Original Article

Clinical Relevance and Prognostic Value of Inflammatory Biomarkers: A prospective Study in Terminal Cancer Patients Receiving Palliative Care

Gabriella da Costa Cunha, RD, Karla Santos da Costa Rosa, RD, Emanuelly Varea Maria Wiegert, RD, PhD, and Livia Costa de Oliveira, RD, PhD

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

Abstract

Context. Inflammatory biomarkers have prognostic value in cancer patients, but the feasibility of their use with terminal cancer patients and the related cutoff points are poorly explored.

Objectives. To describe the percentiles values of inflammatory biomarkers; to identify their cutoff points in relation to death; and to determine the prognostic value of C-reactive protein (CRP), leukocytes, neutrophils, neutrophil/lymphocyte ratio (NLR), CRP/albumin ratio (CAR), and modified Glasgow Prognostic Score for death within 90 days, in terminal cancer patients receiving palliative care.

Methods. Prospective cohort study that included patients who received palliative care at the Palliative Care Unit of the National Cancer Institute (Brazil) between October 2019 and March 2020. Receiver operating characteristic curves were used to identify the optimal cutoff points of the inflammatory biomarkers for the prediction of death in 90 days. Kaplan-Meier curves and Cox regression were used to verify the prognostic value of these cutoff points and concordance statistic (C-statistic) was used to test their predictive accuracy.

Results. A total 205 patients (mean age: 62.5 years; female: 59%) were included in the study. The optimal cutoff points were CRP ≥6.7mg/L, CAR ≥2.0, leukocytes ≥9300/μL, neutrophils ≥7426/μL and NLR ≥6.0. All biomarkers showed prognostic value and good predictive accuracy when their cutoff points were used, especially CAR, which presented excellent discrimination power (C-statistic: 0.80).

Conclusion. The inflammatory biomarkers analyzed are independent predictive factors for death within 90 days in terminal cancer patients. CAR appears to be the most useful parameter for predicting survival in these patients. J Pain Symptom Manage 2021;62:978−986.

Key Words

Cancer, survival, prognosis, terminal care, palliative care, biomarkers

Key Message

Few studies have described specific cutoff values of inflammatory biomarkers for prognosis prediction in terminal-stage cancer patients. In this study, optimal cutoff points for predicting survival were determined and all biomarkers showed prognostic value and good predictive accuracy, especially CRP/albumin ratio, which presented excellent discrimination power.

Introduction

Determining prognosis in advanced cancer is of key importance in establishing a care plan, helping optimize treatment strategies and the efficient use of available resources.[1] However, healthcare providers may experience difficulty in identifying terminal cancer patients with a short survival period.[2] Although there are different validated prognostic tools, several of them

Address correspondence to: Livia Costa de Oliveira, PhD, Rua Visconde de Santa Isabel, 274, Vila Isabel, Rio de Janeiro − RJ, Brazil. E-mail: lillycostaoliveira@gmail.com

Accepted for publication: 15 April 2021.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2021.04.009

are based on subjective criteria, which can result in inaccurate estimates, impacting their applicability. It has therefore been suggested that more simple, objective prognostic factors that can be evaluated by the entire multidisciplinary team should be established.[3] In this context, biomarkers have been recognized for their prognostic potential and clinical utility.[4]

Several studies have demonstrated the prognostic value of inflammatory biomarkers in patients with a variety of advanced solid tumors.[4,5,6] Indeed, there is strong evidence that chronic systemic inflammatory response is associated with more advanced stages of the disease.[7] Dolan et al. [5] showed that systemic inflammatory response, as evidenced by a number of markers at clinical thresholds, may have independent prognostic value across tumor types. Of these markers, C-reactive protein (CRP), albumin, leukocyte count, neutrophils, lymphocytes, and the indexes derived from these biomarkers, such as the modified Glasgow Prognostic Score (mGPS), CRP/albumin ratio (CAR), and neutrophil/lymphocyte ratio (NLR), have been consistently studied worldwide. However, there is considerable variation in the thresholds established for the inflammatory biomarkers between studies.[5,8,9]

Although inflammatory biomarkers have a recognized role in predicting survival in the context of advanced cancer, whether this association applies to terminal cancer patients with more than 30 days' survival is unclear. In addition, few studies have described specific cutoff values for prognosis prediction in terminal-stage cancer patients. Accordingly, the objectives of the present study were: 1) to describe percentiles values of inflammatory biomarkers; 2) to identify their cutoff points related to death; and 3) to determine the prognostic value of CRP, leukocytes, neutrophils, NLR, CAR and mGPS for death within 90 days, in terminal cancer patients receiving palliative care.

Methods

Study Design and Participants

This prospective study included data from consecutive patients who received palliative care at the National Cancer Institute José Alencar Gomes da Silva (INCA), in Rio de Janeiro, Brazil, between October 2019 and March 2020. The focus of care in the Palliative Care Unit (PCU) is symptom-oriented. It commences when anti-tumor and/or curative treatment is discontinued because of lack of effect or severe side-effects or lack of clinical conditions to continue with specific treatment, in patients whose life expectancy is a few months or less. Therefore, no patient was being actively treated with chemotherapy.

The inclusion criteria were: 1) histologically or clinically confirmed locally advanced malignancy or distant metastasis; 2) not receiving any antineoplastic treatment with curative intent; 3) age ≥20 years; 4) Karnofsky Performance Status (KPS) ≥30% at the time of recruitment. The study was approved by the ethics review board of the INCA Ethics Committee (Protocol 3.550.658 of 2019) and written informed consent was obtained from patients or their relatives or caregivers.

Including inpatient and outpatient, 295 patients were admitted to the PCU during the study period. A total of 90 patients were excluded, either because they did not meet the eligibility criteria ($n = 84$) or because they declined the invitation to participate in the study ($n = 6$). As such, 205 terminal cancer patients were finally included in the present study (Supplementary Figure 1).

Biomarkers Assessments

Non-fasting blood samples were obtained by the PCU team from the outpatients on their day of inclusion in the study and from the inpatients within 48 hours of admission to the unit. For each patient laboratory measures including CRP, serum albumin, and complete blood count were obtained. The laboratory results were collected from the patients' electronic records. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[10] Similarly, CAR was calculated by dividing the absolute CRP concentration (mg/L) by the serum albumin value (g/dL).[11] The mGPS was classified as two when albumin <3.5g/dL and CRP >10mg/L; as 1 when albumin ≥3.5g/dL and CRP >10mg/L; and as 0 when CRP ≤10mg/L.[12] The CAR, mGPS, NLR values were calculated using the same blood samples. Due to missing data on CRP and albumin, the sample value was different from the total sample for the variables CRP ($n = 142$), CAR ($n = 123$) and mGPS ($n = 142$). In addition, due to the low prevalence of mGPS 1, we gathered the data for mGPS 1 and 2.

Covariates Assessment

The demographic data (age, gender) and clinical data (primary tumor site, distant metastasis, comorbidities) were collected from the electronic records. KPS score (ranging from 0% [death] to 100% [full function]) was assigned by trained researchers according to patient-reported daily physical function.[13]

Survival

Overall survival (OS) was defined as the time in days from the date the patient was included in the study (first visit to the PCU) until to the date of death, which was obtained from electronic records. All patients who were alive after the end of follow-up (90 days) were censored for survival analysis.

Statistical Analysis

Statistical analysis was performed using Stata 13.1 (Stata Corp., College Station, Texas, USA). Statistical significance was set at $P < 0.05$.

The Kolmogorov-Smirnov test was used to assess the distribution of variables. Numerical variables were described as mean ± standard deviation (SD) or median with interquartile range (IQR, 25th and 75th percentiles), according to distribution and normality. Categorical variables were described as absolute frequency (n) and relative frequency (%). Proportions were compared using the Chi-squared test, means were compared using Student's t-test, and medians were compared using the corresponding non-parametric test, the Mann-Whitney U test.

Biomarker values were expressed as percentiles (1^{st}, 5^{th}, 10^{th}, 15^{th}, 25^{th}, 50^{th}, 75^{th}, 85^{th}, 90^{th}, 95^{th}, and 99^{th}) and their medians were compared in relation to the occurrence of death in 90 days. After that, the biomarkers with $P < 0.05$, namely CRP, leukocytes, neutrophils, CAR, and NLR were selected to determine their predictive cutoff points. Receiver-operating characteristic curves (ROC) were constructed to determine the optimal cutoff points related to death within 90 days. Cutoff points with higher sensitivity and specificity values were selected, prioritizing a higher degree of specificity (individuals with a better prognosis), because when false-positive results can lead to patients not being given potentially beneficial treatment, tests with higher specificity are required.[14]

Kaplan-Meier curves were used to evaluate probability of OS and the log-rank test was used to compare survival curves according to each inflammatory biomarker using the cutoff point found. Additionally, the Cox proportional hazard model was used to assess the predictive ability of cutoff points. The stepwise selection method was used, in which variables with $P < 0.05$ in the univariate regressions were included in the final models. Six multiple models were made, one for each biomarker, adjusted by age, primary tumor site, KPS, and current health care setting (inpatient vs. outpatient).

The concordance statistic (C-statistic) was used to assess the discriminatory power of the cutoff points to predict OS. A C-statistic of 0.50 indicates that the model predicts the outcome as well as chance (i.e., equal numbers of true and false positives); 0.70 to <0.80 indicates good discrimination; 0.80 to <0.90 indicates excellent discrimination; 0.90 to <1.00 is outstanding discrimination; and 1.00 is perfect prediction.[15]

To verify our sampling power, we calculated a post hoc test using the online tool: https://clincalc.com/Stats/Power.aspx; and considered dichotomous results for two independent groups, with an alpha error of 0.05. It was found a sample power of 92.9%, 98.5%, 99.2%, 97.2%, 91.3% and 77.7% for CRP, leukocytes, neutrophils, CAR, NLR, and mGPS, respectively.

Results

Two hundred and five patients were included in the study. The mean age was 62.5 (± 0.9) years, with a predominance of females (59.0%). The most prevalent primary tumor site were gynecological (18.5%) and head and neck (17.1%). Patients who died within 90 days had significantly higher prevalence of KPS ≤40% ($P = 0.001$) and mGPS 1 and 2 ($P = 0.004$) (Table 1). In addition, the data showed that patients who died within 90 days presented significantly higher median values of CRP ($P < 0.001$), CAR ($P < 0.001$), leukocytes ($P < 0.001$), neutrophils ($P < 0.001$), and NLR ($P = 0.002$) than the patients who survived more than 90 days (Table 2).

According to the ROC analysis, the optimal cutoff points for OS were CRP ≥6.7mg/L, leukocytes ≥9300/μL, neutrophils ≥7426/μL, CAR ≥2.0, and NLR ≥6.0 (Table 3). It was observed that high CAR was the inflammatory biomarker with the best discriminatory ability to predict 90-day mortality [AUC: 0.74 (95% confidence interval: 0.65−0.83)] (Fig. 1).

The median OS for all patients was 33 (IQR: 11−73) days. The Kaplan-Meier curves showed that the probability of OS was four times shorter when CAR ($P < 0.001$) and neutrophils ($P < 0.001$) were above the cutoff points; almost four times shorter when CRP ($P < 0.001$) and leukocytes ($P < 0.001$) were above the cutoff points; and three times shorter when NLR ($P = 0.010$) was above the cutoff point. In addition, the survival rate of patients with mGPS 1 and 2 was almost four times shorter than that of patients with mGPS 0 ($P < 0.001$) (Fig. 2).

Cox proportional hazard model demonstrated a significantly increased risk of 90-day mortality when the biomarker value was above the cutoff points identified, regardless of the inflammatory biomarker. For example, the patients with a high CAR had a 2.42-fold higher risk of death than those with a low CAR. Moreover, it was observed that patients with CAR ≥2.0 had a higher risk of mortality when compared to the other biomarkers, and that this biomarker also had excellent predictive accuracy according to the C-statistic (0.80) (Table 4).

Discussion

In this study, we described the values of biomarkers as percentiles, identified their cutoff points related to death, and evaluated their clinical applicability for predicting OS in patients with terminal cancer in palliative care. Our results showed that inflammatory biomarkers

Table 1
Demographic and Clinical Characteristics of Terminal Cancer Patients Receiving Palliative Care ($n = 205$)

Variables	Total	Death Within 90 days		*P* value
		Yes ($n = 135$; 65.9%)	No ($n = 70$; 34.1%)	
Age (years)[a]	62.5 (±0.9)	62.4 (±1.1)	62.8 (±1.6)	0.829
Gender[b]				
Male	84 (41%)	58 (69.1%)	26 (30.9%)	0.422
Female	121 (59%)	77 (63.6%)	44 (36.4%)	
Primary tumor site[b]				
Gynecological	38 (18.5%)	24 (63.2%)	14 (36.8%)	0.068
Head and neck[c]	35 (17.1%)	19 (54.3%)	16 (45.7%)	
Breast	31 (15.1%)	19 (61.3%)	12 (38.7%)	
Gastrointestinal tract	28 (13.7%)	25 (89.3%)	3 (10.7%)	
Lung	22 (10.7%)	17 (77.3%)	5 (22.7%)	
Skin, bones and soft tissues	17 (8.3%)	12 (70.6%)	5 (29.4%)	
Others[d]	34 (16.6%)	19 (54.3%)	15 (45.7%)	
Distant metastasis[b]				
No	40 (19.5%)	28 (70.0%)	12 (30.0%)	0.506
Yes	165 (80.5%)	107 (64.8%)	58 (35.2%)	
SAH[b]				
No	124 (60.5%)	81 (65.3%)	43 (34.7%)	0.843
Yes	81 (39.5%)	54 (66.7%)	27 (33.3%)	
DM[b]				
No	173 (84.4%)	113 (65.3%)	60 (34.7%)	0.707
Yes	32 (15.6%)	22 (68.7%)	10 (31.3%)	
KPS ≤40%[b]				
No	106 (51.7%)	59 (55.7%)	47 (44.3%)	**0.001**
Yes	99 (48.3%)	76 (76.8%)	23 (23.2%)	
mGPS[b,e]				
0	90 (63.4%)	49 (54.4%)	41 (45.6%)	**0.004**
1 and 2	52 (36.6%)	41 (78.9%)	11 (21.1%)	
Current health care setting[b]				
Inpatient	82 (40.0%)	70 (85.4%)	12 (14.6%)	**<0.001**
Outpatient	123 (60.0%)	65 (52.8%)	58 (47.2%)	

Note: n = number of observations; SAH = systemic arterial hypertension; DM = diabetes mellitus; KPS = Karnofsky Performance Status; mGPS = modified Glasgow Prognostic Score.
[a]Mean (standard deviation)/Student's t test;
[b]Number of observations (frequency)/chi-square test for proportions;
[c]Oral and nasal cavity, pharynx, larynx, salivary glands, paranasal sinuses, eyes, and thyroid;
[d]Leukemia, lymphoma, myeloma, central nervous system, kidney and urinary tract, male genital organs, peritoneum, mediastinum, and unrecognized site + Leukemia, lymphoma, myeloma;
[e]Variable with missing data.

Table 2
Percentiles and Medians values of Inflammatory Biomarkers Related to Death within 90 Days in Terminal Cancer Patients Receiving Palliative Care.

Variables	n	Total									Death		*P* value[a]
		P1st	P5th	P10th	P25th	P50th	P75th	P90th	P95th	P99th	Yes Median	No	
CRP (mg/L)[b]	142	0.05	0.17	0.90	3.05	7.10	14.55	28.49	32.10	40.26	8.47	4.66	**<0.001**
CAR[b]	123	0	0	0.20	0.80	2.00	5.40	9.90	13.10	16.80	2.55	1.10	**<0.001**
Leukocytes (/μL)	205	3200	4400	4800	6700	9300	13200	17300	22000	47100	10400	7300	**<0.001**
Neutrophils (/μL)	205	1644	2590	3231	4810	7426	10819	14754	19844	25816	8262	5606	**<0.001**
Lymphocytes (/μL)	205	0	277	493	821	1069	1588	2184	2419	3478	1028	1132	0.148
NLR	205	0.70	1.70	2.46	3.84	6.23	10.52	18.13	23.94	68.13	7.15	5.37	**0.002**

Note: n = number of observations; P = percentile; CRP = C-reactive protein; CAR = CRP/albumin ratio; NLR = neutrophil/lymphocyte ratio.
[a]Mann-Whitney U test;
[b]Variable with missing data.

were a simple and useful tool for prognostic prediction in terminal cancer patients within 90 days of follow-up, particularly CAR, which presented a better performance than the other biomarkers.

The percentile distribution of biomarkers reflected the increase in inflammation in the terminal phase of oncological diseases.[7] Additionally, the median CRP, CAR, leukocyte, neutrophil, and NLR values were significantly higher in the patients who died within 90 days. Only lymphocyte count did not show a statistically significant difference, but a plausible trend was observed, in which lower median value was found in patients who died. Data from a cohort of patients with cancer in palliative care described median values of

Table 3

Accuracy Measures of the Best Cutoff Points According to ROC Curves for Biomarkers Related to Death Within 90 Days in Terminal Cancer Patients Receiving Palliative Care

	CRP ≥6.7mg/L (n = 77; 54.2%[a])	CAR ≥2.0 (n = 62; 50.4%[a])	Leukocytes ≥9300/μL (n = 103; 50.2%[a])	Neutrophils ≥7426/μL (n = 103; 50.2%[a])	NLR ≥6.0 (n = 106; 51.7%[a])
Sensitivity	65.6%	61.8%	60.7%	60.0%	62.3%
Specificity	65.4%	72.3%	70.0%	68.6%	64.3%
LR+	1.89	2.23	2.02	1.91	1.74
LR-	0.53	0.53	0.56	0.58	0.59

Note: n = number of observations; CRP = C-reactive protein; CAR = CRP/albumin ratio; NLR = neutrophil/lymphocyte ratio; LR = likehood ratio; ROC = Receiver-operating characteristic.
[a]Percentage in relation to the total biomarker sample.

CRP 44mg/L and leukocytes 9600/μL in the last 31−60 days of life.[6] Nakamura et al.[16] found that median NLR values in terminal cancer patients were 3.83 at three months before death, while in another retrospective study of advanced cancer patients in palliative care who died within 360 days, median CAR was 1.80.[17]

Regarding the cutoff points established in our study, a similar neutrophil cutoff, of >8000/μL, was found in a retrospective cohort of patients with advanced cancer in palliative care in China.[18] Zhang et al. [17] suggested

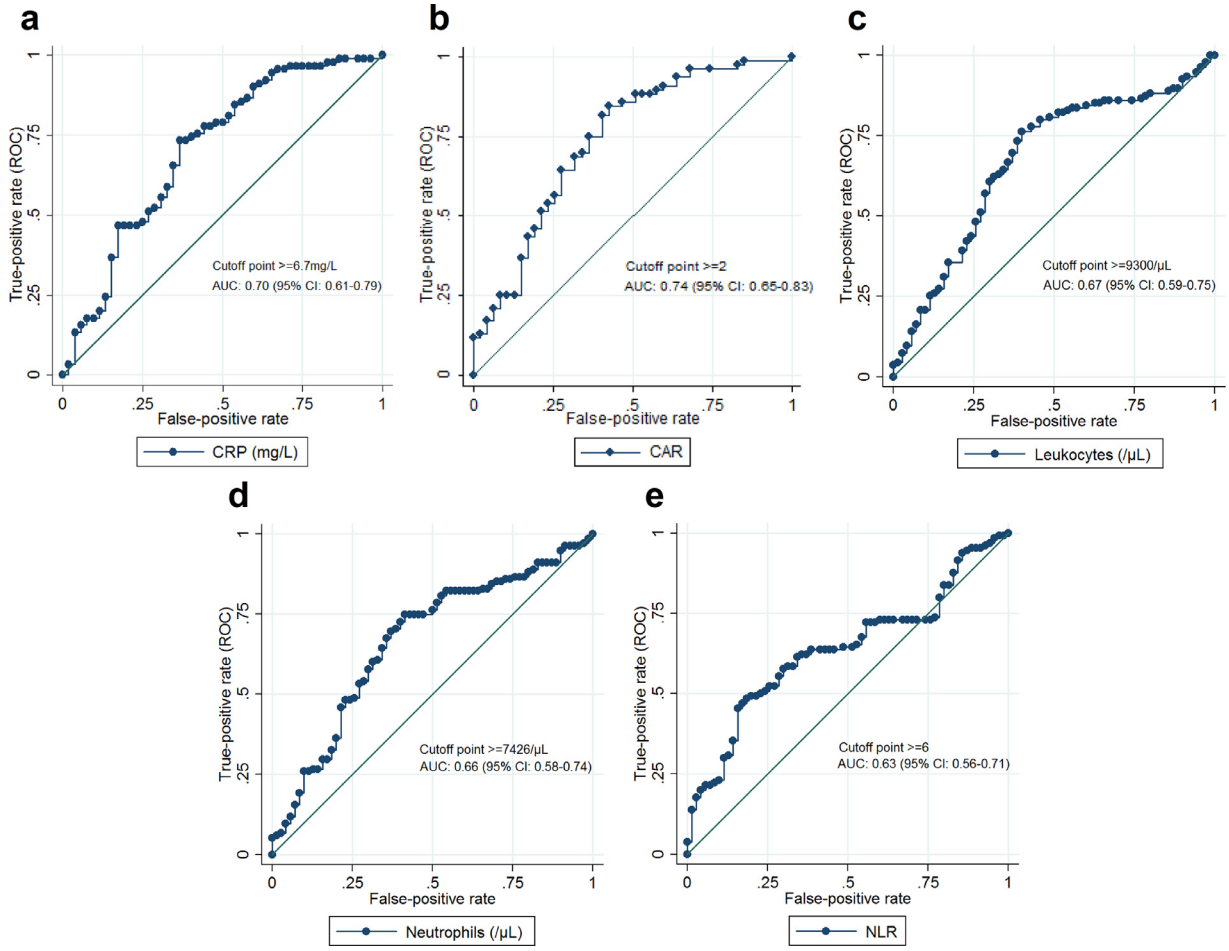

Fig. 1. ROC curves of the best cutoff point for serum concentrations of a) C-reactive protein, b) C-reactive protein/albumin ratio, c) leukocytes, d) neutrophils and e) neutrophil/lymphocyte ratio related to death within 90 days in terminal cancer patients receiving palliative care.

Note: AUC = area under the curve; CI = confidence interval; CRP = C-reactive protein; CAR = CRP/albumin ratio; NRL = neutrophil/lymphocyte ratio; ROC = Receiver-operating characteristic.

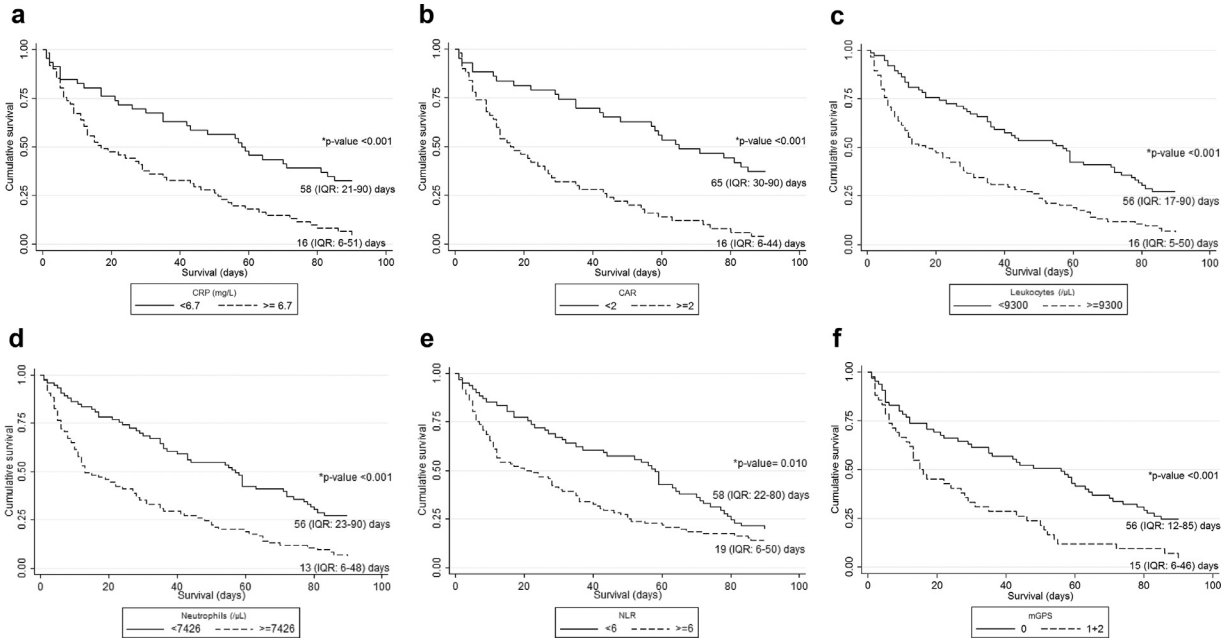

Fig. 2. Survival curves stratified by a) C-reactive protein, b) C-reactive protein/albumin ratio, c) leukocytes, d) neutrophils, e) neutrophil/lymphocyte ratio and f) modified Glasgow Prognostic Score of terminal cancer patients receiving palliative care.

Note: IQR = interquartile range; CRP = C-reactive protein; CAR = CRP/albumin ratio; NRL = neutrophil/lymphocyte ratio; mGPS = modified Glasgow Prognostic Score. **P*-value refers to the log-rank test.

an optimal CAR cutoff point of 1.31 for palliative cancer patients. In another retrospective cohort study with advanced non-small cell lung cancer, the CAR and NLR cutoff points were 0.2 and 2.1, respectively.[8] Nakamura et al. [16] found 9.21 to be the best NLR cutoff for estimating life expectancy of less than four weeks. These findings are consistent with the literature, in which a variety of different inflammatory biomarker cutoff points have been presented. Also, in our study population, the median concentrations of some biomarkers were higher than those found in other advanced cancer patients. This could be explained a reflection of the intrinsic variability among populations, which is also related to systemic and individual responses to tumors, as well as previous treatments.

In this study, we show that a simpler prognostic model based on the predictive capacity of inflammatory biomarkers could perform similarly well to more complex models that contain a large number of variables. Mei et al. [19] developed a prognostic model

Table 4

Cox Proportional Hazard Model According to Biomarkers Cutoff points in Terminal Cancer Patients Receiving Palliative Care

Variables	n	Univariate HR (95% CI)	CRP Multivariate HR (95% CI)	CAR Multivariate HR (95% CI)	Leukocytes Multivariate HR (95% CI)	Neutrophils Multivariate HR (95% CI)	NLR Multivariate HR (95% CI)	mGPS Multivariate HR (95% CI)	C-statistic
CRP ≥6.7mg/L	107	2.42 (155-3.77)[a]	1.94 (1.21-3.10)[a]	-	-	-	-	-	0.76
CAR ≥2.0	107	3.20 (1.96-5.23)[a]	-	2.42 (1.45-4.05)[a]	-	-	-	-	0.80
Leukocytes ≥9300/μL	158	2.23 (1.57-3.18)[a]	-	-	2.19 (1.53-3.15)[a]	-	-	-	0.75
Neutrophils ≥7426/μL	158	2.28 (1.60-3.24)[a]	-	-	-	2.23 (1.55-3.20)[a]	-	-	0.74
NLR ≥6.0	158	1.59 (1.11-2.28)[a]	-	-	-	-	1.64 (1.14-2.38)[a]	-	0.73
mGPS 1 and 2	107	2.14 (1.39-3.28)[a]	-	-	-	-	-	1.64 (1.05-2.56)[a]	0.74
Adjusting factors									
Age (years)	158	1.13 (1.02-1.81)[a]	1.03 (1.02-1.07)[a]	1.01 (1.01-1.06)[a]	1.05 (1.01-1.09)[a]	1.11 (1.04-1.14)[a]	1.05 (1.01-1.07)[a]	1.01 (1.01-1.04)[a]	-
Primary tumor site (gastrointestinal tract)	158	2.18 (1.23-3.87)[a]	1.94 (1.85-3.05)[a]	1.84 (1.73-2.12)[a]	1.90 (1.62-2.74)[a]	1.92 (1.77-2.64)[a]	1.71 (1.63-2.11)[a]	1.54 (1.24-2.08)[a]	-
Cancer stage (distant metastasis)	158	1.37 (1.11-1.60)[a]	1.23 (1.05-2.04)[a]	1.31 (1.11-2.47)[a]	1.17 (1.02-2.11)[a]	1.54 (1.33-2.21)[a]	1.41 (1.09-1.99)[a]	1.23 (1.10-2.07)[a]	-
KPS (≤40%)	158	2.05 (1.45-2.90)[a]	1.24 (1.11-1.89)[a]	1.18 (1.03-1.94)[a]	1.22 (1.09-1.77)[a]	1.17 (1.10-1.90)[a]	1.31 (1.14-1.92)[a]	1.25 (1.08-1.98)[a]	-
Current health care setting (inpatient)	158	2.89 (2.04-4.09)[a]	1.68 (1.47-1.98)[a]	1.46 (1.20-1.78)[a]	1.23 (1.07-1.70)[a]	1.81 (1.21-1.99)[a]	1.28 (1.17-1.68)[a]	1.60 (1.39-1.82)[a]	-

Note: *n* = number of observations; HR = hazard ratio; CI = confidence interval; KPS = Karnofsky Performance Status; CRP = C-reactive protein; CAR = CRP/albumin ratio; NLR = neutrophil/lymphocyte ratio; mGPS = modified Glasgow Prognostic Score.

[a] *P* value < 0.05

including the Palliative Performance Scale and found an AUC value of 0.70 to predict 90-day survival in a prospective cohort of patients with advanced cancer in a palliative care unit. A retrospective study in a home palliative care setting in China described AUC of 0.67 for Palliative Prognostic Index (PPI), 0.67 for Performance Status-Based PPI and 0.70 for the Chinese Prognosis Scale for prediction of 90-day survival.[20] A prospective cohort study in Italy evaluated the accuracy of the Palliative Prognostic Score, Objective Prognostic Score, and PPI in predicting 30-day OS in patients with terminal cancer, finding AUC of 0.82, 0.70, and 0.72, respectively.[21]

We demonstrated that patients with biomarkers above the cutoff points and with mGPS 1 and 2 had significantly shorter OS than the others, showing the relationship between exacerbated systemic inflammation and the approach of death.[22] A previous study conducted at the same PCU showed a lower probability of 90-day OS among patients with mGPS ≥1.[23] Another study developed with advanced cancer patients in Australia observed that patients with NLR ≥5 and with mGPS 2 had a significantly shorter median OS than the others,[24] corroborating our results. In the cohort study conducted by Zhang et al.,[17] the median OS of patients with CAR ≥1.31 was significantly worse than in those with lower CAR values.

All the inflammatory biomarkers evaluated were significantly associated with a higher risk of death, being considered independent prognostic factors. Kim et al. [25] investigated prognostic factors in terminal cancer patients in South Korea and pointed to the fact that NLR ≥5 and CRP ≥10mg/L were independent prognostic factors. Others studies likewise show that neutrophils,[18] leukocytes,[26] CAR,[8,9,17] and mGPS [23,26] can predict death.

Our findings indicate a better prognostic performance for CAR than the other biomarkers studied. Previous studies corroborate these findings.[8,27,28,29] Ni et al. [8] found CAR to be positively correlated with Glasgow Prognostic Score, mGPS, NLR, platelet/lymphocyte ratio, and monocyte/lymphocyte ratio, and an independent predictive prognostic factor. Some biological mechanisms may explain the association between high levels of CAR with reduced survival in patients with terminal cancer. Inflammation is a critical component of tumor progression, influencing the tumor microenvironment in a way that favors proliferation, survival and migration in the neoplastic process.[30] The synthesis of CRP, by the liver, is induced by pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α,[31] which promote a systemic inflammatory response.[5] In turn, this systemic inflammatory response contributes to muscle catabolism, hypoalbuminemia, and the subsequent death of patients with terminal cancer.[22] In a study with acute myeloid leukemia patients, Gradel et al. [32] observed that albumin is an inflammatory biomarker due to its inverse correlation with CRP levels and its rapid changes over a few days, unrelated to changes in nutritional status or chronic diseases.

The mGPS is a widely accepted index for characterizing systemic inflammation and is known to be of reliable prognostic value in patients with advanced cancer.[5] However, although high CRP and low albumin are part of the score, CAR could be a better prognostic factor for generating a continuous value based on CRP and albumin levels, effectively reflecting a deterioration of the inflammatory state as the disease progresses, making it a potentially promising parameter for use in clinical practice.

We must highlight the practical utility of inflammatory biomarkers, which are subjectivity-free tools, easy to perform and which can be included in the routine of laboratory tests at health units. In addition, they are accessible to any health professional and their evaluation does not show interobserver variability. These characteristics favor the prognostic evaluation because it depends less on subjective evaluations by clinicians and are easier to interpret by all members of the multidisciplinary team.

Limitations

This study was carried out at a single center, had a limited number of patients with CRP and CAR data, did not evaluate the variations of the biomarkers longitudinally and did not exclude patients with acute infection. In addition, it analyzed patients with various types of cancer and it is not known whether the significance of the biomarkers for predicting life expectancy is consistent across cancer types. Multicenter studies could confirm the predictive value of the inflammatory biomarkers evaluated and further studies are required to validate the cutoff points of these biomarkers.

Conclusion

Inflammatory biomarkers were found to be feasible factors for estimating the prognosis of terminal cancer patients receiving palliative care. Of the biomarkers studied, CRP, leukocytes, neutrophils, CAR, NLR, and mGPS showed good discrimination for predicting OS, with CAR presenting the best results. CAR could be particularly useful in the clinical evaluation of terminal cancer, as it could be used by clinicians and even healthcare providers who do not specialize in palliative care.

Disclosures and Acknowledgments

Disclosures/Conflict of interest: The authors declared no potential conflicts of interest with respect

to the research, authorship, and/or publication of this article.

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

Data Statement

The data and analysis material related to this study are maintained and managed according to ethical regulations. To maintain confidentiality and anonymity of patients, this information will not be made publicly available. Requests for further information can be directed to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jpainsymman.2021.04.009.

References

1. Hui D, Paiva CE, Del Fabbro EG, et al. Prognostication in advanced cancer: update and directions for future research. Support Care Cancer 2019;27:1973–1984.

2. Hui D. Prognostication of survival in patients with advanced cancer: predicting the unpredictable? Cancer Control 2015;22:489–497.

3. Simmons CPL, McMillan DC, McWilliams K, et al. Prognostic tools in patients with advanced cancer: a systematic review. J Pain Symptom Manage 2017;53:962–970.

4. Reid VL, McDonald R, Nwosu AC, et al. A systematically structured review of biomarkers of dying in cancer patients in the last months of life; an exploration of the biology of dying. PLoS ONE 2017;12:e0175123.

5. 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;116:134–146.

6. 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.

7. Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. J Clin Invest 2015;125:3347–3355.

8. Ni XF, Wu J, Ji M, et al. Effect of C-reactive protein/albumin ratio on prognosis in advanced non-small-cell lung cancer. Asia Pac J Clin Oncol 2018;14:402–409.

9. Ju SY, Ma SJ. High C-reactive protein to albumin ratio and the short-term survival prognosis within 30 days in terminal cancer patients receiving palliative care in a hospital setting: a retrospective analysis. Medicine 2020;99:e19350.

10. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 2005;91:181–184.

11. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med 2009;9:30–33.

12. McMillan DC, Crozier JEM, Canna K, Angerson WJ, McArdle CS. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis 2007;22:881–886.

13. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of chemotherapeutic agents, New York: Columbia Univ Press; 1949:191–205.

14. Menezes AMB, Santos IS. Curso de epidemiologia básica para pneumologistas. J Pneumol 1999;25:321–326.

15. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: John Wiley & Sons; 2000.

16. Nakamura Y, Watanabe R, Katagiri M, et al. Neutrophil/lymphocyte ratio has a prognostic value for patients with terminal cancer. World J Surg Oncol 2016;14:148.

17. Zhang J, Zhang C, Li Q, et al. C-reactive protein/albumin ratio is an independent prognostic predictor of survival in advanced cancer patients receiving palliative care. J Palliat Med 2019;22:1536–1545.

18. Zhao W, Wang P, Jia H, et al. Neutrophil count and percentage: potential independent prognostic indicators for advanced cancer patients in a palliative care setting. Oncotarget 2017;8:64499–64508.

19. Mei AHY, Jin WLC, Hwang MKY, et al. Value of the Palliative performance scale in the prognostication of advanced cancer patients in a tertiary care setting. J Palliat Med 2013;16:887–893.

20. Zhou J, Xu S, Cao Z, et al. Validation of the palliative prognostic index, performance status−based palliative prognostic index and Chinese prognostic scale in a home palliative care setting for patients with advanced cancer in China. BMC Palliative Care 2020;19:167.

21. Ermacora P, Mazzer M, Isola M, et al. Prognostic evaluation in palliative care: final results from a prospective cohort study. Support Care Cancer 2019;27:2095–2102.

22. McMillan DC, Watson WS, O'Gorman P, et al. Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. Nutr Cancer 2001;39:210–213.

23. Cunha MS, Wiegert EVM, Calixto-Lima L, Oliveira LC. Relationship of nutritional status and inflammation with survival in patients with advanced cancer in palliative care. Nutrition 2018;51-52:98–103.

24. Tan CSY, Read JA, Phan VH, et al. The relationship between nutritional status, inflammatory markers and survival in patients with advanced cancer: a prospective cohort study. Support Care Cancer 2015;23:385–391.

25. Kim YJ, Kim SJ, Lee JK, et al. Prediction of survival in terminally ill cancer patients at the time of terminal cancer diagnosis. J Cancer Res Clin Oncol 2014;140:1567–1574.

26. Partridge M, Fallon M, Bray C, et al. Prognostication in advanced cancer: a study examining an inflammation-based score. J Pain Symptom Manage 2012;44:161–167.

27. Zhang Y, Zhou G, Liu X, et al. Exploration and validation of C-reactive protein/albumin ratio as a novel

inflammation-based prognostic marker in nasopharyngeal carcinoma. J Cancer 2016;7:1406–1412.

28. Ni X, Wu P, Wu J, et al. C-reactive protein/albumin ratio as a predictor of survival of metastatic colorectal cancer patients receiving chemotherapy. Int J Clin Exp Pathol 2016;9:5525–5534.

29. Zhou T, Zhao Y, Zhao S, et al. Comparison of the prognostic value of systemic inflammation response markers in small cell lung cancer patients. J Cancer 2019;10:1685–1692.

30. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–867.

31. Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. Curr Oncol Rep 2002;4:205–255.

32. Gradel KO, Póvoa P, Garvik OS, et al. Longitudinal trajectory patterns of plasma albumin and C-reactive protein levels around diagnosis, relapse, bacteraemia, and death of acute myeloid leukaemia patients. BMC Cancer 2020;20:249.