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Value of Prognostic Nutritional Index for Predicting Survival in Patients with Advanced Esophageal Squamous Cell Carcinoma Treated with Chemoradiotherapy

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Abstract: *Background:* Esophageal cancer is the sixth leading cause of cancer-related death worldwide. Despite the advances in the surgical approach, chemotherapy and radiotherapy regimens, and the continuous development of biological agents, survival outcomes for these patients remain low. The identification of new biomarkers capable of predicting worse survival regardless of the clinical stage is necessary. *Purpose:* The aim of this study is to evaluate the association between Prognostic Nutritional Index (PNI) and overall survival in patients with advanced squamous esophageal carcinoma. *Methods:* A retrospective and observational study was conducted in patients with diagnosis of advanced esophageal squamous cell carcinoma treated at Hermanos Ameijeiras Hospital from January 2013 to June 2019. The PNI was calculated using the following formula: 10 x Albumin (g/dL) + 0.005 x Lymphocyte counts ($x10^9$). *Results:* A total of 94 patients were enrolled in this study. The area under the curve (AUC) was 0,583 and the optimal cut-off value was 40. PNI was significantly associated with hemoglobin level, platelet count, total lymphocyte count, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and therapeutic response. PNI was negatively correlated with inflammatory indexes. Patients with PNI <40 had a significantly shorter median overall survival compared to patients with PNI ≥40. Multivariate analysis identified that ECOG ≥1, platelet count, NLR≥4 and PNI<40 were independent prognostic factors for poor overall survival. *Conclusion:* The present study demonstrated that pretreatment PNI is a useful marker for predicting survival outcome in patients with advanced esophageal squamous cell carcinoma.

Keywords: Esophageal Cancer, Albumin, Lymphocyte, Inflammation, Nimotuzumab

1. Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide [1]. Despite the advances in surgical approach and systemic therapies, survival outcomes for these patients remain low. On the other hand, patients with the same clinical stage according to TNM system show great variation in response to similar treatments, some of which show rapid deterioration and poor survival. Therefore, the identification of new biomarkers capable of predicting worse survival regardless of the clinical stage is necessary [2, 3].

Recent studies on relationship among nutrition, inflammation and cancer have shown that poor nutritional status affects the immunologic reaction and treatment response to cancer therapy. In addition, severe malnutrition and cachexia can entail chronic inflammation in cancer patients, which in related to poor prognosis [4]. Increasing

evidence indicates that systemic inflammatory response and nutritional status are involved in tumor development and progression. The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) have been identified as useful inflammation-based prognostic scores that can predict survival outcomes in digestives tumors including esophageal squamous carcinoma [5-7].

Prognostic nutritional index (PNI) is calculated by the serum albumin level and peripheral lymphocyte count. The association between albumin and lymphocyte can reflect the nutritional and immunological status in same index. The PNI was first used by Onodera et al, as an indicator of preoperative nutritional status for predict postoperative complications in patients with gastrointestinal cancers [8]. Several studies have demonstrated that low preoperative nutritional status is associated with higher rate of postoperative complications, in-hospital mortality, longer duration of postoperative stay, lower postoperative survival and lower survival rate in patients with advanced tumors treated with chemotherapy [9-11].

The relationship between PNI and esophageal cancer has been explored in several studies, but the results are conflicting. Therefore, the aim of this study is to evaluate the association between PNI and overall survival (OS) in patients with advanced squamous esophageal carcinoma.

2. Methods

A retrospective and observational study was conducted in patients with diagnosis of advanced esophageal squamous cell carcinoma treated at Hermanos Ameijeiras Hospital from January 2013 to June 2019.

All patients included in the analysis met the following inclusion criteria: (I) diagnosis of esophageal squamous cell carcinoma by histology or citology; (II) not options for surgical treatment; (III) evidence of advanced or metastatic disease by imagenology and/or endoscopy (CT-scan, ultrasound, endoscopic-ultrasound); (IV) patients treated with radiotherapy combined with chemotherapy and nimotuzumab (anti-EGFR receptor monoclonal antibody); (V) data available from blood test 1 week prior to treatment; (VI) not clinical evidence of infection; (VII) no previous malignancies (solid tumors or hematologic neoplasms). A total of 94 patients were selected according the inclusion criteria.

The pre-treatment evaluation for all patients included an esophagogastroscopy, a computed tomography (CT) scan of chest and abdomen, and an ultrasound of the neck and abdominal lymph node. The tissue sample for histological analysis were taken of primary tumor, lymph node or distant metastasis according to the most accessible site. All of the patients were staged based on the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system for ESCC.

All patients were treated with platinum-based chemotherapy combined with radiotherapy: 1,8 Gy daily, for five days a week until completing 50,4 Gy. Nimotuzumab (200 mg) was administered weekly for six weeks (induction phase), and then every 14 days during the maintenance or consolidation phase.

2.1. Data Collection and Definitions

The clinicopathological data including: gender, age, smoking history, tumor location, TNM stage, histological grade, and pre-treatment routine laboratory data. The value of lymphocyte, neutrophil, monocyte and platelet counts were collected using a routine blood test, and the hemoglobin and albumin levels were obtained within 7 days before start the treatment.

The PNI was calculated using the following formula: 10 x Albumin (g/dL) + 0.005 x Lymphocyte counts ($x10^9$). The NLR, PLR and LMR were calculated as follows: NLR = neutrophil counts / lymphocyte counts; PLR = platelet counts / lymphocyte counts and LMR = lymphocyte counts / monocyte counts.

2.2. Data Analysis

A database processed in the statistical package SPSS-v.20.0 (Statistical Package for the Social Sciences) was created. Summary measures were used for qualitative variables, absolute and relative frequencies expressed as percentages. The association between categorical variables were determinate by Pearson's Chi-square statistical test (x^2) and T-student´s test was used for comparative analyses of quantitative variables. Spearman´s correlation analysis were conducted to analyze the correlation among NLR, PLR, LMR and PNI. Overall survival was defined as the interval from date of diagnosis to the date of death or last contact. The cases who were still alive or lost to follow-up were treated as censored data for the analysis of survival rates. The probability of overall survival was estimated using the Kaplan Meier method. For the comparison of the different survival curves, the Log-Rank and Breslow test were used. Cox regression analysis was performed to assess the association between overall survival and clinical characteristics. The prognostic capacity of the PNI was evaluated using the ROC (Receiver Operating Characteristic) curve. The area under the curve (AUC), and the sensitivity, specificity and predictive values for different cut-off points of probability of dying were estimated punctually and by 95% confidence interval. The epidemiological analysis of data was performed using Epidat 3.1. In all tests, a significance level of 0.05 was set, with a confidence interval (CI) of 95%.

2.3. Ethical Aspects

The privacy, confidentiality, and integrity of the data obtained from the patients were respected. The research protocol was evaluated and approved by the Scientific Council and the Research Ethics Committee of the Hermanos Ameijeiras Hospital. The therapeutic procedures applied to the patients were explained initially or when a change had to be made in the treatment, which are part of the healthcare action protocol for care of this disease, with the healthcare informed consent. Hence, it was not necessary to request

informed consent from the patient specifically for this research.

3. Results

A receiver operating characteristic (ROC) curve was plotted to assess the prognostic value of PNI (Figure 1). The area under the curve (AUC) was 0,583 and the optimal cut-off value was 40 (sensitivity: 69.2% and specificity: 31.2% for prediction of mortality). For the subsequent analysis, the patients were divided into 2 groups according to the cut-off value: low-IPN (<40) and high-IPN (≥40).

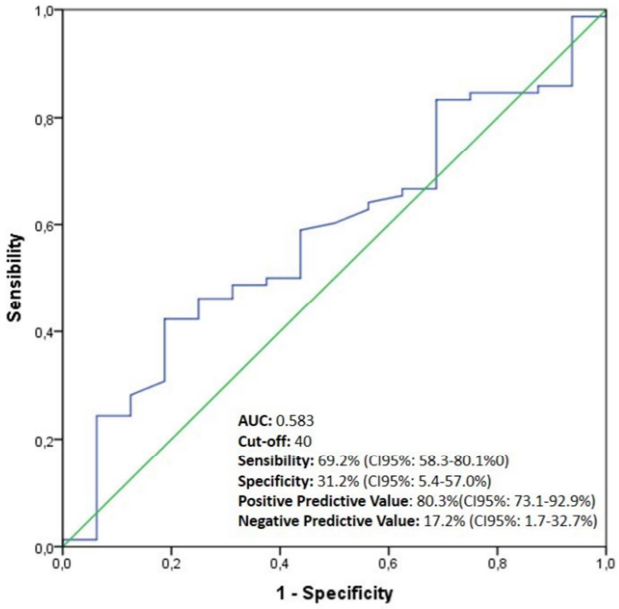

Figure 1. *Receiver operating characteristic (ROC) curve analysis of prognostic nutritional index. (Abbreviations: PNI: prognostic nutritional index; AUC: area under curve; CI: confidence interval).*

A total of 94 patients who met the inclusion criteria were enrolled in the study (Table 1). There were 81 males (86.2%) and 13 females (13.8%), with a median age of 62.0 years (range: 38-88). Regarding the characteristics of the disease, most patients had locally advanced disease at diagnosis (87.2%), most tumors were moderately differentiated (40.4%) and located in the middle esophagus (83.0%). Regarding hematological parameters, most patients presented hemoglobin <12 g/dL, platelet count <400 x10^9, lymphocyte count ≥1.0 x10^9, NLR ≥4, LMR <3.5 and PLR ≥200. We found that PNI was significantly associated with hemoglobin level (p<0.001), platelet count (p=0.037), total lymphocyte count (p=0.047), NLR (p<0.001), LMR (p=0.018) and PLR (p=0.027).

Regarding the value of the inflammatory indexes, patients with NLR ≥4 (35.2 vs 39.3; p<0.0001), PLR≥200 (36.2 vs 38.9; p=0.0175) and LMR<3.5 (35.8 vs 38.7; p=0.0045) had a significantly lower PNI (Figure 2). PNI was negatively correlated with NLR and PLR (r = -0.532; p<0.001 and r = -0.484; p<0.001; respectively), In addition, the PNI and LMR have a weak but significant positive correlation (r = 0.291; p=0.004) (Figure 3).

The survival analysis (Figure 4) shown that patients with PNI <40 had a significantly lower median overall survival compared to patients with PNI ≥40 (10.6 months versus 20.8 months; p=0.004).

Univariate cox regression analysis identified that ECOG ≥1 (p<0.001), hemoglobin <12 g/dL (p=0.002), platelet count ≥400 x10 ^{9} (p <0.001), NLR≥ 4 (p <0.001), LMR <3.5 (p= 0.024) and PNI<40 (p=0.005) were variables associated with poor overall survival. Multivariate analysis identified that ECOG ≥1 (HR: 4.14; CI95%: 2.43-7.06; p<0.001), platelet count ≥400 x10 ^{9} (HR: 2.47; CI95%: 1.39-4.38; p=0.002), NLR≥4 (HR: 2.23; CI95%: 1.29-3.87; p=0.004) and PNI<40 (HR: 2, 01; CI95%: 1.02-3.12; p=0.039) were independent prognostic factors for poor overall survival (Table 2).

Table 1. *Clinical characteristics.*

Characteristics	n	%	PNI		p
			<40	≥40	
Gender					
Male	81	86.2	51	30	0.662
Female	13	13.8	9	4	
Age					
Mean (range)	62,0 (38-88)		-	-	
<60 years	36	38.3	24	12	0.652
≥60 years	58	61.7	36	22	
Clinical stage					
III	82	87.2	53	29	0.671
IV	12	12.8	7	5	
Histological grade					
Good	35	37.2	23	12	
Moderately	38	40.4	24	14	0.954
Poorly	21	22.3	13	8	
Tumor Location					
Top 1/3	9	9.6	4	5	
1/3 Median	78	83.0	50	28	0.232
Lower 1/3	7	7.4	6	1	
ECOG scale					
0	33	35.1	18	15	0.168
≥1	61	64.9	42	19	
Hemoglobin					
<12g/dL	51	54.3	41	10	<0.001
≥12g/dL	43	45.7	19	24	
Platelet counts					
<400 x 10 ^{9}	65	69.1	37	28	0.037
≥400 x 10 ^{9}	29	30.9	23	6	
Lymphocyte counts					
<1.0 x 10 ^{9}	11	11.7	10	1	0.047
≥1.0 x 10 ^{9}	83	88.3	50	33	
NLR					
<4	40	42.6	18	22	<0.001
≥4	54	57.4	42	12	
LMR					
<3.5	59	62.8	43	16	0.018
≥3.5	35	37.2	17	18	
PLR					
<200	26	27.7	12	14	0.027
≥200	68	72.3	48	20	

Abbreviations: PNI: Prognostic Nutritional Index; ECOG: Eastern Cooperative Oncology Group; NLR: neutrophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; PLR: platelet to lymphocyte ratio

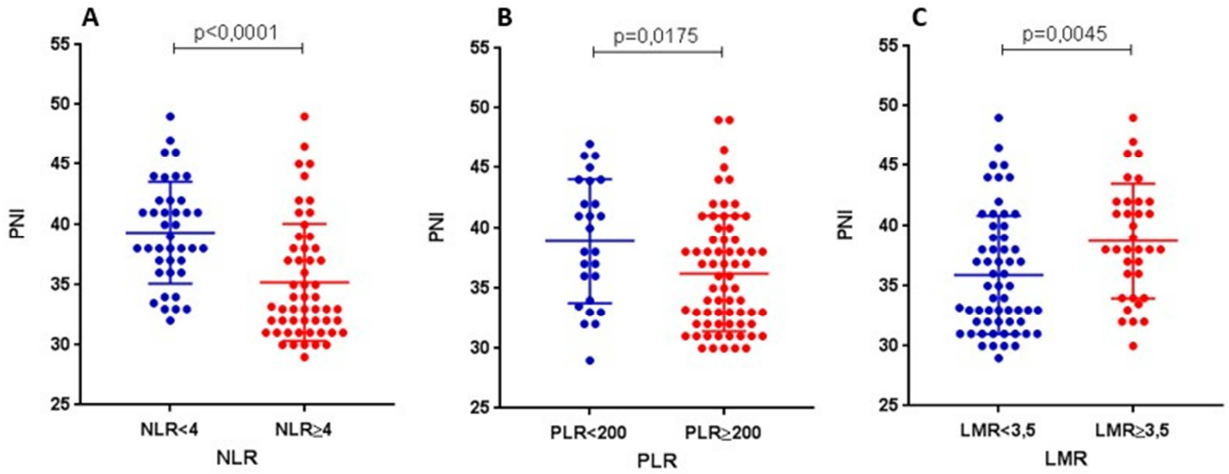

Figure 2. *Mean of prognostic nutritional index according to neutrophil to lymphocyte ratio (a), platelet to lymphocyte ratio (b) and lymphocyte to monocyte ratio (c). (Abbreviations: PNI: prognostic nutritional index; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LMR: lymphocyte to monocyte ratio).*

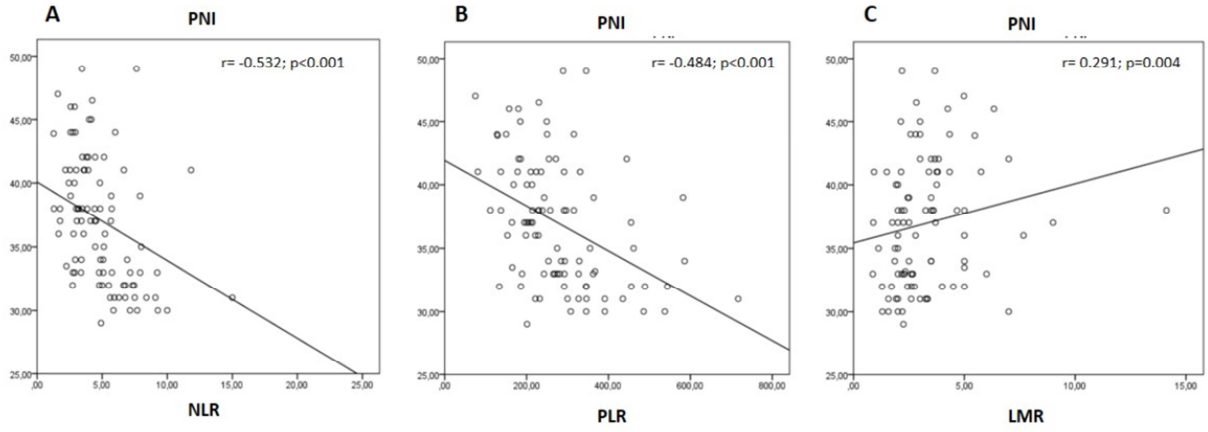

Figure 3. *Spearman´s correlation analysis between prognostic nutritional index neutrophil to lymphocyte ratio (a), platelet to lymphocyte ratio (b) and lymphocyte to monocyte ratio (c). (Abbreviations: PNI: prognostic nutritional index; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LMR: lymphocyte to monocyte ratio).*

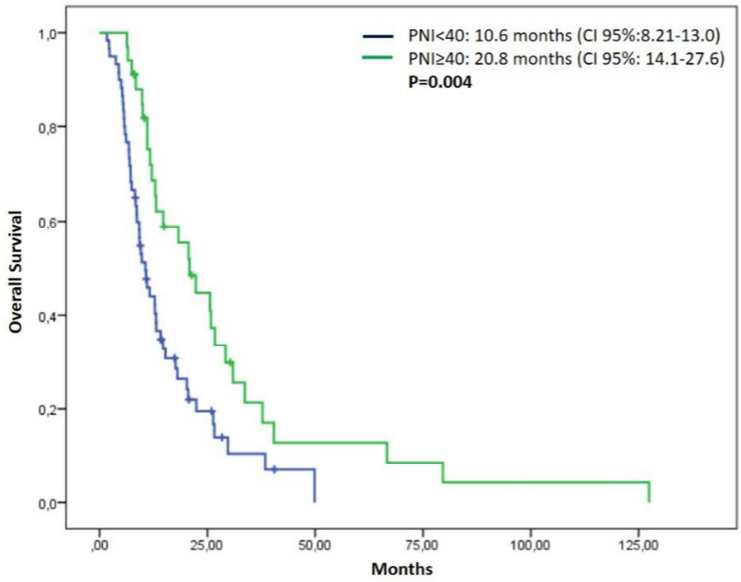

Figure 4. *Kapplan-Meier overall survival curves according to prognostic nutritional index. (Abbreviations: PNI: prognostic nutritional index; CI: confidence interval).*

Table 2. *Univariate and multivariate analysis of prognostic factors for overall survival.*

Characteristic	Univariate Analysis			Multivariate analysis		
	HR	CI 95%	p	HR	CI 95%	p
Sex (Male)	1.47	0.74-2.88	0.263	-	-	-
Age (>60 years)	0.87	0.55-1.37	0.563	-	-	-
Differentiation (Poor Differentiation)	1.25	0.75-2.07	0.378	-	-	-
Location (Middle/Lower Esophagus)	1.80	0.77-4.16	0.169	-	-	-
ECOG (≥1)	3.51	2.12-5.80	<0.001	4.14	2.43-7.06	<0.001
Stage (IV)	1.71	0.86-3.41	0.122	-	-	-
Hemoglobin (<12 g/dL)	2.18	1.34-3.54	0.002	1.06	0.60-1.87	0.820
Platelets (≥400 x10 ^{9})	2.63	1.56-4.42	<0.001	2.47	1.39-4.38	0.002
Lymphocytes (<1.0 x10 ^{9})	1.40	0.69-2.82	0.346	-	-	-
NLR≥4	2.58	1.61-4.13	<0.001	2.23	1.29-3.87	0.004
PLR≥200	1.41	0.84-2.36	0.188	-	-	-
LMR<3.5	1.74	1.07-2.81	0.024	1.39	0.82-2.33	0.212
PNI<40	2.01	1.23-3.28	0.005	1.79	1.02-3.12	0.039

Abbreviations: HR: Hazard ratio; CI: Confidence Interval; PNI: Prognostic Nutritional Index; ECOG: Eastern Cooperative Oncology Group; NLR: neutrophil to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; PLR: platelet to lymphocyte ratio

4. Discussion

In the present study, we evaluated the prognostic impact of the PNI in patients with advanced ESCC treated with neoadjuvant chemotherapy. The most important finding of the present study is that the pre-treatment PNI is associated with poor prognosis. Furthermore, our results showed that PNI is negatively correlated with inflammatory indexes (NLR and PLR).

Esophageal cancer triggers malnutrition caused by esophageal stenosis, immunosuppression, and inflammation. Nutritional parameters, such as, the body mass index, serum albumin and hemoglobin are significantly reduced in patients with esophageal cancer [12, 13]. The PNI is based on the serum albumin and lymphocyte count, therefore, the PNI may integrate the nutritional and immunological status of patients. Lymphocytes have been implicated in immunomodulation in tumor microenvironment, which might establish the human immune response to tumor cell. Thus low lymphocyte counts are related with an immunosuppressed status, which may provide a favorable microenvironment for tumor proliferation [14].

Our study found that patients with elevated systemic inflammatory markers (NLR and PLR) had a significantly lower PNI. In addition, it was shown that there is a significant negative correlation between PNI and systemic inflammatory markers. This behavior could be explained because in solid tumors, increased inflammatory-related cytokine production such as IL-6, modulates a decrease hepatic production of albumin by hepatocytes, whereas TNF-α production increases the permeability of the microvasculature to albumin [15, 16]. On the other hand, it has been shown that there is a relationship between the inflammatory state and the phenotype of T cell subset [17]. Based on our results, the PNI could also be used as an indirect indicator of the inflammatory status.

Previous studies about the prognostic value of PNI and ESCC are mainly based on surgery and indicate that PNI can predict the survival prognosis in patients with ESCC [18-21]. The use of PNI prior to the start of neoadjuvant chemotherapy has been less studied, but several studies have shown that a low PNI is associated with worse survival. The patients included in the present study presented locally advanced or metastatic disease, which contraindicates surgical treatment. Our results suggest that PNI could be an independent prognostic factor related with overall survival for patients with advanced stages. This result are consistent with others researches carried out in patients with advanced stages where the PNI has been shown to be a prognostic factor related with overall survival [22-24].

Chemotherapy can paradoxically cause both deterioration of the nutritional status due to toxicity and improvement of the nutritional status by reducing the overall tumor bulk [14, 25]. Several studies have demonstrated a significant decrease in the parameters associated with nutritional status, such as body mass index, serum albumin, and hemoglobin following chemotherapy or CRT in EC patients. Moreover, radiotherapy causes death of neoplastic cells directly and indirectly and may stimulate an inflammatory response. The inflammatory response is caused by the elimination of death cells, which leads to immunomodulation of tumor microenvironment, which may have a dual effect. It can increase immunity within certain limits, but it can also cause resistance to treatment, tumor recurrence and significant toxicity. Radiotherapy also causes lymphocytopenia at the peripheral level, due to the great sensitivity of this cell population to radiation, which can cause an alteration in the balance between neutrophils and lymphocytes [26, 27]. PNI variation during neoadjuvant treatment has been shown to significantly influence survival and treatment response. Takao et al, showed that patients with low pre-treatment PNI values who increase this value at the end of treatment had a significantly higher survival than patients who remain with low PNI at end of treatment [14].

Regarding the optimal cut-off point, there is a great difference between the studies. These differences can be explained by the different methodology for its determination and variations in the characteristics of the patients. In the present study, the cut-off point was determined by ROC curve analysis, which reduces the overestimation bias and recognizes the most favorable values for stratification. Further researches are needed for to determine the optimal cut-off for PNI in patients with advanced stage.

This study had several limitation: (1) this was a single-center retrospective study with a small sample size, and, (2) the TNM classification was only clinical, and although the recommended imaging studies were used, these methods do not have the evaluation capacity of pathological analysis.

5. Conclusion

In conclusion, the present study demonstrated that pretreatment PNI is a useful marker for predicting survival outcome in patients with advanced ESCC. In addition, due to the negative correlation between PNI and systemic inflammatory markers, PNI can be used as a surrogate marker of cancer-related inflammation.

The PNI represents a simple and inexpensive tool that can help to classify patients with a higher probability of mortality that require more intensive therapeutic management and nutritional support during treatment with chemotherapy. Future research should be carried out with the aim of evaluating the benefit of therapeutic interventions specifically in patients with poor nutritional status and elevated systemic markers of inflammation.

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