Serum Albumin is Independent Predictor of Hospital Mortality in Patients with Cancer

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A Albumina Sérica é Preditor Independente de Mortalidade Hospitalar em Pacientes com Câncer

La Albúmina Sérica es un Predictor Independiente de Mortalidad Hospitalaria en Pacientes con Cáncer

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ABSTRACT

Introduction: Cancer is one of the leading causes of morbidity and mortality worldwide. There are few studies showing adjusted models with other predictors of mortality by a conceptual model perspective. **Objective:** The objective of this study was to verify the prediction of albumin and Prognostic Nutritional Index (PNI) with in-hospital mortality in cancer patients. **Method:** Retrospective study was performed from 2014 to 2016 with 262 cancer patients (gastrointestinal tract, male genital organs, breast, metastasis, urinary tract, head and neck and others). Demographic data, blood counts, C-reactive protein, albumin, and haematological indexes (Prognosis nutritional index - PNI, Neutrophils to lymphocytes ratio - NLR, Monocytes lymphocytes ratio - MLR, Platelets to lymphocytes ratio - PLR and Platelets to albumin ratio - PAR), nutritional diagnoses and hospital outcomes (discharge or death) were collected. The cumulative probability of death was calculated by Kaplan-Meier curves, and survival analyses were performed using the Cox proportional hazards model. **Results:** The frequency of death among the study patients was 10.7% (28). Among the patients who died, 99.2% (26) presented some degree of malnutrition (p=0.004). In the multivariate analysis, serum albumin (<3 g/dL) was independently associated with in-hospital mortality (HR=3.43, 95% CI 1.11-10.63). On the other hand, the PNI was not associated with in-hospital mortality. **Conclusion:** Serum albumin levels during hospitalization were predictors of in-hospital mortality in the population evaluated. These results suggest that the serum levels of this protein can be used in clinical practice, adding prognostic information in patients with cancer.

Key words: Serum Albumin; Hospital Mortality; Nutritional Assessment; Neoplasms; Prognosis.

RESUMO

Introdução: O câncer é uma das principais causas de morbidade e mortalidade em todo o mundo. Existem poucos estudos mostrando modelos ajustados com outros preditores de mortalidade por uma perspectiva de modelo conceitual. **Objetivo:** Verificar a predição de albumina e do Índice Nutricional Prognóstico (IPN) com mortalidade intra-hospitalar em pacientes com câncer. **Método:** Estudo retrospectivo realizado de 2014 a 2016 com 262 pacientes com câncer (trato gastrointestinal, órgãos genitais masculinos, mama, metástases, trato urinário, cabeça e pescoço e outros). Foram coletados dados demográficos, hemograma, proteína C reativa, albumina e índices hematológicos (índice de prognóstico nutricional - IPN; relação neutrófilo por linfócitos - RNL; relação monócitos por linfócitos - RML; relação plaquetas por linfócitos - RPL; e relação plaquetas por albumina – RPA), diagnósticos nutricionais e desfechos hospitalares (alta ou óbito). A probabilidade cumulativa de morte foi calculada pelas curvas de Kaplan-Meier e as análises de sobrevivência realizadas usando o modelo de risco proporcional de Cox. **Resultados:** A frequência de óbito entre os pacientes do estudo foi de 10,7% (28). Entre os pacientes que morreram, 99,2% (26) apresentavam algum grau de desnutrição (p=0,004). Na análise multivariada, a albumina sérica (<3 g/dL) associou-se de forma independente à mortalidade hospitalar (HR=3,43, IC95% 1,11-10,63). Por outro lado, o IPN não foi associado com mortalidade intra-hospitalar. **Conclusão:** Os níveis de albumina sérica durante a internação foram preditores de mortalidade intra-hospitalar na população avaliada. Esses resultados sugerem que os níveis séricos dessa proteína podem ser utilizados na prática clínica, agregando informações prognósticas em pacientes com câncer.

Palavras-chave: Albumina Sérica; Mortalidade Hospitalar; Avaliação Nutricional; Neoplasias; Prognóstico.

RESUMEN

Introducción: El cáncer es una de las principales causas de morbilidad y mortalidad en todo el mundo. Hay pocos estudios que muestren modelos ajustados con otros predictores de mortalidad desde una perspectiva de modelo conceptual. **Objetivo:** El objetivo de este estudio fue verificar la predicción de la albúmina y el Índice Nutricional Pronóstico (IPN) con la mortalidad hospitalaria en pacientes con cáncer (tracto gastrointestinal, órganos genitales masculinos, mama, metástasis, tracto urinario, cabeza y cuello y otros). Método**:** Se realizó un estudio retrospectivo de 2014 a 2016 con 262 pacientes con cáncer. Se recogieron datos demográficos, hemogramas, proteína C reactiva, albúmina y índices hematológicos (Índice de Pronóstico Nutricional - IPN, proporción neutrófilos/linfocitos - NLR, proporción monocitos/linfocitos - MLR, proporción plaquetas/linfocitos - PLR y proporción plaquetas/albúmina - PAR), diagnósticos nutricionales y resultados hospitalarios (alta o muerte). La probabilidad acumulada de muerte se calculó mediante curvas de Kaplan-Meier y se realizaron análisis supervivencia utilizando el modelo de riesgos proporcionales de Cox. **Resultados:** La frecuencia de muerte entre los pacientes del estudio fue del 10,7% (28). Entre los pacientes fallecidos, el 99,2% (26) presentaba algún grado de desnutrición (p=0,004). En el análisis multivariado, la albúmina sérica (<3 g/dL) se asoció de forma independiente con la mortalidad hospitalaria (HR=3,43, IC 95% 1,11-10,63). Por otro lado, el IPN no se asoció con mortalidad intrahospitalaria. **Conclusión:** Los niveles de albúmina sérica durante la hospitalización fueron predictores de mortalidad intrahospitalaria en la población evaluada. Nuestros resultados sugieren que los niveles séricos de esta proteína se pueden utilizar en la práctica clínica, agregando información de pronóstico en pacientes con cáncer.

Palabras clave: Albúmina Sérica; Mortalidad Hospitalaria; Evaluación Nutricional; Neoplasias; Prognóstico.

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INTRODUCTION

Cancer is one of the main causes of morbidity and mortality worldwide, despite advances in detection and treatment in recent years[1]. The complexity of clinical-pathological factors related to individuals and disease[2,3] influences the prognosis of patients with cancer. The knowledge of these factors is extremely important for risk stratification and definition of the most appropriate therapy[4].

The relationship between prognosis and laboratory tests as markers of inflammation in cancer patients was evaluated in several studies utilizing univariate analyses or mean indexes based on scoring systems, demonstrating the association of these markers with long-term mortality[2,5].

Albumin was associated with low long-term survival in various types of cancer[6,7]. In addition to the increase of protein catabolism and chronic malnutrition, low serum levels of this protein can reflect in elevation of the systemic inflammatory response[8]. However, few studies have investigated serum albumin levels during hospitalization as a prognostic factor for mortality and hospital discharge. The recognition of this parameter as a prognostic factor during hospitalization would allow early intervention, for better recovery and survival.

The Prognostic Nutritional Index (PNI), based on serum albumin values and total lymphocyte count, was able to reflect the nutritional and immunological status of the individual[9] and was described as a prognostic factor of long-term mortality for patients with cancer[3,10,11], on peritoneal dialysis[12] and more recently with coronary artery disease[13,14].

Red blood cell distribution width (RDW) was also described in some studies as a prognostic marker in cancer patients[15-18], patients with congenital heart disease[19] and in-hospital mortality in elderly patients hospitalized for all causes[20].

Although some studies have previously analysed the association between hypoalbuminemia and increased in-hospital mortality in patients with various types of disease[21-24], little is known about the association of serum levels of albumin or PNI with in-hospital mortality in cancer patients. Besides, the available studies differ in relation to the populations evaluated, considering only a specific type of cancer and few considered aspects related to nutritional status and other variables, such as haematological indexes. Classical analysis strategies supported the authors' evaluations with multivariate models. So far, there are still no studies in the literature with the same objectives based in statistics conceptual models. Thus, the objective of this study was to evaluate the association of albumin and PNI with length of hospital stay and in-hospital mortality, considering other laboratory measures and prognostics indexes.

METHOD

Study design and patients

Retrospective study with 262 patients with cancer hospitalized in a university hospital from January 2014 to December 2016. All cancer patients hospitalized with data about nutritional status were included. All patients were diagnosed with cancer at the time of admission. Of the patients with more than one hospitalization during the study period, information was considered only from the first hospitalization. The clinical-pathological data were obtained from the Hospital Information System (HIS). The study patients were selected from the wards of Internal Medicine, Surgical I (Traumatology, Neurology and Urology), Surgical II (Thoracic, Gastrointestinal Tract and General) and Surgical III (Vascular and General), Coronary Unit, Chest Pain Unit, Infectious Diseases and Emergency Room.

Data extraction and patients' characteristics

Sociodemographic, clinical, biochemical and hospital outcome data were extracted from HIS. The following results for laboratory tests were obtained: complete blood count, albumin, and C-reactive protein (CRP). The data of the nutritional status of the patients were obtained from the subjective global assessment (SGA). This instrument assesses the history of weight, changes in food intake, presence of gastrointestinal symptoms, functional capacity, and physical examination. The patient is classified according to its nutritional status, as well nourished (A), risk of malnutrition or moderate malnutrition (B) and severe malnutrition (C).

For the collection of laboratory tests, the first results obtained during hospitalization were considered. Also, a maximum of 30 days between the date of the exam and the date of completion of the SGA[25] was allowed in order to minimize possible analysis bias.

The values described in Proctor et al.[26] were considered to determine the modified Glasgow Prognostic Score (mGPS), where a score of 0 was assigned to patients who did not have alterations in their CRP and albumin values, a score of 1 to those with CRP>10 mg/L and a score of 2 to those who had serum levels of albumin <3.5 mg/dL and CRP>10 mg/L). The PNI was calculated from the following: 10 x serum value of albumin (g/dL) + 0.005 x total lymphocyte count (TLC) in peripheral blood (mm^3)[9]. The albumin values were categorised according to Blackburn and Thornton[27] as moderate malnutrition (<3.0) and mild malnutrition (>3.0), and also according to those found in previous studies[24,28].

Other indexes were calculated including neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR) and platelet to albumin ratio (PAR).

Potential confounding variables

The potential confounding variables sex, age range (<60 years and ≥60 years), nutritional status (with and without malnutrition), immunological markers (neutrophils) and inflammatory markers (RDW) were considered.

Statistical analyses and ethical aspects

Descriptive statistics were expressed as mean of percentage, mean and standard deviations or medians (IQ25-75%). To evaluate the differences between the patients who died and the patients who were discharged from the hospital, the Pearson Chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables were used.

Kaplan-Meier survival curves were used to evaluate the cumulative probability of survival, and the differences between the curves were compared through the log-rank test. The predictors of mortality were identified through univariate and multivariate regression using the Cox proportional hazards model, and two models were created to identify the independent factors associated with in-hospital mortality. Cancer death as an event of interest, the time until the occurrence of the event and the length of hospital stay were considered. The models were adjusted based in a conceptual model, considering the possibility of confounding variables after literature review. In the first model, albumin (≥3 g/dL/<3 g/dL), demographic variables (sex and age group), nutritional status, neutrophils and RDW were included. In the second model, the PNI to verify its influence on the TLC.

All statistical analyses were run using the Statistical Package for the Social Sciences (SPSS) for Windows, version 20.1 (SPSS®, Inc., Chicago, USA), with a *p*-value ≤0.05 and 95% confidence interval (CI) were considered statistically significant.

This study was conducted in accordance with the Helsinki Declaration[29] and was approved by the Institutional Review Board (CAAE 66930517.0.0000.5152).

RESULTS

Of the 262 patients enrolled in the study, 50.4% were men with a mean age of 62.24 years, 62.6% were 60 years or older and 54.6% had a length of stay ≥ 10 days. The frequency of metastasis was 35.5%, followed by gastrointestinal tract tumours (32.1%) and male genital organ tumours (11.1%). Regarding nutritional status, 69.1% (181) were malnourished. Finally, the frequency of death was of 10.7% (Table 1).

Malnutrition (p=0.004), lowest PNI score (p=0.002) and ward (p=0.011) were associated with in-hospital mortality (Table 1).

Many laboratory measures and their indexes were associated with in-hospital mortality, such as the levels of leukocytes, lymphocytes, neutrophils, RDW, CRP, albumin, red blood cells, haemoglobin, haematocrit, NLR and PAR. It was not observed association of in-hospital mortality with other indexes, as MLR and PLR (Table 2).

The analysis of survival curves showed that the patients with values of albumin <3 g/dL had lower survival (p=0.003) (Figure 1A). The cumulative probability of in-hospital survival was not associated with nutritional status (Figure 1B) or the age group (Figure 1C) by log-rank test (p=0.605 and p=0.082, respectively), although it was observed that the frequency was higher in older adults and malnourished.

It was observed that the levels of lymphocytes (p=0.024), neutrophils (p=0.040), RDW (p<0.001), albumin (≥3 g/dL/<3 g/dL) (p=0.007), red blood cells (p=0.001), haemoglobin (p=0.003), haematocrit (p=0.002) and PNI (p=0.038) were significantly associated with in-hospital mortality in the samples evaluated by univariate analyses (Table 3).

The main exposure and the univariate and multivariate models are shown in Table 3. The PNI was not associated with in-hospital mortality after adjustment of the model (HR=2.22, 95% CI 0.70-6.98). On the other hand, patients with albumin <3 g/dL (model 2) showed 3.3 times greater risk for death compared to those with appropriate values (HR=3.31, 95% CI 1.05–10.42) independent of age, sex, nutritional status, and level of anisocytosis.

DISCUSSION

In the present study, it was possible to identify the prognostic factors associated with in-hospital mortality. It was verified that serum albumin levels <3.0 g/dL were an independent predictor of death during hospitalization in patients with cancer, even after adjustment for possible confounding variables (sex, age range, nutritional status (by SGA), neutrophils and RDW). Serum levels of this protein <3.0 g/dL increased the risk of in-hospital mortality by 3.3 times in this population (Table 3, Figure 1A). Although discussed in the literature, it did not happen with the PNI. Despite albumin and PNI are associated with low survival in patients with cancer, studies comparing the prognostic value of these variables in different models for the same population were not found; besides, few studies adjusted

Table 1. Description of the demographic, clinical and nutritional characteristics of patients with cancer according to clinical outcome

Variables	Hospital discharge	Death	*p*-value*
	234 (89.3)	28 (10.7)	
Sex			
Male	120 (51.3)	12 (42.9)	0.399
Female	114 (48.7)	16 (57.1)	
Age (years)			
<60	88 (37.6)	10 (35.7)	0.845
≥60	146 (62.4)	18 (64.3)	
SGA			
Well nourished (A)	79 (33.8)	2 (7.1)	0.004
Malnutrition (B+C)	155 (66.2)	26 (92.9)	
mGPS			
0	15 (9.9)	1 (4.2)	0.096
1	103 (68.2)	13 (54.2)	
2	33 (21.9)	10 (41.7)	
PNI			
>38.4	55 (44.7)	17 (81)	0.002
≤38.4	68 (55.3)	4 (19)	
Ward			
Internal medicine	31 (13.2)	4 (14.3)	0.011
Surgical II	158 (67.5)	16 (57.1)	
CU + CPU	5 (2.1)	0	
Infectious Diseases	10 (4.3)	1 (3.6)	
Emergency room	0	1 (3.6)	
Others[a]	30 (12.9)	6 (21.4)	
Hospital-stay (days)			
<10	132 (56.4)	11 (39.3)	0.085
≥10	102 (43.6)	17 (60.7)	
Tumour site			
Gastrointestinal tract	76 (32.5)	9 (32.1)	0.859
Male genital organs	26 (11.1)	3 (10.7)	
Breast	4 (1.7)	0	
Metastasis	80 (32.4)	14 (50)	
Urinary tract	10 (4.3)	0	
Head and neck	12 (5.1)	0	
Others[b]	26 (11)	2 (7.2)	

Captions: SGA = Subjective global assessment; mGPS = Modified Glasgow Prognostic Score; PNI = Prognosis nutritional index; CU + CPU = Coronary unit + chest pain unit; Others[a] = Surgical I + surgical III; Others[b] = Female genital organs + trachea + hematological + lung + skin + osteosarcoma.
(*) Pearson chi-square test.

the variables related to nutrition, inflammatory and immunological status.

The laboratory exams reflect the impact of the disease and treatment together with other non-modifiable factors, such as age and sex. Some studies explored the albumin levels in clinic situations, finding a negative association between albumin and in-hospital mortality in patients with oesophageal cancer[30]. Bonilla-Palomas et al.[22] observed that in patients with acute heart failure, hypoalbuminemia was associated with in-hospital mortality and was an independent predictor of mortality after discharge, especially in the first 6-10 months, indicating an association of low albumin with short-term and long-term hospital outcomes[22].

Gupta and Lis verified in a systematic review that albumin in antineoplastic pre-treatment has significant prognostic meaning, being a good prognostic marker of mortality[7]. Other studies observed that hypoalbuminemia has been associated with in-hospital mortality[31], worse functional status and longer hospitalization time in older adults[23]. Recently, Miyazaki et al[24] observed that low levels of albumin at admission and during the first week of hospitalization were independent predictors of in-hospital mortality over 30 days in patients with community-acquired pneumonia. The patients with albumin <3 g/dL had a mortality rate higher than individuals with albumin ≥ 3 g/dL, increasing according to pneumonia severity.

Table 2. Comparison of laboratory measures of patients with cancer by in-hospital death

Variables	Hospital discharge			Death			p-value*
	n	Mean ± (SD)	Median (IQ25 – 75%)	n	Mean ± (SD)	Median (IQ25 – 75%)	
Leukocytes (mm^3)	206	9.26 (4.32)	8.55 (6.10– 11.80)	25	11.92 (4.67)	11.50 (7.85 – 15.25)	0.004
Lymphocytes (%)	205	18.50 (10.51)	18.00 (10.00 – 25.00)	25	11.16 (7.13)	10.00 (6.00 – 13.50)	0.001
Red cells (%)	194	6.13 (8.91)	3.00 (1.00 – 7.00)	24	6.17 (5.34)	5.50 (2.00 – 9.00)	0.986
Neutrophils (%)	205	67.00 (12.25)	68.00 (29.00 – 75.50)	25	74.62 (11.40)	77.00 (67.20 – 82.50)	0.003
Eosinophils (mm^3)	203	1.91 (2.39)	1.00 (0.00 – 3.00)	25	1.02 (1.20)	1.00 (0.00 – 2.00)	0.067
Basophils (mm^3)	201	0.28 (0.53)	0.00 (0.00– 0.35)	25	0.31 (0.61)	0.00 (0.00 – 0.40)	0.759
Monocytes (mm^3)	205	6.39 (3.08)	6.00 (4.00 – 8.50)	25	6.66 (4.09)	7.00 (3.50 – 8.50)	0.690
Platelets (mm^3)	206	261.28 (119.06)	231.50 (182.00 – 314.25)	25	280.96 (153.90)	259.00 (182.50 – 385.50)	0.451
TLC	205	1500.81 (836.52)	1406.00 (860.50 – 2065.00)	25	1165.10 (581.98)	1080.00 (785.00 – 1471.50)	0.053
RDW (%)	228	13.98 (2.18)	13.05 (12.70 – 15.00)	26	16.04 (3.81)	15.00 (13.45 – 17.25)	<0.001
CRP (mg/dL)	180	8.46 (9.07)	4.67 (0.00 – 46.80)	24	12.77 (7.85)	11.70 (6.62 – 18.97)	0.028
Albumin (g/dL)	134	3.24 (0.66)	3.30 (2.81 – 3.80)	23	2.63 (0.60)	2.64 (2.40 – 2.91)	<0.001
PNI	123	39.79 (8.45)	39.50 (34.70 – 45.65)	21	31.91 (7.81)	30.24 (26.25 – 39.87)	<0.001
CRP/Albumin	63	2.68 (4.20)	1.48 (0.25 – 3.76)	11	4.40 (2.88)	4.28 (2.62 – 5.60)	0.199
Erythrocytes (millions/mm^3)	206	4.01 (0.70)	4.05 (3.60 – 4.48)	25	3.31 (0.66)	3.41 (2.72 – 3.87)	<0.001
Hemoglobin (g%)	228	11.47 (2.25)	11.70 (10.10 – 13.00)	27	9.44 (1.98)	9.80 (7.90 – 10.6)	<0.001
Hematocrit (%)	228	34.87 (6.39)	35.25 (30.65 – 39.27)	27	29.17 (5.81)	29.40 (24.70 – 33.20)	<0.001
MCV	206	87.41 (7.54)	8.35 (82.90 – 92.30)	25	88.89 (9.85)	87.30 (84.15 – 94.35)	0.374
MCH	206	28.74 (3.15)	29.15 (27.40 – 30.70)	25	28.82 (3.46)	28.30 (20.80 – 38.80)	0.898
MCHC	206	32.82 (1.61)	32.90 (31.90 – 33.82)	25	32.42 (1.58)	32.40 (27.00 – 30.60)	0.239
NLR	205	6.93 (10.46)	3.75 (2.41 – 7.80)	25	12.34 (15.96)	7.50 (5.11 – 13.16)	0.023
MLR	205	0.52 (0.51)	0.36 (0.20 – 0.62)	25	0.72 (0.55)	0.51 (0.34 – 1.00)	0.067
PAR	124	88.82 (53.88)	77.62 (53.78 – 104.49)	21	119.54 (87.04)	100.00 (66.65 – 149.15)	0.031
PLR	205	0.24 (0.24)	0.18 (0.12 – 0.27)	25	0.31 (0.25)	0.05 (0.17 – 0.39)	0.154

Captions: TLC = Total lymphocyte count; RDW = Red blood cell distribution width; CRP = C-reactive protein; PNI = Prognosis nutritional index; SD = Standard deviation; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; NLR = Neutrophils to lymphocytes ratio; MLR = Monocytes to lymphocytes ratio; PAR = Platelets to albumin ratio; PLR = Platelets to lymphocytes ratio; IQ = Interquartile.
(*) ANOVA test.

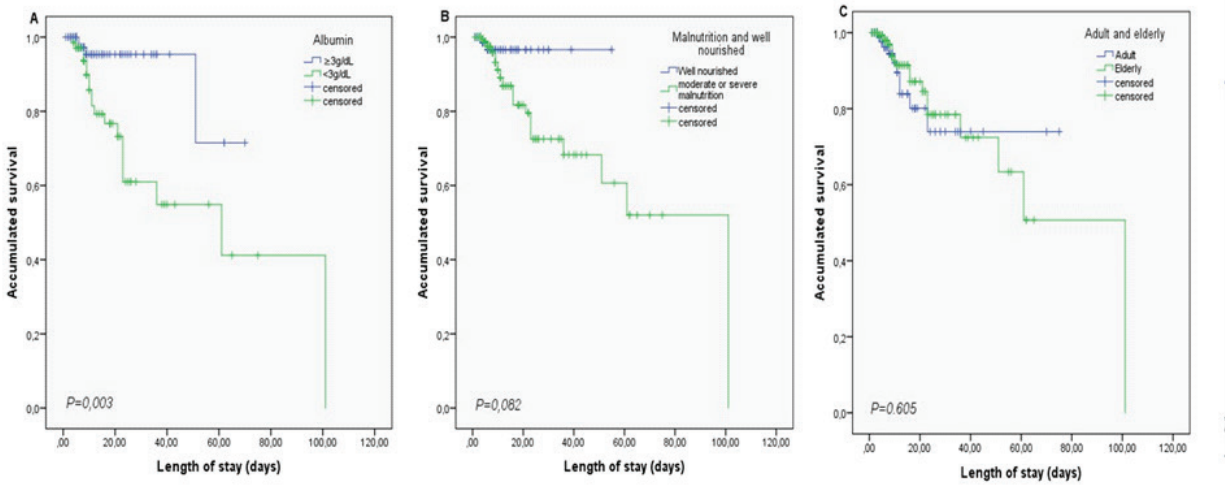

Figure 1. Kaplan-Meier curves stratified for serum albumin (<3/≥3g/dL) (**A**), nutritional status by subjective global assessment (no malnutrition/moderate or severe malnutrition) (**B**) and age range (<60/≥60 years) (**C**)

In this study, the PNI showed significant association with in-hospital mortality in the univariate analysis (HR=0.94, 95% CI 0.899–0.997). However, when it was adjusted for the same confounding variables used for albumin, the association was not significant (HR=2.22, 95% CI 0.709–6.981), demonstrating a likely superiority in the use of isolated albumin as an independent prognostic factor of in-hospital mortality in patients with cancer.

The mechanisms involved in the decline of serum albumin levels in cancer patients are not completely elucidated yet. Hypoalbuminemia was independently associated with total body cell mass and CRP of men with cancer, suggesting that the presence of inflammatory responses in these patients leads to an increase in demand of amino acids intended for production of acute-phase protein levels (such as CRP and fibrinogen), resulting in a reduction of the *pool* of albumin and body cell mass, which in a prolonged way, could be associated with mortality in these patients[32]. This identification of hypoalbuminemia could be useful to detect previous cell mass loss, for more effective intervention in the nutritional status of these individuals[32].

Albumin plays important functions in organisms, such as maintenance of colloid-osmotic pressure, of acid-basic balance, transport of substances (such as hormones, ions and drugs) and providing amino acids for tissues[33]. The reduction in serum concentrations of this protein, wherefore, could be related to reduction of survival.

Furthermore, the presence of cytokines produced by tumours, such as interleukin-6 and -2 and TNF-alpha, leads to modulation of the production of albumin by hepatocytes, inhibiting its synthesis[7,22,34,35]. Consequently, this reinforces the need to investigate variables that correlate to the inflammatory context as well.

Recognising the association of albumin and RDW with inflammation, RDW was considered a possible confounding variable in this multivariate analysis model. Previous studies verified the association of RDW as a prognostic factor in patients with cancer[5,17]. Koma et al[18] showed that changes in the RDW reflect both the nutritional status and the chronic inflammation in cancer patients.

Although RDW has been associated with mortality in a meaningful way in univariate analysis (p<0.001), this significance was reduced by the levels of albumin in multivariate analysis (p<0.064) (Table 4). Montagnana and Danese[36] concluded that although many studies demonstrate this association, when the RDW is adjusted by other variables, this association is lost, as also observed in other studies[16,37,38]. In addition, most of the studies available used different cut-off points, providing the replication and validation of this variable as a prognostic indicator. Yu et al.[17] verified the association of RDW and cancer in a systematic review and meta-analysis of 16 studies where the cut-off points varied from 13.45% to 50%. As a result, it was decided to incorporate the variable continuously in a multivariate model, different from other studies.

Other indexes were also evaluated, such as NLR, MLR, PLR and PAR; however, these were not associated with in-hospital mortality. Despite leukocytes being associated with mortality[39-41], these studies did not assess short-term mortality. Furthermore, the pathophysiological levels may be altered in different clinical conditions, leading to an increase of infections and in the use of glucocorticoids, but may be reduced in malnutrition[42,43], which is why its validity in major prognostic determinations should be done cautiously[2].

Table 3. Predictors of in-hospital mortality of patients with cancer by Cox proportional hazard model

Variables	Univariate		PNI Multivariate		Albumin Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex	1.68 (0.78 – 3.63)	0.184	1.65 (0.64 – 4.26)	0.297	1.23 (0.46 – 3.30)	0.668
Age range (<60/≥60y)	0.81 (0.37 – 1.78)	0.608	1.83 (0.62 – 5.42)	0.273	2.15 (0.72 – 6.35)	0.165
mGPS	1.99 (0.91 – 4.13)	0.064	-	-	-	-
Ward	1.17 (0.86 – 1.60)	0.297	-	-	-	-
Nutritional status (SGA)	3.32 (0.78 – 14.10)	0.103	2.29 (0.30 – 17.42)	0.423	2.27 (0.29 – 17.80)	0.435
Leukocytes	1.06 (0.98 – 1.13)	0.106	-	-	-	-
Lymphocytes	0.94 (0.89 – 0.99)	0.024	-	-	-	-
Red cells	0.99 (0.95 – 1.04)	0.807	-	-	-	-
Neutrophils	1.03 (1.00 – 1.07)	0.040	-	-	1.03 (0.99 – 1.08)	0.099
Eosinophils	0.73 (0.53 – 1.00)	0.054	-	-	-	-
Basophils	1.13 (0.58 – 2.19)	0.714	-	-	-	-
Monocytes	1.01 (0.89 – 1.15)	0.787	-	-	-	-
Platelets	0.99 (0.99 – 1.00)	0.702	-	-	-	-
TLC	1.00 (0.99 – 1.00)	0.221	-	-	-	-
RDW	1.22 (1.09 – 1.37)	<0.001	1.15 (0.99 – 1.33)	0.054	1.10 (0.95 – 1.27)	0.199
CRP	1.02 (0.98 – 1.06)	0.178	-	-	-	-
Albumin (g/dL)	0.59 (0.33 – 0.05)	0.074	-	-	-	-
CRP/Albumin	1.01 (0.92 – 1.10)	0.759	-	-	-	-
Erythrocytes	0.24 (0.26 – 0.67)	0.001	-	-	-	-
Hemoglobin	0.78 (0.66 – 0.91)	0.003	-	-	-	-
Hematocrit	0.91 (0.86 – 0.97)	0.002	-	-	-	-
MCV	1.03 (0.98 – 1.08)	0.198	-	-	-	-
MCH	1.04 (0.92 – 1.17)	0.523	-	-	-	-
MCHC	0.93 (0.73 – 1.17)	0.538	-	-	-	-
NLR	1.01 (0.99 – 1.03)	0.230	-	-	-	-
MLR	1.16 (0.66 – 2.03)	0.588	-	-	-	-
PLR	1.207 (0.34 – 4.16)	0.766	-	-	-	-
PAR	0.99 (0.99 – 1.00)	0.771	-	-	-	-
PNI						
≥38.4	1	-	-	-	1	-
<38.4	0.94 (0.899 – 0.997)	0.038	2.22 (0.70 – 6.98)	0.170	-	-
Albumin						
≥3g/dL	1	-	-	-	1	-
<3 g/dL	4.40 (1.488 – 13.031)	0.007	-	-	3.31 (1.05 – 10.42)	0.040

Captions: CI = Confidence Interval; mGPS = Modified Glasgow Prognostic Score; SGA = Subjective global assessment; TLC = Total lymphocyte count; RDW = Red blood cell distribution width; CRP = C-reactive protein; PNI = Prognosis nutritional index; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; NLR = Neutrophils to lymphocytes ratio; MLR = Monocytes to lymphocytes ratio; PLR = Platelets to lymphocytes ratio; PAR = Platelets to albumin ratio; HR = Hazard ratio.

The mGPS was described as an independent prognostic factor in various types of cancer and was validated in different countries, types of studies and of tumours[44]. In this study, there was no association between mGPS and in-hospital mortality (HR=1.99, 95% CI 0.96-4.13). However, the differences in these results probably occurred because most studies investigate a particular type of cancer and its long-term survival, whereas in the present investigation, the sample contains patients with different cancer types and evaluated short-term mortality.

Recognising the relationship of albumin with both nutritional and inflammatory status may be useful for nutritional assessment and possible early intervention[6,7], considering the clinical setting of each patient together with other assessment methods in clinical practice[45]. This necessity for intensive and early intervention may highlight albumin as a marker of improvement in nutritional status allowing better recovery and a potential increase in survival.

The measurement of albumin serum levels is simple, low-cost, easily accessible and reproducible, and it is routinely performed in the hospital. However, the disadvantages are related to a number of factors that can affect these levels, such as liver insufficiency, kidney disease, hydration status and metabolic stress[6,22,46].

Some limitations can be found in this study, among them, the retrospective design, which may be subject to some degree of sample loss if the information was unavailable. However, the existing assessment data of the nutritional status of all the patients with cancer hospitalized in the period have been adequately collected. Furthermore, the patients had different types of cancer and stages and tumour-node-metastasis (TNM) classifications of malignant tumours, in addition to other hospital comorbidities that were unable to be evaluated. Finally, it is recognised that albumin is influenced by other factors, such as hydration status and hepatic and kidney insufficiency. For the states of inflammation, infection and change in nutritional status, the biases were minimized since all possible exposure factors have been tested.

CONCLUSION

Albumin <3 g/dL was associated with an increase of in-hospital mortality in patients with cancer, independent of nutritional, inflammatory, and immunological status. Besides being commonly used in routine, this laboratory measure is simple and easy to use compared with score systems. Therefore, it is a tool that can be used to identify risks and during therapeutic planning. The recommendation is to evaluate serum albumin levels as soon as possible during hospital stay, adding prognostic information in patients with cancer.

CONTRIBUTIONS

All authors contributed equally to the design and planning of the study, data collection, analysis and interpretation, wording, critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTEREST

There is no conflict of interest to declare.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108. doi: https://doi.org/10.3322/caac.21262
2. Dupré A, Malik HZ. Inflammation and cancer: what a surgical oncologist should know. Eur J Surg Oncol. 2018;44(5):566-70. doi: https://doi.org/10.1016/j.ejso.2018.02.209
3. Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2014;140(9):1537-49. doi: https://doi.org/10.1007/s00432-014-1714-3
4. Hirahara N, Matsubara T, Hayashi H, et al. Impact of inflammation-based prognostic score on survival after curative thoracoscopic esophagectomy for esophageal cancer. Eur J Surg Oncol. 2015;41(10):1308-15. doi: https://doi.org/10.1016/j.ejso.2015.07.008
5. Zhu Y, Li JH, Yang J, et al. Inflammation-nutrition scope predicts prognosis of early-stage hepatocellular carcinoma after curative resection. Medicine (Baltimore). 2017;96(39):e8056. doi: https://doi.org/10.1097/MD.0000000000008056
6. Lis CG, Grutsch JF, Vashi PG, et al. Is serum albumin an independent predictor of survival in patients with breast cancer? JPEN J Parenter Enter Nutr. 2003;27(1):10-5. doi: https://doi.org/10.1177/014860710302700110
7. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9:69. doi: https://doi.org/10.1186/1475-2891-9-69
8. Nakayama M, Tabuchi K, Hara A. Clinical utility of the modified Glasgow prognostic score in patients with advanced head and neck cancer. Head Neck.

2015;37(12):1745-9. doi: https://doi.org/10.1002/hed.23823

9. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi. 1984;85(9):1001-5. Japanese.
10. Nakatani M, Migita K, Matsumoto S, et al. Prognostic significance of the prognostic nutritional index in patients with recurrent esophageal squamous cell carcinoma. Nutr Cancer. 2018;70(3):467-73. doi: https://doi.org/10.1080/01635581.2018.1445771
11. Watanabe I, Kanauchi N, Watanabe H. Preoperative prognostic nutritional index as a predictor of outcomes in elderly patients after surgery for lung cancer. Jpn J Clin Oncol. 2018;48(4):382-7. doi: https://doi.org/10.1093/jjco/hyy014
12. Kang SH, Cho KH, Park JW, et al. Onodera's prognostic nutritional index as a risk factor for mortality in peritoneal dialysis patients. J Korean Med Sci. 2012;27(11):1354-8. doi: https://doi.org/10.3346/jkms.2012.27.11.1354
13. Wada H, Dohi T, Miyauchi K, et al. Relationship between the prognostic nutritional index and long-term clinical outcomes in patients with stable coronary artery disease. J Cardiol. 2018;72(2):155-61. doi: https://doi.org/10.1016/j.jjcc.2018.01.012
14. Keskin M, İpek G, Aldağ M, et al. Effect of nutritional status on mortality in patients undergoing coronary artery bypass grafting. Nutrition. 2018;48:82-6. doi: https://doi.org/10.1016/j.nut.2017.10.024
15. Hirahara N, Matsubara T, Kawahara D, et al. Prognostic value of hematological parameters in patients undergoing esophagectomy for esophageal squamous cell carcinoma. Int J Clin Oncol. 2016;21(5):909-19. doi: https://doi.org/10.1007/s10147-016-0986-9
16. Lee H, Kong SY, Sohn JY, et al. Elevated red blood cell distribution width as a simple prognostic factor in patients with symptomatic multiple myeloma. Biomed Res Int. 2014;2014: 145619. doi: https://doi.org/10.1155/2014/145619
17. Yu M, Yongzhi H, Chen S, et al. The prognostic value of GLUT1 in cancers: a systematic review and meta-analysis. Oncotarget. 2017;8(26):43356-67. doi: https://doi.org/10.18632/oncotarget.17445
18. Koma Y, Onishi A, Matsuoka H, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. PLoS One. 2013;8(11):e80240. doi: https://doi.org/10.1371/journal.pone.0080240
19. Baggen VJM, van den Bosch AE, van Kimmenade RR, et al. Red cell distribution width in adults with congenital heart disease: a worldwide available and low-cost predictor of cardiovascular events. Int J Cardiol. 2018;260:60-5. doi: https://doi.org/10.1016/j.ijcard.2018.02.118
20. Kim SH, Yeon JH, Park KN, et al. The association of Red cell distribution width and in-hospital mortality in older adults admitted to the emergency department. Scand J Trauma Resusc Emerg Med. 2016;24:81. doi: https://doi.org/10.1186/s13049-016-0274-8
21. Delgado-Rodríguez M, Medina-Cuadros M, Gómez-Ortega A, et al. Cholesterol and serum albumin levels as predictors of cross infection, death, and length of hospital stay. Arch Surg. 2002;137(7):805-12. doi: https://doi.org/10.1001/archsurg.137.7.805
22. Bonilla-Palomas JL, Gámez-López AL, Moreno-Conde M, et al. Hypoalbuminemia in acute heart failure patients: causes and its impact on hospital and long-term mortality. J Card Fail. 2014;20(5):350-8. doi: https://doi.org/10.1016/j.cardfail.2014.01.016
23. Hsu HY, Hwang LC, Lin CH, et al. Impact of serum albumin on functional status and hospital outcome in oldest-old inpatients. Int J Gerontol. 2015;9(4):220-2. doi: https://doi.org/10.1016/j.ijge.2014.06.008
24. Miyazaki H, Nagata N, Akagi T, et al. Comprehensive analysis of prognostic factors in hospitalized patients with pneumonia occurring outside hospital: serum albumin is not less important than pneumonia severity assessment scale. J Infect Chemother. 2018;24(8):602-9. doi: https://doi.org/10.1016/j.jiac.2018.03.006
25. Detsky A, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8-13. doi: https://doi.org/10.1177/014860718701100108
26. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a glasgow inflammation outcome study. Br J Cancer. 2011;104(4):726-34. doi: https://doi.org/10.1038/sj.bjc.6606087
27. Blackburn GL, Thornton PA. Nutritional assessment of the hospitalized patient. Med Clin North Am. 1979;63(5):1103-15. doi: https://doi.org/10.1016/S0025-7125(16)31663-7
28. Han S, Huang Y, Li Z, et al. The prognostic role of preoperative serum albumin levels in glioblastoma patients. BMC Cancer. 2015;15(1):108. doi: https://doi.org/10.1186/s12885-015-1125-0
29. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4. doi: https://doi.org/10.1001/jama.2013.281053
30. Park DP, Welch CA, Harrison DA, et al. Outcomes following oesophagectomy in patients with oesophageal cancer: a secondary analysis of the ICNARC Case Mix Programme Database. Crit Care. 2009;13(Suppl 2):S1. doi: https://doi.org/10.1186/cc7868
31. Silva TJA, Jerussalmy CS, Farfel JM, et al. Predictors of in-hospital mortality among older patients. Clinics. 2009;64(7):613-8. doi: https://doi.org/10.1590/S1807-59322009000700002

32. 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(2):210-3. doi: https://doi.org/10.1207/S15327914nc392_8

33. Santos NSJ, Draibe SA, Kamimura MA, et al. Albumina sérica como marcador nutricional de pacientes em hemodiálise. Rev Nutr. 2004;17(3):339-49. doi: https://doi.org/10.1590/S1415-52732004000300007

34. Seebacher V, Grimm C, Reinthaller A, et al. The value of serum albumin as a novel independent marker for prognosis in patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2013;171(1):101-6. doi: https://doi.org/10.1016/j.ejogrb.2013.07.044

35. Liu J, Dai Y, Zhou F, et al. The prognostic role of preoperative serum albumin/globulin ratio in patients with bladder urothelial carcinoma undergoing radical cystectomy. Urol Oncol. 2016;34(11):484.e1-484.e8. doi: https://doi.org/10.1016/j.urolonc.2016.05.024

36. Montagnana M, Danese E. Red cell distribution width and cancer. Ann Transl Med. 2016;4(20):399. doi: https://doi.org/10.21037/atm.2016.10.50

37. Zhang F, Chen Z, Wang P, Hu X, Gao Y, He J. Combination of platelet count and mean platelet volume (COP-MPV) predicts postoperative prognosis in both resectable early and advanced stage esophageal squamous cell cancer patients. Tumor Biol. 2016;37(7):9323-31. doi: https://doi.org/10.1007/s13277-015-4774-3

38. Baicus C, Caraiola S, Rimbas M, et al. Utility of routine hematological and inflammation parameters for the diagnosis of cancer in involuntary weight loss. J Investig Med. 2011;59(6):951-5. doi: https://doi.org/10.2310/JIM.0b013e31822467a3

39. Chmielewski PP, Strzelec B. Elevated leukocyte count as a harbinger of systemic inflammation, disease progression, and poor prognosis: a review. Folia Morphol (Warsz). 2018;77(2):171-8. doi: https://doi.org/10.5603/FM.a2017.0101

40. Ruggiero C, Metter EJ, Cherubini A, et al. White blood cell count and mortality in the Baltimore longitudinal study of aging. J Am Coll Cardiol. 2007;49(18):1841-50. doi: https://doi.org/10.1016/j.jacc.2007.01.076

41. Benej M, Čapov I, Skřičková J, et al. Association of the postoperative white blood cells (WBC) count in peripheral blood after radical surgical treatment of left upper lobe non-small cell lung cancer (NSCLC) with overall survival - single center results. Bratisl Lek Listy. 2017;118(5):299-301. doi: https://doi.org/10.4149/BLL_2017_073

42. González Madroño A, Mancha A, Rodríguez FJ, et al. The use of biochemical and immunological parameters in nutritional screening and assessment. Nutr Hosp. 2011;26(3):594-601. doi: https://doi.org/10.1590/S0212-16112011000300024

43. Shronts EP. Basic concepts of immunology and its application to clinical nutrition. Nutr Clin Pract. 1993;8(4):177-83. doi: https://doi.org/10.1177/0115426593008004177

44. McMillan DC. The systemic inflammation-based glasgow prognostic score: a decade of experience in patients with cancer. Cancer Treat Rev. 2013;39(5):534-40. doi: https://doi.org/10.1016/j.ctrv.2012.08.003

45. Goh SL, De Silva RP, Dhital K, et al. Is low serum albumin associated with postoperative complications in patients undergoing oesophagectomy for oesophageal malignancies? Interact Cardiovasc Thorac Surg. 2015;20(1):107-13. doi: https://doi.org/10.1093/icvts/ivu324

46. Gupta D, Lammersfeld CA, Vashi PG, et al. Is serum albumin an independent predictor of survival in ovarian cancer? Clin Ovarian Cancer. 2009;2(1):52-6. doi: https://doi.org/10.3816/COC.2009.n.008

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