Conjecturas

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# Predictive value of inflammatory indices: a prospective study in critical oncological patients

## Valor preditivo dos índices inflamatórios: um estudo prospectivo em pacientes oncológicos críticos

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**ABSTRACT**

The aim of this study was to evaluate the association of inflammatory indices and survival in critical cancer patients. This is a prospective, observational cohort study in which patients were followed up for 28 days after admission to the intensive care unit (ICU) of a reference hospital specialized in oncology. The neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), and modified Glasgow Prognostic Score (mGPS) were calculated within 24 hours of admission to the ICU. Spearman's correlation, Kaplan-Meier survival curve, and Cox regression were used to associate the selected variables with survival. One hundred patients were selected, 78% of whom had active cancer, and 27 of whom died. Patients with mGPS 1 and 2 had a lower probability of 28-day survival and were 4.1 times more likely to die than the patients with mGPS 0. mGPS is a better predictor of survival than NLR, PLR, and MLR in critically ill patients diagnosed with solid tumors. Further studies are needed to establish the precise cutoff point for mGPS in relation to mortality and to assess its applicability in clinical practice.

**Keywords:** inflammation; critical care; neoplasms; prognosis.

**RESUMO**

O objetivo deste estudo foi avaliar a associação de índices inflamatórios e sobrevida em pacientes críticos com câncer. Trata-se de um estudo de coorte prospectivo, observacional, no qual os pacientes foram acompanhados por 28 dias após admissão na unidade de terapia intensiva (UTI) de um hospital de referência especializado em oncologia. A razão neutrófilo/linfócito (NLR), razão monócito/linfócito (MLR), razão plaqueta/linfócito (PLR) e Escore Prognóstico de Glasgow modificado (mGPS) foram calculados dentro de 24 horas após a admissão na UTI. A Correlação de Spearman, curva de sobrevida de Kaplan-Meier e regressão de Cox foram utilizadas para associar as variáveis selecionadas à sobrevida. Cem pacientes foram selecionados, dos quais 78% tinham câncer ativo e 27 foram à óbito. Pacientes com mGPS 1 e 2 tiveram uma probabilidade menor de sobrevida em 28 dias e foram 4,1 vezes mais propensos a morrer do que os pacientes com mGPS 0. O mGPS foi superior como preditor de sobrevida do que NLR, PLR e MLR em pacientes críticos diagnosticados com tumores sólidos. Mais estudos são necessários para estabelecer o ponto de corte preciso da mGPS em relação à mortalidade e avaliar sua aplicabilidade na prática clínica.

**Palavras-chave:** inflamação; cuidado crítico; neoplasias; prognóstico.

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## INTRODUCTION

The admission of cancer patients to intensive care units is a very recent phenomenon. Until 1980, intensive care was not recommended for such patients and it was only in 1990, with the publication of new research on the subject, that the scenario began to change (WIGMORE et al., 2013). Since then, cancer patients have increasingly been admitted to intensive care, to treat either the side effects of cancer treatment or complications associated with the disease itself (AZOULAY; AFESSA, 2006). Indeed, it is estimated that one in ten cancer patients will have intensive care at some time (SHELTON, 2010).

However, as health system resources are limited, a prognostic or severity assessment is required before a patient can be admitted to an ICU (LE GALL, 1994; NIEWINSKI; KANSKI, 2012; KEEGAN et al., 2012). Prognostic measures/markers are used to orient the intensive care received, preventing the futile or disproportionate use of therapies in advanced cancer. The Acute Physiology and Chronic Health Evaluation (APACHE) score is recommended for evaluating the admission of patients to ICU, as established in the Ministry of Health (KNAUS et al., 1981; KNAUS et al., 1985; NOGUEIRA et al., 2007; BRASIL, 1998).

In the oncology setting, other prognostic methods have been studied and widely validated, such as the modified Glasgow Prognostic Score (mGPS), the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), and the monocyte/lymphocyte ratio (MLR) at different stages of the disease (CHEN et al., 2017; DOLAN et al., 2020; KANG et al., 2019; HIRAHARA et al., 2019; SHIMIZU et al., 2019).

To date, no study has evaluated the clinical usefulness of these parameters in critical cancer patients. Knowledge about the prognosis of critical cancer patients should be expanded, as there are conflicting factors at play between referral to intensive care and efficient resource management. Thus, the aim of this study was to evaluate the prognostic power of different inflammatory indices in critical cancer patients, with emphasis on mGPS.

## METHODOLOGY

## Study design and population

This is a prospective, observational cohort study that took place between March 2019 and February 2020, involving cancer patients admitted to the ICU of a reference oncology hospital, due to cancer complications. Patients were followed up for 28 days after admission to the ICU.

Patients of both sexes, aged ≥ 20 years at the time of admission to the ICU, who were diagnosed with a solid tumor, and with sepsis or septic shock were included in the study. Exclusion criteria were: transfer from other institutions; having liver or hematological cancer; being in the immediate postoperative period; having no diagnosis of sepsis or septic shock; being readmitted to the ICU; or refusal to sign the informed consent form (by the patient or their parent or guardian).

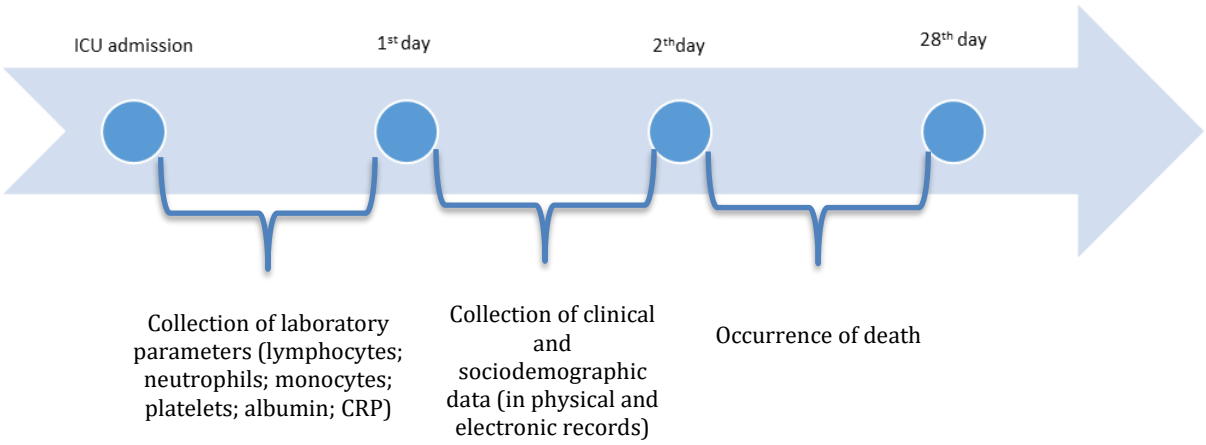
Patients were divided into two groups: active vs. inactive cancer. The patients with active cancer were classified as those undergoing chemotherapy, radiotherapy, immunotherapy, or curative or palliative surgery (RODRIGUES et al., 2016). The patients with inactive cancer were those who had a negative histopathological test for cancer and/or had been diagnosed with cancer before but were in remission after undergoing disease-modifying treatment (BROWN et al., 2001).

Sepsis was defined as infection or suspected infection and ≥ 2 points on the Sequential Organ Failure Assessment (SOFA). Patients with septic shock were identified from the clinical symptoms of sepsis and persistent hypotension, requiring administration of vasopressors to maintain mean blood pressure ≥ 65 mmHg and presenting serum lactate levels > 2 mmol/L (18 mg/dL), even with adequate fluid resuscitation (SINGER et al., 2016).

## Data collection

The data collection flow is outlined in **Figure 1**.

**Figure 1** – Data collection flow




ICU – Intensive Care Unit; CRP – C-reactive protein.

### Biochemical parameters

Serum concentrations of lymphocytes (cells/µl), neutrophils (cells/µl), monocytes (cells/µl), and platelet counts (mil/µl) were collected from medical records within 24 hours of admission to the ICU, based on which NLR, MLR, and PLR were calculated.

Serum CRP (mg/L) and albumin (g/dL) concentrations were collected. Patients were classified has having hypoalbuminemia when serum albumin concentrations were < 3.5 g/dL (LIAO et al., 2020). mGPS scores were allocated according to the serum concentrations of these two markers, as follows: 0 (CRP ≤ 10.0 mg/L and albumin ≥ 3.5 g/dL); 1 (CRP > 10 mg/L or albumin < 3.5 g/dL); and 2 (CRP > 10.0 mg/L and albumin < 3.5 g/dL) (MCMILLAN, 2013).

### Covariables

Sociodemographic information (age and gender) and clinical data (tumor location, performance status, and tumor staging) were obtained from medical records using a standardized form.

### Survival

Patients were followed up for 28 days from admission to the ICU, and information on death from any cause was obtained from medical records. Survival time was calculated

from the date of admission to the ICU until the date of death or the end of follow-up within 28 days.

### Statistical analysis

The Kolmogorov-Smirnov test was used to assess the symmetry of the data distribution. Continuous variables with non-normal distribution were expressed as median and interquartile range (IQR) and were compared using the Mann-Whitney U test; categorical variables were expressed as percentage (%) and were compared using the chi-square test ($X^2$). Variables with statistical significance ($p < 0.20$) were selected for correlation analysis.

Spearman's correlation was used to relate the occurrence of death within 28 days and clinical outcomes. The degree of correlation was classified as weak when $0 < r < 0.4$, moderate when $0.4 < r < 0.7$, and strong when $0.7 < r < 1.0$ (SIQUEIRA; TIBURCIO, 2011).

The log-rank test was done to ascertain the difference in survival probability for the groups classified according to the selected variables. The Kaplan-Meier curve was constructed to assess survival probability according to variables with p-value < 0.20 in the log-rank test.

Additionally, Cox proportional hazards model was used to conduct multiple regression analysis, yielding hazard ratios (HR) with a 95% confidence interval (95%CI), to assess the predictive capacity of mGPS for 28-day mortality in critically ill cancer patients. Multiple regression was controlled for cancer diagnosis and disease stage.

Analyses were performed using SPSS for Windows 22.0 (IBM Corp., Armonk, USA), with p-value < 0.05 being considered statistically significant.

## RESULTS

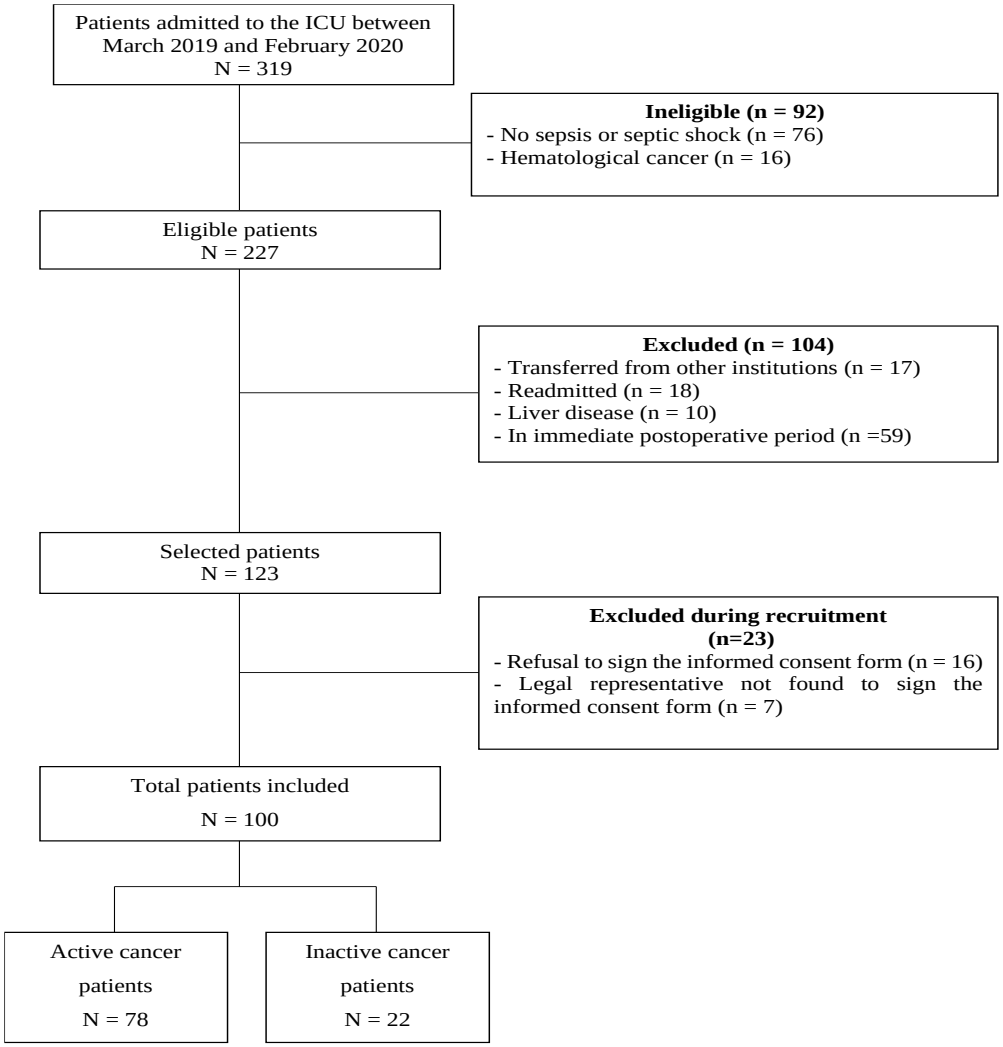
One hundred patients were selected, 78 (78.0%) of whom had active cancer (**Figure 2**). The median age was 64 years (IQR 56–71), with a predominance of women (51.0%). Most were admitted to the ICU with a diagnosis of sepsis (62.0%) and low functionality (95.0%). In those with active cancer, the most prevalent tumor location was in the gastrointestinal tract (38.5%), followed by head and neck (26.9%), and most were

at an advanced stage of the disease (71.8%). Twenty-seven patients with active cancer (27.0%) and eight without cancer (8.0%) died during follow-up (**Table 1**).

The highest proportion of patients with active cancer who died during the follow-up period had mGPS 1 and 2 (p = 0.043). Similar results were not observed in patients with inactive cancer (p = 0.235) (**Table 2**).

No statistically significant differences were found between the NLR, PLR, and MLR of the patients with active cancer (p = 0.987, 0.614, and 0.207, respectively) and inactive cancer (p = 0.665, 0.315, and 0.402, respectively) for 28-day mortality (**Table 2**). These prognostic indices were divided into tertiles, with the third terciles being 21, 409, and 0.6 for NLR, PLR, and MLR, respectively.

**Figure 2** – Patients included in the survey




ICU – Intensive Care Unit

**Table 1** – Demographic and clinical characteristics according to the occurrence of death within 28 days

| | ACTIVE CANCER (A)[f] | | | | | INACTIVE CANCER (B)[g] | | | | A vs B[e] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **Total (n = 100; 100.0%)** | **Total (n = 78; 78.0%)** | **Survived (n = 51; 51.0%)** | **Died within 28 days (n=27; 27.0%)** | **p-value** | **Total (n = 22; 22.0%)** | **Survived (n=14; 14.0%)** | **Died within 28 days (n=8; 8.0%)** | **p-value** | **p-value** |
| **Age (years)** [a,c] | 64 (56–71) | 66 (53–72) | 63 (54–69) | 68 (56–74) | 0.434 | 65 (56-73) | 62 (54-70) | 73 (63-82) | 0.066 | 0.538 |
| **Gender**[b] | | | | | | | | | | |
| Female | 51 (51.0%) | 39 (39.0%) | 24 (24.0%) | 15 (15.0%) | 0.475 | 12 (12.0%) | 8 (8.0%) | 4 (4.0%) | 0.746 | 0.706 |
| Male | 49 (49.0%) | 39 (39.0%) | 27 (27.0%) | 12 (12.0%) | | 10 (10.0%) | 6 (6.0%) | 4 (4.0%) | | |
| **Tumor site**[b] | | | | | | | | | | |
| Digestive tract | 30 (38.5%) | 30 (30.0%) | 22 (22.0%) | 8 (8.0%) | 0.093 | - | - | - | - | - |
| Head and neck | 21 (26.9%) | 21 (21.0%) | 16 (16.0%) | 5 (5.0%) | | - | - | - | | |
| Urinary system | 8 (10.2%) | 8 (8.0%) | 5 (5.0%) | 3 (3.0%) | | - | - | - | | |
| Lung | 5 (6.4%) | 5 (5.0%) | 1 (1.0%) | 4 (4.0%) | | - | - | - | | |
| Other | 14 (18.0%) | 14 (14.0%) | 7 (7.0%) | 7 (7.0%) | | - | - | - | | |
| **Stage**[b] | | | | | | | | | | |
| I/II | 22 (28.2%) | 22 (22.0%) | 16 (16.0%) | 6 (6.0%) | 0.365 | - | - | - | - | - |
| III/IV | 56 (71.8%) | 56 (56.0%) | 34 (34.0%) | 22 (22.0%) | | - | - | - | | |
| **Reason for admission to ICU**[b] | | | | | | | | | | |
| Sepsis | 62 (62.0%) | 49 (49.0%) | 33 (33.0%) | 16 (16.0%) | 0.636 | 13 (13.0%) | 10(10.0%) | 3 (3.0%) | 0.141 | 0.166 |
| Septic Shock | 38 (38.0%) | 29 (29.0%) | 18 (18.0%) | 11 (11.0%) | | 9 (9.0%) | 4 (4.0%) | 5 (5.0%) | | |
| **Performance Status**[b] | | | | | | | | | | |
| 0–2 | 5 (5.0%) | 4 (4.0%) | 4 (4.0%) | 0 | 0.135 | 1 (1.0%) | 1 (1.0%) | 0 | 0.439 | 0.912 |
| ≥ 3 | 95 (95.0%) | 74 (74.0%) | 47 (47.0%) | 27 (27.0%) | | 21 (21.0%) | 13 (13.0%) | 8 (8.0%) | | |
| **Number of comorbidities**[b] | | | | | | | | | | |
| 0 | 28 (28.0%) | 21 (21.0%) | 15 (15.0%) | 6 (6.0%) | 0.412 | 7 (7.0%) | 5 (5.0%) | 2 (2.0%) | 0.795 | 0.797 |
| 1 | 33 (33.0%) | 27 (27.0%) | 15 (15.0%) | 12 (12.0%) | | 6 (6.0%) | 4 (4.0%) | 2 (2.0%) | | |
| ≥ 2 | 39 (39.0%) | 30 (30.0%) | 21 (21.0%) | 9 (9.0%) | | 9 (9.0%) | 5 (5.0%) | 4 (4.0%) | | |

[a] Chi-square test; [b] Mann-Whitney U test; [c] Median [IQR (Q1-Q3)]; [d] Absolute number (%); [e] Comparison of total active and inactive cancer patients according to the selected variables; [f]Active cancer patients were those currently undergoing curative or palliative chemotherapy, radiotherapy, immunotherapy, or surgery. [g]Inactive cancer patients were those who had a negative histopathological examination for cancer and/or had been diagnosed with cancer but were currently free of the disease after undergoing treatment. IQR: interquartile range; ICU: intensive care unit; *statistical significance $p < 0.05$.

**Table 2** – Inflammatory indices according to the occurrence of death within 28 days

| | | ACTIVE CANCER (A) | | | | INACTIVE CANCER (B) | | | | A vs B |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **Total (n = 100; 100.0%)** | **Total (n = 78; 78.0%)** | **Survived (n = 51; 51.0%)** | **Died within 28 days (n = 27; 27.0%)** | **p-value** | **Total (n = 22; 22.0%)** | **Survived (n = 14; 14.0%)** | **Died within 28 days (n = 8; 8.0%)** | **p-value** | **p-value** |
| **CRP** [a c] | | | | | | | | | | |
| < 22.9 mg/L | 68 (68.0%) | 52 (52.0%) | 36 (36.0%) | 16 (16.0%) | 0.313 | 15 (15.0%) | 9 (9.0%) | 6 (6.0%) | 0.604 | 0.590 |
| > 22.9 mg/L | 32 (32.0%) | 26 (26.0%) | 15 (15.0%) | 11 (11.0%) | | 7 (22.0%) | 5 (5.0%) | 2 (2.0%) | | |
| **Albumin** [a b] | | | | | | | | | | |
| >2.6 g/dL | 61 (61.0%) | 49 (49.0%) | 34 (69.4%) | 15 (30.6%) | 0.334 | 15 (15.0%) | 11 (73.3%) | 4 (26.7%) | 0.166 | 0.144 |
| <2.6 g/dL | 39 (39.0%) | 29 (29.0%) | 17 (58.6%) | 12 (41.4%) | | 7 (7.0%) | 3 (42.9%) | 4 (57.1%) | | |
| **mGPS** [a] | | | | | | | | | | |
| 0 | 29 (29.0%) | 22 (22.0%) | 18 (18.0%) | 4 (4.0%) | **0.049*** | 7 (22.0%) | 2 (2.0%) | 5 (5.0%) | 0.540 | 0.235 |
| 1 and 2 | 71 (71.0%) | 56 (56.0%) | 33 (33.0%) | 23 (23.0%) | | 15 (15.0%) | 3 (3.0%) | 12 (12.0%) | | |
| **NLR** [a c] | | | | | | | | | | |
| < 21 | 67 (67.0%) | 52 (52.0%) | 34 (34.0%) | 18 (18.0%) | 0.987 | 15 (15.0%) | 10 (10.0%) | 5 (5.0%) | 0.665 | 0.894 |
| ≥ 21 | 33 (33.0%) | 26 (26.0%) | 17 (17.0%) | 9 (9.0%) | | 7 (22.0%) | 4 (4.0%) | 3 (3.0%) | | |
| **PLR** [a c] | | | | | | | | | | |
| < 409 | 66 (66.0%) | 52 (52.0%) | 33 (33.0%) | 19 (19.0%) | 0.614 | 15 (15.0%) | 10 (10.0%) | 4 (4.0%) | 0.315 | 0.791 |
| ≥ 409 | 34 (34.0%) | 26 (26.0%) | 18 (18.0%) | 8 (8.0%) | | 7 (22.0%) | 4 (4.0%) | 4 (4.0%) | | |
| **MLR** [a b] | | | | | | | | | | |
| > 0.6 | 70 (70.0%) | 56 (56.0%) | 39 (39.0%) | 17 (17.0%) | 0.207 | 14 (14.0%) | 8 (8.0%) | 6 (6.0%) | 0.402 | 0.461 |
| ≤ 0.6 | 30 (30.0%) | 22 (22.0%) | 12 (12.0%) | 10 (10.0%) | | 8 (8.0%) | 6 (6.0%) | 2 (2.0%) | | |

[a]Absolute number (%)/Chi-square test; [b]1st tercile vs. 2nd + 3rd tercile; [c]3rd tercile vs. 1st + 2nd tercile; IQR: interquartile range; CRP: C-reactive protein; mGPS: modified Glasgow Prognostic Score; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; MLR: monocyte/lymphocyte ratio * statistical significance $p < 0.05$.

**Table 3** shows that among the patients with active cancer, tumor location correlated weakly ($r = 0.250$; $p = 0.027$) and mGPS correlated moderately ($r = 0.498$; $p = 0.050$) with 28-day mortality. There was no significant correlation between mGPS and death within 28 days in the patients with inactive cancer.

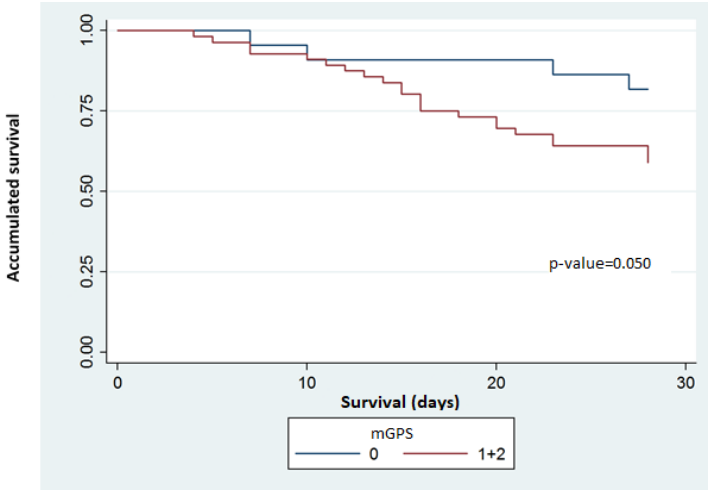
**Table 3** – Correlation analysis between the occurrence of death within 28 days and selected variables (n = 100)

| VARIABLES | ACTIVE CANCER (n = 78)[a] | | INACTIVE CANCER (n = 22)[b] | |
|---|---|---|---|---|
| | R | p-value | R | p-value |
| **Age** | 0.089 | 0.437 | 0.418 | 0.053 |
| **Tumor site** | 0.250 | **0.027*** | - | - |
| **Reason for admission to ICU** | 0.054 | 0.641 | 0.284 | 0.200 |
| **Performance status** | 0.169 | 0.139 | 0.165 | 0.463 |
| **Albumin** | -0.046 | 0.691 | 0.295 | 0.182 |
| **mGPS** | 0.498 | **0.050*** | 0.217 | 0.058 |

[a]Active cancer patients were those currently undergoing curative or palliative chemotherapy, radiotherapy, immunotherapy. or surgery. [b]Inactive cancer patients were those who had a negative histopathological examination for cancer and/or had been diagnosed with cancer but were currently free of the disease after undergoing treatment. R: Spearman's rank correlation coefficient. CRP: C-reactive protein; ICU: intensive care unit; mGPS: modified Glasgow Prognostic Score; *Statistical significance $p < 0.05$.

The patients with active cancer and mGPS 1 or 2 had a lower probability of survival, with a median of 28 (17–28) days (**Figure 3**, **Table 4)**. These patients were 4.10 times more likely to die than the patients from the same group with mGPS 0 (95% CI 1.36–12.33; p = 0.012), highlighting the predictive power of this inflammatory biomarker (**Table 5**).

**Figure 3** – Association between mGPS and death in critically ill cancer patients with active cancer according to the Kaplan-Meier curve.




mGPS: modified Glasgow Prognostic Score.

**Table 4** – 28-day survival according to selected variables (n = 100)

| VARIABLES | ACTIVE CANCER (n = 78)[a] | | | INACTIVE CANCER (n = 22)[b] | | |
|---|---|---|---|---|---|---|
| | Events n (%) | Median (IQR) days | p-value | Events n (%) | Median (IQR) days | p-value |
| **Tumor site** | | | | | | |
| Digestive tract | 8 (10.3%) | 28 (19-28) | 0.123 | - | - | - |
| Head and neck | 5 (6.4%) | 28 (23-28) | | - | - | - |
| Urinary system | 3 (3.8%) | 12 (10-25) | | - | - | - |
| Lung | 4 (5.1%) | 9 (4-22) | | - | - | - |
| Other | 7 (9.0%) | 28 (26-28) | | - | - | - |
| **Reason for admission to ICU** | | | | | | |
| Sepsis | 16 (20.5%) | 28 (21-28) | 0.762 | 0 | 28 (28-28) | 0.127 |
| Septic shock | 11 (14.1%) | 28 (23-28) | | 5 (36.3%) | 28 (10-28) | |
| **Performance status** | | | | | | |
| < 3 | 0 | 28 (28-28) | 0.278 | 0 | 28 (28-28) | 0.487 |
| ≥ 3 | 27 (34.6%) | 28 (22-28) | | 8 (36.3%) | 28 (28-28) | |
| **Albumin** | | | | | | |
| > 2.6 g/dL | 15 (19.2%) | 28 (23-28) | 0.374 | 0 | 28 (28-28) | 0.218 |
| ≤ 2.6 g/dL | 12 (15.4%) | 28 (21-28) | | 4 (36.3%) | 28 (20-28) | |
| **mGPS** | | | | | | |
| 0 | 0 | 28 (28-28) | **0.050*** | 1 (4.5%) | 28 (28-28) | 0.070 |
| 1 and 2 | 23 (34.6%) | 28 (17-28) | | 3 (31.8%) | 28 (26-28) | |

[a]Active cancer patients were those currently undergoing curative or palliative chemotherapy, radiotherapy, immunotherapy, or surgery. [b]Inactive cancer patients those who had a negative histopathological examination for cancer and/or had been diagnosed with cancer but were currently free of the disease after undergoing treatment. CRP: C-reactive protein; ICU: intensive care unit; mGPS: modified Glasgow Prognostic Score; *Statistical significance $p < 0.05$.

Furthermore, when the patients with active cancer were compared according to tumor location, only the patients with urologic cancer had worse survival, being 16.03 times more likely to die than the patients with other tumor locations (95% CI = 3.86–66.62; $p < 0.001$) (**Table 5**).

**Table 5** – Cox univariate and multivariate regression analysis, with relative risk and 95% confidence interval for death in critically ill cancer patients according to selected variables (n = 100)

| VARIABLES | ACTIVE CANCER[a] | | | | INACTIVE CANCER[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | UNIVARIATE | | MULTIVARIATE | | UNIVARIATE | | MULTIVARIATE | |
| | OR (CI 95%) | p-value[a] | OR (CI 95%) | p-value[a] | OR (CI 95%) | p-value[a] | OR (CI 95%) | p-value[a] |
| **Tumor site** | | | | | | | | |
| Digestive tract | 1.00 | | 1.00 | | - | - | - | - |
| Head and neck | 1.19 (0.39-3.63) | 0.765 | 1.41 (0.46-4.33) | 0.547 | - | - | - | - |
| Urinary system | 7.54 (2.00-28.36) | **0.003*** | 16.03 (3.86-66.62) | **<0.001*** | - | - | - | - |
| Lung | 2.05 (0.49-8.59) | 0.326 | 2.28 (0.54-9.54) | 0.264 | - | - | - | - |
| Other | 2.41 (0.76-7.59) | 0.134 | 2.84 (0.89-9.05) | 0.077 | - | - | - | - |
| **Septic shock** | 1.12 (0.52-2.42) | 0.764 | - | - | 1.67 (0.60-4.64) | 0.324 | - | - |
| **mGPS (score 1 and 2)** | 2.59 (1.02-7.50) | **0.049*** | 4.10 (1.36-12.33) | **0.012*** | 1.18 (0.04-3.54) | 0.567 | - | |

Adjusted for diagnose and stage;

[a]Active cancer patients were those currently undergoing curative or palliative chemotherapy, radiotherapy, immunotherapy, or surgery. [b]Inactive cancer patients those who had a negative histopathological examination for cancer and/or had been diagnosed with cancer but were currently free of the disease after undergoing treatment. mGPS: modified Glasgow Prognostic Score; CI: confidence interval; OR: odds ratio. *Statistical significance $p < 0.05$.

## DISCUSSION

This is a pioneering study evaluating the predictive power of inflammatory indices in critical cancer patients at a specialized oncology hospital. Our main result demonstrates that an mGPS score of 1 or 2 is a biomarker of worse survival in such patients.

To determine adequate treatment, it is important to be able to make an accurate prognosis. Although several tools have been suggested to predict mortality, there are few that are accurate, easy to use, and readily available (KNAUS et al., 1981).

The mGPS is calculated based on the serum levels of CRP and albumin, thus reflecting patients' inflammatory profile and nutritional status. CRP is an acute phase protein and is mainly produced by hepatocytes in response to inflammation, tissue damage, and infection. Elevated CRP levels have been reported as a negative prognostic

factor in several types of cancer. Meanwhile, hypoalbuminemia is considered an indicator of malnutrition and cachexia, reflecting worsened physical condition (LIAO et al., 2020; HU et al., 2014).

Our data demonstrate that critically ill patients with solid tumors and an mGPS score of 1 or 2 were 4.10 times more likely to die within 28 days (95% CI = 1.36–12.33; p = 0.012) than patients with an mGPS score of 0. However, no significant difference was found for the critically ill patients with inactive cancer (95% CI = 0.04–3.54; p = 0.567). This could be because cancer cells activate inflammatory pathways in order to enable cell proliferation, tumor progression, and metastasis (ABE et al., 2018).

Our data contribute to a growing body of evidence that indicates that high mGPS scores predict worse survival in patients with solid tumors, regardless of tumor location (MCMILLAN, 2013). In a study of patients with colon cancer who underwent cancer surgery and later sought the emergency room for some complication related to the surgery, Crozier et al. (2009) demonstrated that mGPS 1 and 2 was an independent risk factor for worse survival and, according to multivariate Cox regression, meant that patients with this score were 2.22 times more likely to die within 28 days than patients with mGPS 0 (95% CI= 1.04-4.74; p=0.0391).

Additionally, critically ill patients also experience increased systemic inflammation (DJORDJEVIC et al., 2018). A recent multicenter study evaluating 336 patients with COVID-19 admitted to an ICU inferred that mGPS was strongly associated with mortality risk, with patients with mGPS 2 being 3.33 times more likely to die within 28 days (95% CI = 1.45–7.66; p = 0.006) than patients mGPS 0 and 1 (PITRE et al., 2021). Corroborating these findings, a study that evaluated patients with lung cancer after pneumonectomy indicated that GPS 2 was predictive of a longer ICU stay (PETRELLA et al, 2016). However, to date, no study has been found in the scientific literature using mGPS in critical non-surgical cancer patients.

Two studies have compared the prognostic value of mGPS with that of other markers of systemic inflammatory response, such as NLR and PLR, concluding that mGPS is a better predictor of survival than the other parameters (PROCTOR et al., 2011; SHAFIQUE et al., 2012). In our sample, we also found the prognostic value of mGPS to be superior to that of NLR, PLR, and MLR in critically ill patients with active cancer; however, neither it nor the other markers yielded any significant results in the patients with inactive cancer.

NLR is an indicator of systemic inflammation based on values provided by the blood count. It was previously shown to predict outcomes in cancer patients (GUTHRIE et al., 2013) and in surgical cancer patients (WALSH et al., 2005), but there are few studies involving critical non-surgical patients (SALCICCIOLI et al., 2015) and only one study was found with non-surgical cancer patients admitted to the ICU (ZAHOREC, 2001).

The role of NLR as a predictor of mortality in patients with sepsis is not clear. Guo et al. (2021) and Pitre et al. (2021) evaluated the 28-day mortality of patients with COVID-19 admitted to an ICU, demonstrating that NRL $\geq$ 8.48 and NRL 6.1 predicted higher mortality in this population, respectively. However, in an analysis of patients with septic shock, Hwang et al. (2017) found that the patients at risk of early death had low NLR, while late death was related to increased NLR values.

In our study, the value found for NRL in critically ill patients with active and inactive cancer was 21 (the 3$^{rd}$ tertile). Ham et al. (2020), when analyzing 1154 patients admitted to an ICU, found that the incidence of one-year mortality was significantly higher in the 3rd tertile (NLR = 24.28 $\pm$ 22.48; $p < 0.001$). However, this was not confirmed in our research.

In general, the blood neutrophil count increases as the inflammatory disease progresses, but in certain conditions such as cachexia, the neutrophil count does not increase, resulting in a "false negative." Lymphocyte counts reflects a patient's immune status and generally decreases as the inflammatory disease progresses; however, this decrease can be delayed (VIDAL et al., 2018; TANEJA et al., 2004).

Regarding PLR and MLR, we did not find significant difference between the survival of the critically ill patients with active and inactive cancer. Data on MLR and PLR in the literature are scarce. Although both appear to be predictors of mortality, their role is more pronounced in systemic inflammation than in septic shock (LIBERSKI et al., 2020). Djordjevic et al. (2018) demonstrated that PLR was higher ($p < 0.01$) in non-survivors with sepsis and/or trauma admitted to a surgical ICU. Meanwhile, Liberski et al. (2020) analyzing 138 ICU patients with a diagnosis of sepsis and septic shock, demonstrated that PLR and MLR were not predictors of mortality ($p = 0.64$ and $p = 0.62$, respectively), which is consistent with our findings.

The explanation of our results is unclear. Our studied population is very specific compared to other research in the area. However, this more limited scope could be interpreted as a strength of our research.

Regarding tumor location, in our study it was found that the patients with urological cancer had a lower survival rate and were 16.03 more likely to die within 28 days than the patients whose tumors were in other locations. The most frequent types of cancer in the men were lung (14.5%), prostate (13.5%), colon and rectal (10.9%), stomach (7.2%), and liver (6.3%) cancer. In the women, the highest incidences were breast (24.2%), colon and rectal (9.5%), lung (8.4%), and cervical (6.6%) cancer (BRAY et al., 2018). There were 15,391 deaths from prostate cancer in 2017, equivalent to 15.25/100,000 men (BRASIL, 2019), behind only lung and bronchial cancer. Our study confirmed the impact of this type of cancer on the survival of cancer patients and the importance of early detection.

The main limitation of our study is the sample size and the different tumor locations and stages of disease. To minimize this fact, a diagnosis of sepsis and septic shock and having solid tumors were stipulated as inclusion criteria.

## CONCLUSION

mGPS is a better predictor of survival than NLR, PLR, and MLR in critically ill patients diagnosed with active solid tumors. However, in critically ill patients with inactive cancer, no significant difference was found for any of the inflammatory indices studied, demonstrating the dual impact of cancer-related inflammation and critical illness.

Furthermore, upon admission to ICU, patients with urologic cancer have a lower survival rate than patients with other tumor locations.

Studies with a larger sample of critically ill cancer patients are needed to establish the precise cutoff point for the mGPS in relation to mortality and to assess its applicability in clinical practice.

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