (41.1%)	33 (58.9%)		12	8-18	

n = Number of observations; IQR = Interquartile range; GIT = Gastrointestinal tract; HN = Head and neck; CBT = Connective bone tissue; KPS = Karnofsky Performance Status; PG-SGA SF© = Patient-Generated Subjective Global Assessment short form; CRP = C-reactive protein; mGPS = Modified Glasgow Prognostic Score; CAR = C-reactive protein albumin ratio.
Notes: [a]p-value refers to chi-square test or Fisher's exact; [b]p-value refers to the log-rank test; [c]Leukemia, lymphoma, myeloma, central nervous system, kidney and urinary tract, male genitals, peritoneum, mediastinum, and unrecognized site.

According to the Cox univariate regression analyses, the primary tumor site, KPS, PG-SGA SF©, serum albumin concentration, CRP, and CAR were candidates for the multiple model. In the multivariate analysis, the primary tumor site located in the GIT (HR: 1.61, 95%CI: 1.11-2.82), KPS=30% (HR: 1.73, 95%CI: 1.09-3.00), PG-SGA SF© ≥9 points (HR: 4.58, 95%CI: 1.62-12.92), and serum albumin concentrations <3g/dL (HR: 1.88, 95%CI: 1.05-3.34) were retained as prognostic factor within 30-day. However, only albumin showed acceptable discrimination, with a C-statistic value of 0.75 (Table 2).

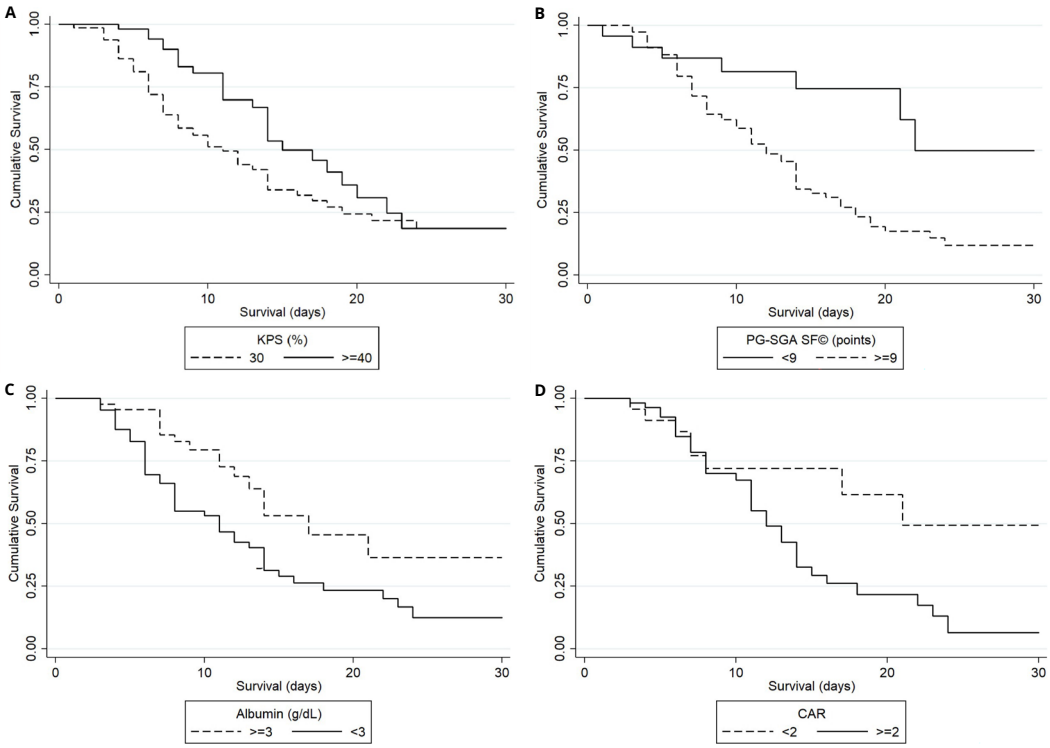

Figure 1. Survival curves of inpatients with advanced cancer according to selected variables (n=136).
Abbreviations: n = Number of observations; KPS = Karnofsky Performance Status; PG-SGA SF© = Patient-Generated Subjective Global Assessment short form; CAR = C-reactive protein albumin ratio.

Table 2. Prognostic factors within 30-day among inpatients with advanced cancer (n=136).

Variables	HR	Univariate 95% CI	p[a]	HR	Multivariate 95% CI	p[b]	C-statistic
Types of tumor							
GIT	1.83	1.10-3.05	**0.021**	1.61	1.11-2.82	**0.049**	0.67
Others	1.00			1.00			
KPS (%)							
30%	1.69	1.05-2.73	**0.031**	1.73	1.09-3.00	**0.042**	0.69
≥40%	1.00			1.00			
PG-SGA SF© (points)							
<9	1.00		**0.005**	1.00		**0.004**	0.69
≥9	3.10	1.41-6.77		4.58	1.62-12.92		
Albumin (g/dL)							
<3	2.15	1.21-3.81	**0.009**	1.88	1.05-3.34	**0.033**	0.75
≥3	1.00			1.00			
CRP (mg/L)							
<5	1.00		0.141	-	-	-	-
≥5	1.76	0.83-3.72					
mGPS							
0	1.00						
1+2	1.36	0.79-2.34	0.264	-	-	-	-
CAR							
<2	1.00						
≥2	2.45	1.12-5.36	0.024	-	-	-	-

Abbreviations: n = Number of observations; HR = Hazard ratio; CI = Confidence interval; GIT = Gastrointestinal tract; KPS = Karnofsky Performance Status; PG-SGA SF© = Patient-Generated Subjective Global Assessment short form; CRP = C-reactive protein; mGPS = Modified Glasgow prognostic score; CAR = C-reactive protein albumin ratio.
Notes: [a]p-value refers to univariate Cox proportional hazard model; [b]p-value refers to multivariate Cox proportional hazard model.

DISCUSSION

In this study, we identified the prognostic factors and their discriminatory capacity in patients with advanced cancer hospitalized at a specialized PCU at a reference hospital for cancer care. Our results showed that the patients with advanced GIT cancer who presented at the time of hospitalization with impaired functionality, reduced serum albumin, and nutritional risk had a worse prognosis. Among these prognostic factors, serum albumin concentration showed better discriminatory.

Prognostic assessments are challenging for health professionals and researchers, especially for inpatients with advanced cancer. Despite the availability of validated objective tools and prognostic factors, consideration should be given to the method to be applied, since its accuracy may vary according to the population, environment, and forecast period. Death is a prevalent outcome for patients hospitalized with advanced cancer, calling for the use of specific prognostic factors to guide important personal and clinical decisions[11]. However, there is not a great deal of scientific evidence at the present time that focuses exclusively on cancer inpatients in palliative care.

The hospitalized patients in palliative cancer care from our study had low survival (10 days [IQR: 6-14]), which is consistent with the findings of other studies[5,12]. In an Argentine cohort, hospitalized cancer patients in palliative care were found to have a higher risk of death than those receiving outpatient follow-up (HR: 1.87, 95%CI: 1.24-2.84, *p*-value: 0.003)[13].

The cutoff points selected for biomarkers analysis (albumin<3.0[5], CAR≥2.0[14], CRP≥5[15], and scores GPS 1+2[16] were based on previous studies, which observed lower survival when using them. Considering a context of lower survival, we used more severe cutoff points to better support the care plan for these patients.

Turning to tumor location, other cohort studies carried out at the same referral center found a high prevalence of GIT and gynecological cancer[4,17,18]. The multivariate Cox regression used in our study found that patients with GIT cancer had a worse prognosis (HR: 1.61, 95%CI: 1.11-2.82, *p*-value: 0.049), which is similar to the findings of Martin et al. (2010)[19] (HR: 1.69, 95%CI: 1.30-2.19, *p*-value<0.001). This could be attributed to the fact that this type of cancer is associated with a greater nutritional impact, and consequently with repercussions on overall survival.[20] In a Brazilian multicentric study, upper digestive cancer had a strong association with malnutrition [odds ratio (OR): 4.51, 95%CI: 3.31-6.1, *p*-value<0.001].[21]

Functional capacity is recognized as a relevant prognostic factor in different health contexts, including in cancer patients, where it is considered a strong independent predictor of survival.[22] In their multivariate analysis, Fiorin de Vasconcellos et al. (2019)[23] found that patients with solid tumors at an advanced stage and with worse functionality had a higher risk of death within 30 days (HR: 2.01, 95%CI: 1.14-3.53, *p*-value: 0.016). Furthermore, the median KPS at admission was significantly lower in those who progressed to death than in those whose outcome was discharge.[24] These data corroborate our findings, as our multivariate analysis revealed that the presence of KPS=30% was a prognostic factor within 30 days (HR: 1.73, 95%CI: 1.09-3.00, *p*-value: 0.042). Consistent with this, some specific prognostic tools for patients in palliative care – such as the palliative performance scale, the palliative prognostic score, and the palliative prognostic index – include functionality as a crucial variable in their composition.[25]

As expected, most of our inpatients (83.1%) had an overall PG-SGA SF© score ≥9 points (HR: 4.58, 95%CI: 1.62-12.92, *p*-value: 0.004), which indicates nutritional risk, considered an important prognostic factor. A previous publication, based on research developed at the same PCU, demonstrated that PG-SGA SF© was associated with lower survival and a higher risk of 90-day mortality, making it an indicator of a worse prognosis[16]. This cutoff point, despite not being validated for the Brazilian cancer population, is widely used to classify patients at nutritional risk.[26]

As for albumin, in addition to its good prognostic power, it is also a marker of nutritional status and a simple parameter capable of reflecting inflammatory status.[27] In a study of patients with inoperable advanced esophageal cancer, survival was significantly shorter in those with a serum concentration of this acute-phase protein was lower than 3.5g/dL.[28] In a cohort study developed at the same PCU, the presence of hypoalbuminemia was also an independent prognostic factor within 90-day (HR: 2.04, 95%CI: 1.16-3.58, *p*-value: 0.013).[16] Furthermore, in a systematic review and meta-analysis, Dolan et al. (2017)[29] found studies in which patients with serum albumin levels <3.0g/dL had lower survival (HR: 1.57, 95%CI: 1.26-1.95, *p*-value<0.0001), corroborating our findings (HR: 1.88, 95%CI: 1.05-3.34, *p*-value<0.033).[29]

There are some limitations of our study that deserve to be highlighted. First, the study was undertaken at a single site and had a small sample size, which could interfere with the power of the statistical tests used. Larger studies would be needed to overcome this limitation. Meanwhile, the study's strength is that it analyzes simple and objective elements for prognostic assessment that could be used by any member of the multidisciplinary team, making it more easily applied in the clinical setting.

CONCLUSION

Inpatients with advanced cancer in the GIT (primary site), impaired functionality, reduced serum albumin, and nutritional risk at admission have a worse prognosis. Serum albumin concentration has better discriminatory ability than the other factors identified. Although this relationship is well explored in the literature, the use of these variables and, some of them, with more severe cutoff points, specifically for hospitalized patients, is an issue that has not yet been explored, which can better support the care plan in this specific group.

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