

# Predictive Factors of Death on Hospitalization in Patients With Advanced Cancer in Palliative Care

American Journal of Hospice & Palliative Medicine®  
2021, Vol. 38(10) 1189-1194  
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DOI: 10.1177/1049909120976398  
journals.sagepub.com/home/ajh



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## Abstract

**Background:** Prognostic assessment is essential to plan the care of patients with advanced cancer in palliative care. **Objective:** Thus, this study aims to assess the predictors of death in inpatients with advanced cancer in palliative care. **Methods:** This is a clinical, observational cohort study with patients aged >20 years, of both genders, evaluated within 48 hours of the first hospitalization. The independent variables were tumor location, nutritional risk [through the Patient-Generated Subjective Global Assessment (PG-SGA) short form], laboratory tests [C-reactive protein and albumin] and Karnofsky Performance Status (KPS). Logistic regression analyses were performed. **Results:** Eighty-two patients were evaluated, whose mean age was 61.8 ( $\pm$  13.2) years. Forty-nine (59.8%) patients died during hospitalization, among which the majority had KPS of 30-40% (p-value = 0.043), higher means of the total score of the PG-SGA (p-value = 0.050) and lower serum albumin concentrations (p-value = 0.011). According to the multivariate model, tumor location in the gastrointestinal (GI) tract (OR: 1.73; 95% CI: 1.57-1.94), 30-40% KPS (OR: 1.29; 95% CI: 1.07-1.63) and albumin concentrations <3.5 g/dL (OR: 4.65; 95% CI: 1.22-17.7) were independent factors associated with an increased chance of death from hospitalization. **Conclusion:** Presenting an advanced tumor with localization in the GI tract, KPS  $\leq$ 40% and serum albumin concentration <3.5 g/dL at admission were predictors of death in inpatients under palliative care.

## Keywords

advanced cancer, palliative care, prognosis, mortality, albumin, functionality

## Introduction

Palliative care is defined by the World Health Organization (WHO)<sup>1</sup> as an approach that aims to improve the quality of life of patients and their families in the face of a disease that threatens the continuity of life, through the prevention and relief of suffering, identification assessment, assessment and treatment of pain and other physical, psychosocial and spiritual symptoms. Early palliative care reduces unnecessary hospitalizations and the use of health services, contributing to efficient use of resources.<sup>2</sup>

In patients with advanced cancer in palliative care, the use of prognostic measures/markers assumes a guiding role in the establishment of care planning, contributing to the improvement of treatment strategies and the efficient use of available resources. Prognostic assessment minimizes the risk of undertreatment or futile and disproportionate therapies in advancing cancer.<sup>3</sup> And, among the various predictors of survival, reduced functional capacity, exacerbated systemic inflammation and impaired nutritional status, among others, have been described in the literature as useful prognostic indicators in clinical practice.<sup>4-6</sup>

Considering the role of prognostic evaluation in establishing the care and assistance plan for patients in palliative oncology

care, it is extremely important to recognize the determinants of unfavorable clinical outcomes. Thus, this study aims to assess the factors associated with death in patients with advanced cancer, admitted to an exclusive Palliative Care Unit (PCU).

## Methods

This is a clinical, observational, prospective cohort study with patients treated at the PCU at the National Cancer Institute José Alencar Gomes da Silva (INCA), that offers comprehensive care to cancer patient with no current cure, in exclusive palliative care, in the city of Rio de Janeiro/RJ. Patients were evaluated within 48 hours of the first hospital admission to the PCU, from October 2019 to March 2020, with individuals with advanced cancer, regardless of tumor location, of both genders,

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aged  $\geq 20$  years, being eligible, Karnofsky Performance Status (KPS) 30% and able to adequately answer the necessary information. The patients had generalized malignant disease or advanced local tumor growth and were not receiving any anti-neoplastic treatment with curative intent. The participants provided written agreement to participate in the research by signing the Free and Informed Consent Term. The study was approved by the INCA Ethics Committee (3.550.658).

## Variables of Analysis

The variables of analysis were collected within 48 hours of the first hospital admission to the unit, regardless of the outcome.

### Karnofsky Performance Status

The KPS is a percentage scale that classifies the individual in terms of the ability to perform active, self-care work and the need for regular medical care due to greater evidence of illness (100%: full function—0%: death).<sup>6</sup>

### Sociodemographic and Clinical Data

The following sociodemographic data were obtained through interviews—age (years), gender (male vs. female), marital status (married vs. others), residential municipality (Rio de Janeiro vs. others) and self-reported skin color: white vs. brown vs. black).

Clinical data were obtained by consulting medical records, as follows: diagnosis [gynecological cancer vs. gastrointestinal (GI) tract vs. breast vs. head and neck (HN) vs. lung vs. connective bone tissue (CBT) vs. others], disease progression (only local vs. only remote vs. local and remote simultaneously), prior treatment [surgery (yes vs. no), chemotherapy (yes vs. no) and radiation therapy (yes vs. no)] and presence of comorbidities [hypertension (yes vs. no) and diabetes mellitus (yes vs. no)].

### Patient-Generated Subjective Global Assessment Short Form

The version translated into Portuguese of the Patient-Generated Subjective Global Assessment (PG-SGA) short form (©FD Ottery, 2005, 2006, 2015),<sup>7</sup> available in pt-global.org, was used after permission. The tool is answered by the patient and allows us to evaluate: (1) body weight change: the score can vary from 0 to 5; (2) food intake: scoring from 0 to 4; (3) presence of symptoms of nutritional impact: scoring up to 24; and (4) functional capacity assessment: scoring from 0 to 3. At the end of the assessment, a numerical score was generated based on the sum of each of the items in the questionnaire. The higher the score, the worse the nutritional status.<sup>8</sup>

### Analytical Assessments

The following serum levels were extracted from medical records: albumin and C-reactive protein (CRP). A nursing

technician collected approximately 15 mL of blood samples by venipuncture, 5 mL of which were collected in anticoagulant for hematological determinations, and 10 mL without additives to obtain the serum intended for biochemical analyses. The samples were centrifuged at 5,000 revolutions per minute, for 10 minutes, and stored in Eppendorf tubes for further analysis. For laboratory analysis, the following methodologies were adopted: green colorimetric method of bromocresol for serum albumin; ultra-sensitive nephelometry (monoclonal antibody against human CRP) for CRP.

In the case of laboratory tests of the PCU routine procedures and extracted from medical records for research, there were some laboratory data that did not exist. Therefore, we analyze only the available data.

### Outcomes of Hospitalization

The primary outcomes assessed were hospital discharge or inpatient hospital death.

### Statistical Analysis

Data analysis were performed using STATA® 13.0. Descriptive analyses were expressed as absolute or relative percentage (%), median and interquartile range (IQR) and mean and standard deviation (SD) accordingly. The Kolmogorov-Smirnov test was used to assess the distribution of numerical variables. To assess the differences between the groups, according to the outcomes of the hospital admission, the Chi-square test was used for proportions for categorical variables, the Student's t-test was used to evaluate the difference between means and the Mann-Whitney U test was used to evaluate the difference between medians.

In addition, bivariate and multivariate logistic regression analyses were used, the odds ratio (OR) with confidence interval (95% CI) being used as a measure of effect. The criterion adopted to determine significance was the 5% level.

### Results

Eighty-two patients were included in this study, whose mean age was 61.8 ( $\pm 13.2$ ) years, with a higher prevalence of women (64.6%), married people (53.7%), living in the city of Rio de Janeiro (59.8%) and brown skin color (53.6%). The most prevalent tumor type was gynecological (21.9%), followed by the GI tract (19.5%) and breast (19.5%). Most patients had progression of local and remote disease simultaneously (67.1%) and KPS of 30-40% (85.4%) (Table 1).

Forty-nine (59.8%) patients died during hospitalization, among which the majority had KPS of 30-40% (p-value = 0.043) (Table 1), in addition to higher means of the total score of the PG-SGA (p-value = 0.050) and lower serum albumin concentrations (p-value = 0.011) on hospital admission (Table 2).

**Table 1.** Sociodemographic and Clinical Characterization of Patients With Advanced Cancer in Palliative Care at Hospitalization (n = 82).

Variables	Total	Outcome		p-value
		Hospital discharge n = 33 (40.2%)	Death n = 49 (59.8%)	
Age (years) <sup>a</sup>	61.8 (13.2)	61.3 (13.7)	62.1 (12.9)	0.776
Age ≥60 years <sup>b</sup>				
No	36 (43.9)	17 (47.2)	19 (52.8)	0.254
Yes	46 (56.1)	16 (34.8)	30 (65.2)	
Gender <sup>b</sup>				
Male	29 (35.4)	12 (41.4)	17 (58.6)	0.877
Female	53 (64.6)	21 (39.6)	32 (60.4)	
Married marital status <sup>b</sup>				
No	38 (46.3)	19 (50.0)	19 (50.0)	0.094
Yes	44 (53.7)	14 (31.8)	30 (68.2)	
Municipality Rio de Janeiro <sup>b</sup>				
No	33 (40.2)	10 (30.3)	23 (69.7)	0.132
Yes	49 (59.8)	23 (46.9)	26 (53.1)	
Skin color <sup>b</sup>				
White	28 (34.1)	9 (32.1)	19 (67.9)	0.517
Brown	44 (53.6)	19 (43.2)	25 (56.8)	
Black	10 (12.3)	5 (50.0)	5 (50.0)	
Diagnosis <sup>b</sup>				
Gynecological	18 (21.9)	5 (27.8)	13 (72.2)	0.004
GI tract	16 (19.5)	3 (18.7)	13 (81.3)	
Breast	16 (19.5)	3 (18.7)	13 (81.3)	
HN	8 (9.8)	2 (25.0)	6 (75.0)	
Lung	8 (9.8)	2 (25.0)	6 (75.0)	
CBT	5 (6.1)	0	5 (100.0)	
Others	11 (13.4)	7 (63.6)	4 (36.4)	
DP <sup>b</sup>				
Local	16 (19.5)	6 (37.5)	10 (62.5)	0.582
Distance	11 (13.4)	6 (54.5)	5 (45.5)	
Local + distance	55 (67.1)	21 (38.2)	34 (61.8)	
Previous surgery <sup>b</sup>				
No	44 (53.6)	16 (36.4)	28 (63.6)	0.441
Yes	38 (46.4)	17 (44.7)	21 (55.3)	
Previous CT <sup>b</sup>				
No	32 (39.0)	10 (31.2)	22 (68.8)	0.184
Yes	50 (61.0)	23 (46.0)	27 (54.0)	
Previous RXT <sup>b</sup>				
No	55 (67.1)	22 (40.0)	33 (60.0)	0.949
Yes	27 (32.9)	11 (40.7)	16 (59.3)	
SAH <sup>b</sup>				
No	49 (59.7)	20 (40.8)	29 (59.2)	0.898
Yes	33 (40.3)	13 (39.4)	20 (60.6)	
DM <sup>b</sup>				
No	71 (86.6)	27 (38.0)	44 (62.0)	0.299
Yes	11 (13.4)	6 (54.5)	5 (45.5)	
KPS ≤40% <sup>b</sup>				
No	70 (85.4)	25 (35.7)	45 (64.3)	0.043
Yes	12 (14.6)	8 (66.7)	4 (33.3)	

**Note:** GI = gastrointestinal; HN = head and neck; CBT = connective bone tissue; DP = disease progression; CT = chemotherapy; RXT = radiotherapy; DM = diabetes mellitus; SAH = systemic artery hypertension; KPS = Karnofsky Performance Status.

<sup>a</sup>Mean (standard deviation)/Student's t test.

<sup>b</sup>Number of observations (frequency)/chi-square test for proportions.

**Table 2.** Nutritional and Inflammatory Characterization of Patients With Advanced Cancer in Palliative Care During Hospitalization (n = 82).

Variables	Total	Outcome of HI		
		Hospital discharge n = 33 (40.2%)	Death n = 49 (59.8%)	p-value
PG-SGA (points) <sup>a</sup>	13.6 (5.7)	12.7 (6.7)	14.2 (5.0)	0.050
PG-SGA ≥9 points <sup>b</sup>				
No	14 (17.1)	8 (57.1)	6 (42.9)	0.157
Yes	68 (82.9)	25 (36.8)	43 (63.2)	
Albumin (g/dL) <sup>bd</sup>	2.9 (2.4-3.3)	3.1 (2.7-3.6)	2.7 (2.2-3.2)	0.011
Albumin <3.5g/dL <sup>cd</sup>				
No	15 (22.0)	10 (66.7)	5 (33.3)	0.023
Yes	53 (78.0)	18 (34.0)	35 (66.0)	
CRP (mg/L) <sup>bd</sup>	11.4 (6.7-23.7)	10.0 (4.3-23.3)	11.9 (6.7-24.6)	0.406
CRP ≥10mg/L <sup>cd</sup>				
No	22 (42.3)	10 (45.4)	12 (54.6)	0.523
Yes	30 (57.7)	11 (36.7)	19 (63.3)	

**Note:** PG-SGA = Patient-Generated Subjective Global Assessment.

CRP = C-reactive protein.

<sup>a</sup>Mean (standard deviation)/Student's t test.

<sup>b</sup>Median (interquartile range)/Mann-Whitney U test.

<sup>c</sup>Number of observations (frequency)/chi-square test for proportions.

<sup>d</sup>Variables with missing data (albumin with 17% of missing and CRP with 37% of missing).

The multivariate logistic regression model showed that patients with tumor location in the GI tract (OR: 1.73; 95% CI: 1.57 -1.94), 30-40% KPS (OR: 1.29; 95% CI: 1.07 -1.63) and albumin <3.5 g/dL (OR: 4.5; 95% CI: 1.22-17.67) at the time of admission, they were more likely to die in that hospital admission (Table 3).

## Discussion

The present study evaluated patients with advanced cancer admitted to hospital to an exclusive palliative care unit and demonstrated that, being recognized as a reserved prognosis group, approximately 60% of them died. Considering the high mortality rate among patients who start palliative care already demanding hospitalization and recognizing the need to better predict the occurrence of this type of outcome, we found that, presenting an advanced tumor with localization in the GI tract, KPS less than 40% and serum albumin concentration less than 3.5 g/dL at admission were predictive factors of this unfavorable outcome.

The prognosis is a dynamic process and can change according to the response to treatment, the development of acute complications or other comorbidities. Thus, sentinel events such as disease progression and hospitalization should trigger

**Table 3.** Logistic Regression of Factors Associated With Increased Chances of Death in Patients With Advanced Cancer in Palliative Care at Hospitalization.

Variables	Raw		Adjusted <sup>a</sup>	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Diagnosis GI tract				
No	1.00		1.00	
Yes	1.79 (1.64 -1.97)	0.025	1.73 (1.57 -1.94)	0.016
KPS ≤40%				
No	1.00		1.00	
Yes	1.28 (1.08 -1.82)	0.053	1.29 (1.07 -1.63)	0.044
PG-SGA				
≥9 points				
No	1.00		—	
Yes	2.29 (0.71-7.37)	0.164	—	
Albumin				
<3.5 (g/dL)				
No	1.00		1.00	
Yes	3.89 (1.15-13.10)	<b>&lt;0.001</b>	4.65 (1.22-17.67)	<b>0.024</b>

**Note:** OR = odds ratio; CI = confidence interval; GI = gastrointestinal; KPS = Karnofsky Performance Status; PG-SGA = Patient-Generated Subjective Global Assessment.

<sup>a</sup>multiple model with p-value variables <0.200 in raw analysis. Adjusted additionally for age and time of diagnosis.

new prognostic discussions.<sup>3</sup> However, the ability to more accurately estimate the survival of patients with advanced cancer has been a constant challenge for healthcare professionals and researchers.<sup>9</sup> In this scenario, our data may be of clinical use in helping to identify patients who are already hospitalized with a worse prognosis, thus minimizing the establishment of useless and disproportionate therapies to the progress of the disease. A deeper knowledge of prognostic factors can mitigate unnecessary strategies that favor dysthanasia and, therefore, increase the use of financial resources irrelevant to this specific group.<sup>3,10</sup>

As for the most prevalent tumor types (gynecological, followed by those from the GI tract) in our study, Wiegert et al.<sup>11</sup> also observed such more frequent neoplasms in a cohort of 120 patients with advanced cancer in palliative care. As it is a population with advanced cancer in palliative care, which normally already has a high degree of fragility in relation to functional capacity,<sup>4,5</sup> linked to the fact that they are probably with complications responsible for the demand for hospitalization, it is not surprising that we verified the presence of an important functionality limitation in most of the population (KPS de 30-40%: 85.4%).

Forty-nine (59.8%) patients died during hospitalization, most of whom had already been admitted with reduced functionality (KPS, p-value = 0.043), high nutritional risk (PG-SGA; p-value = 0.050) and lower serum albumin concentrations (p-value = 0.011). Regarding the importance of the reduced version of the PG-SGA, the median score of patients who died (14.2) was statistically significant when compared to those who were discharged (12.7). Cunha et al.<sup>5</sup> observed in a cohort that

patients in palliative care who had scores greater than 19 had lower survival. Carvalho et al.<sup>12</sup> found that patients with a score greater than 9 had a median survival of 3 months, when compared to those with a lower score on the PG-SGA.

Although different publications found predictive power in PG-SGA, our logistic regression analyses did not confirm an association between this tool and the higher risk of death on hospital admission. However, we observed that the factors related to the higher risk of death were presenting an advanced tumor in the GI tract, KPS less than 40% and serum albumin concentration less than 3.5 g/dL at admission (OR that ranged from 1.29 to 4.65). Despite these factors having previously been related to the worst prognosis in previous studies, we needed to know if there was any difference in relation to patients with advanced cancer affected by an acute event that required hospitalization. Therefore, patients admitted with these clinical conditions could be considered to have a worse prognosis than the others. On the other hand, patients with characteristics different from these, and therefore, with a higher probability of hospital discharge, may have a differentiated care plan with proposed therapies that consider the best prognosis.

Regarding our findings that relate the location of the tumor and the impact on the outcome of hospitalization (death), patients with GI tract cancer are known to have a higher nutritional risk than those with other tumor sites, which can contribute to poor results, which include reduced physical function, significant decline in quality of life and increased mortality.<sup>13-15</sup>

In addition, the presence of serum albumin less than 3.5 g / dL was a risk factor for the outcome of death in logistic regression (OR: 4.65; p < 0.024). This acute-phase protein has often been linked as a marker of nutritional status as well as survival. Its low levels are associated with the worst outcomes,<sup>16</sup> which was corroborated by Dolan et al.,<sup>17</sup> in a systematic review and meta-analysis (HR: 1.77; p < 0.001). Reid et al.<sup>18</sup> elected the concentration of serum albumin, among others, as high quality of evidence on death markers in cancer patients in the last months of life. In patients with primary site in the GI tract, higher levels of albumin were correlated with longer survival.<sup>19</sup>

KPS, in turn, is considered an independent predictor of worse survival,<sup>11</sup> which was corroborated by our study. In addition to a prognostic factor, this scale better demonstrates the patient's functionality, in addition to behavioral and social aspects,<sup>20</sup> and also makes up one of the PaP Score criteria, a tool used to estimate survival time in palliative care, used by doctors.<sup>21,22</sup>

In addition to the factors pointed out in the present study, there are others that are described in the scientific literature as predictors of survival in patients with advanced cancer, among which we can mention the phase angle<sup>23</sup> (PA), the neutrophil-lymphocyte ratio (RNL)<sup>24</sup> and Score Glasgow modified prognosis (EPGm)<sup>25</sup> and some others.

The present study has limitations. First, it contained a small sample, which may have limited the inference power of our statistical analyses. Therefore, larger studies must be

developed. On the other hand, simple and objective elements were used for prognostic evaluation, facilitating the clinical utility of these factors under similar conditions.

## Conclusion

Presenting advanced tumor with localization in the GI tract, KPS less than 40% and serum albumin concentration less than 3.5 g/dL on admission were predictors of death on hospital admission of patients under palliative care. However, more studies should be developed to further explore the role of these predictive factors in the clinical outcomes in this group of patients.


## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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