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Evaluation of the nutritional prognosis index associated with disease severity, comorbidities, laboratory test results, and clinical outcome in patients infected with COVID-19

Avaliação do índice de prognóstico nutricional associado com a gravidade da doença, presença de comorbidades, resultados de exames laboratoriais e desfecho clínico em pacientes infectados com COVID-19

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ABSTRACT

Objective

The COVID-19 has resulted in a global pandemic, and markers for disease prognosis have been studied, such as the Prognostic Nutritional Index. This study aimed to evaluate the associations of the index with disease severity, comorbidities, laboratory test results, and clinical outcomes.

Methods

This retrospective, cross-sectional study was conducted with patients with a positive SARS-CoV RNA result from 2020 to 2022. Measures were Prognostic Nutritional Index, disease severity, comorbidities, laboratory tests, and clinical outcome. Prognostic Nutritional Index was calculated using the equation: serum albumin [g/dL] x 10 + total lymphocyte count [per mm^3 x 0,005). Participants were categorized into severe malnutrition (PNI <35), mild malnutrition (PNI 35-38), and no malnutrition (>38).

Results

The sample (53% male) had a mean age of 56.77±17.42 years. Among those classified as Prognostic Nutritional Index 2, only 23.4% were discharged from the hospital, which was associated with higher mortality ($p<0.01$). PNI classification was associated with disease severity ($p=0.01$), and the highest proportion of critically ill patients was found in the PNI 2 group (60%). PNI 2 also evidenced significantly lower levels of hemoglobin, hematocrit, lymphocytes, and albumin (all with $p<0.01$). In the multivariate analysis, Prognostic Nutritional Index 1 and Prognostic Nutritional Index 2 groups had a higher risk of mortality (OR: 2.54; 95% CI: 1.73-3.72) and cardiomyopathies (OR: 1.92; 95% CI: 1.00-3.69).

Conclusion

The results suggest that Prognostic Nutritional Index may be a relevant marker for risk stratification in COVID-19 patients, with Prognostic Nutritional Index levels 1 and 2 proportionally associated with greater disease severity and mortality.

Keywords: COVID-19. Death. Disease severity. Nutritional prognostic index.

RESUMO

Objetivo

A COVID-19 resultou em uma pandemia global e marcadores para prognóstico da doença vêm sendo estudados, como o Índice de Prognóstico Nutricional. O objetivo do estudo foi avaliar associações do índice com gravidade da doença, presença de comorbidades, resultados de exames laboratoriais e desfecho clínico.

Métodos

As variáveis avaliadas foram o Índice de Prognóstico Nutricional, severidade da doença, comorbidades, exames laboratoriais e desfecho clínico. O Índice de Prognóstico Nutricional foi calculado usando a equação: 10 x albumina sérica [g/dL] + 0,005 x contagem total de linfócitos [n/mm^3*]. Os participantes foram categorizados em desnutrição grave (PNI <35), desnutrição moderada (PNI 35-38) e sem desnutrição (PNI >38).*

Resultados

A amostra (53% de homens) apresentou idade média de 56,8±17,4 anos. Dos participantes classificados com Índice de Prognóstico Nutricional 2, 23,4% obtiveram alta hospitalar, indicando uma associação com alta mortalidade (p<0,01). A classificação do Índice de Prognóstico Nutricional esteve associada com gravidade da doença (p=0,01), com maior proporção de pacientes críticos no grupo com Índice de Prognóstico Nutricional 2 (60%). O Índice de Prognóstico Nutricional 2 também apresentou níveis significativamente mais baixos de hemoglobina, hematócritos, contagem de linfócitos e albumina (todos com p<0,01). Na análise multivariada, níveis do Índice de Prognóstico Nutricional 1 e Índice de Prognóstico Nutricional 2 apresentaram maior risco de mortalidade (OR: 2,54; IC95%: 1,73-3,72), bem como associação com miocardiopatias (OR: 1,92; IC95%: 1,00-3,69).

Conclusão

Os resultados sugerem que o PNI pode ser um marcador relevante na estratificação de risco em pacientes com COVID-19, sendo os níveis de Índice de Prognóstico Nutricional 1 e Índice de Prognóstico Nutricional 2 proporcionalmente associados à maior gravidade e mortalidade.

Palavras-chave: *COVID-19. Óbito. Severidade da doença. Índice prognóstico nutricional.*

INTRODUCTION

The Coronavirus was discovered in 1937 and is an RNA virus of the *Coronaviridae family of the Nidovirales order* [1] that causes respiratory infections, displaying a crown-like shape under the microscope. Coronavirus Disease 2019 (COVID-19) has been a global challenge to health systems, resulting in more than hundreds of millions of confirmed cases and millions of deaths.

Patients with COVID-19 typically have higher inflammatory cytokines, such as IL-6 and TNF-α [2]. Furthermore, patients have high levels of inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, and lactate dehydrogenase. This hyperinflammation plays an important role in viral pathogenesis, and inflammatory cytokines can also modify the levels of several blood cell lines, resulting in lymphocytopenia [3].

The clinical presentation of COVID-19 is quite variable. It can be asymptomatic, with mild or nonspecific symptoms most often appearing, or even more significant manifestations of fever, cough, and dyspnea, which can lead to the need for invasive mechanical ventilation, severe acute respiratory distress syndrome, and death [4]. Patients may develop hypoalbuminemia and lymphopenia compared to those who do not deteriorate. Due to this variable clinical presentation, prognostic scales have been developed to guide the medical team regarding which patient requires the best care at a given moment [5].

The Prognostic Nutritional Index (PNI) is a prognostic scale that assesses the nutritional, inflammatory, and even immunological status of the patient [6]. It adopts absolute lymphocyte values and serum albumin levels as variables to obtain its result, and several studies have been conducted to evaluate the indicator as a prognostic scale at hospital admission, identifying the possibility of deteriorating and evolving to death in the coming days [7-9]. The PNI has been gaining importance over the years and has also been used as a prognostic factor for cardiovascular diseases and neoplasms, considering the tool's simple application [10,11].

The impact of COVID-19 was immediate and significant, affecting healthcare systems, economies, and societies worldwide. The high infection rate, associated with severe cases and deaths, highlighted the urgent need for rapid responses to contain transmission and identify indicators that could contribute to treatments and preventive measures. Therefore, studies were conducted to evaluate several markers, including the PNI.

In 2020, Wang et al. [9] designed a study to develop a prognostic nomogram incorporating the PNI in patients with COVID-19. The authors concluded that the proposed prognostic model was beneficial for assessing disease progression but suggested that further studies be conducted. Karimi et al. [12] reviewed evidence on 11 groups of systemic inflammatory markers to stratify at-risk patients and predict COVID-19-related outcomes and suggested that the PNI is superior to other markers (neutrophil-to-lymphocyte ratio) in predicting outcomes, and that more studies are needed to confirm the importance of inflammatory markers.

This study aimed to evaluate the possible associations between the PNI and the severity of COVID-19, the presence of comorbidities, laboratory parameters, and clinical outcomes, considering PNI stratification as a prognostic tool. This is a novel approach in the literature to date.

METHODS

Study design

A retrospective, cross-sectional study was conducted at the Professor Alberto Antunes University Hospital (HUPAA) of the Federal University of Alagoas. The sample was a census, consisting of all patients who met the inclusion and exclusion criteria, without the application of probability sampling methods. The present study followed the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline to ensure standardization and quality in the presentation of observational studies [13].

Study participants and procedures

The study included data collected from 206 medical records of patients admitted to the HUPAA with a positive throat swab test for SARS-CoV RNA and allocated to the ward and Intensive Care Unit (ICU) from April 2020 to September 2022. The initial sample consisted of 440 medical records, which were narrowed down to 438 records after applying the inclusion criteria (age 18 years or older, regardless of ethnicity and gender). Of these, we excluded 232 medical records of patients with incomplete gender and age information, those who were transferred to another hospital, or who lacked sufficient data for the calculation of the PNI and other variables of interest. Thus, the final sample consisted of 206 medical records, which were eligible under the inclusion and exclusion criteria.

The variables of interest were PNI, disease severity, comorbidities, laboratory test results, and clinical outcome (death or hospital discharge). The PNI score was calculated using the formula: PNI = 10 x serum albumin value (g/dL) + 0.005 x total lymphocyte count in peripheral blood (n/mm^3) [14].

Nutritional status stratification was initially defined by Buzby et al. [15], relating the risk of postoperative complications to baseline nutritional status. Subsequently, Onodera et al. [16] simplified the model, maintaining the albumin and lymphocyte parameters and suggested cutoff points for high surgical and nutritional risk of PNI <40; moderate risk for PNI between 40 and 45; and mild risk ≥45. Narumi et al. [14] defined cutoff PNI values >38 for no malnutrition, PNI between 35 and 38 for mild malnutrition, and those with PNI <35 for severe malnutrition. Finally, Wei et al. [7], in a study of COVID-19 patients, established a nomogram built from the results of multivariate analysis with the same cutoff points. Thus, in the present study, PNI was classified per Wei et al. [7] into: PNI Group 0 − PNI >38 (no malnutrition); PNI Group 1 - PNI between 35 and 38 (mild malnutrition); and PNI Group 2 − PNI <35 (severe malnutrition).

Disease severity was classified per the WHO guidelines [17] as mild disease (nonspecific symptoms); moderate disease (clinical signs of non-severe pneumonia, including peripheral oxygen saturation (SpO_2) ≥90% in room air); severe disease (clinical signs of pneumonia plus one of the findings of SpO_2 <90 mmHg or respiratory rate above 30 breaths per minute, or signs of severe respiratory distress), and critical (clinical picture compatible with acute respiratory response syndrome and/or sepsis, use of mechanical ventilation, and use of vasoactive drugs).

We considered the comorbidities registered in the medical records. Laboratory test results performed within 24 hours of admission included complete blood count, albumin, urea nitrogen, creatinine, and blood glucose. Clinical outcome: patients' clinical outcomes were recorded as death or hospital discharge. This outcome was used to assess the severity and impact of the factors studied on disease progression.

Data collection and analysis

Data were manually collected from electronic medical records by a team of three researchers and then entered into a Microsoft Office Excel® spreadsheet. Two other researchers reviewed these data to ensure accuracy, and medical terminology was standardized. Patient confidentiality and privacy were guaranteed, as data were collected in a dedicated room and the records were identified by numerical coding, without identifying the patients' names.

Categorical variables are presented as relative and absolute frequencies, while continuous variables are presented as mean and standard deviation. Chi-square tests and Fisher's exact tests were performed when expected frequencies were less than 5 to assess the association between PNI classifications and sample characteristics, which were presented as categorical variables. One-way ANOVA tests were performed to assess the difference between PNI classifications and sample characteristics, which were presented as continuous variables.

To assess the association between PNI stratification and its mean values, simple (univariate) and multiple (multivariate) linear regression analyses were performed, considering the PNI categories (PNI 1 and PNI 2) as independent variables and the continuous value of the index itself as the dependent variable. The multivariate analyses were adjusted for gender and age, showing coefficients (β), 95% confidence intervals (95% CI), and *p*-values.

The PNI logistic regressions were performed with the following variables: I) Disease severity; II) Comorbidities; III) Laboratory data; and IV) Clinical outcome. All regressions were performed using univariate and multivariate analyses, the latter adjusted for gender and age.

The Jamovi program version 2.3 (https://www.jamovi.org) was adopted for statistical analysis and to formulate tables and graphs. The Scatter plot was employed, which is a visualization that uses points to show the relationship between two numerical variables, where each point represents a pair of values.

Statistical power analysis was performed to verify the study's ability to detect significant associations, reducing the risk of type II error (β). Sample sizes, the significance level adopted (α=5%), and the effect sizes observed in the primary analyses were considered. The statistical power obtained was greater than 80%, indicating that the sample was adequate to support the study's inferential conclusions.

The study was registered on the *Plataforma Brasil* under No 31116320.3.0000.5013 and approved by the Research Ethics Committee of the Federal University of Alagoas, opinion N° 4.297.975. Privacy and confidentiality were guaranteed during data collection.

RESULTS

The sample consisted of 206 patients with a confirmed diagnosis of COVID-19, admitted to HUPAA/Federal University of Alagoas and stratified into three groups: PNI 0 (n=97; 47.1%), PNI 1 (n=44; 21.4%), and PNI 2 (n=65; 31.5%). Table 1 describes the sociodemographic characteristics of the sample, evidencing a higher frequency of males (54.4%) and self-declared brown individuals (94.1%). No statistically significant differences were observed between the groups regarding gender (*p*=0.48), ethnicity (*p*=0.38), and origin (*p*=0.29).

Table 1 – Sample characteristics, according to the Prognostic Nutritional Index classification, in patients with COVID-19.

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Features	PNI 0		PNI 1		PNI 2		*p*-value[1]
	n	%	n	%	n	%	
Gender (n=206)							0.48
Female	47	48.5	22	50.0	26	40.0	
Male	50	51.5	22	50.0	39	60.0	
Ethnicity (n=205)							0.38
White	0	0.0	0.0	0.0	1	1.5	
Black	1	1.0	1	2.3	3	4.6	
Brown	95	97.9	40	93.0	60	92.3	
Yellow	0	0.0	1	2.3	0	0.0	
Undeclared	1	1.0	1	2.3	1	1.5	
Origin (n=205)							0.29
Capital	45	46.4	23	53.5	33	50.8	
Inland region	47	48.5	17	39.5	32	49.2	
Other state	5	5.2	3	7.0	0	0.0	

Table 1 – Sample characteristics, according to the Prognostic Nutritional Index classification, in patients with COVID-19.

Features	PNI 0		PNI 1		PNI 2		*p*-value[1]
	n	%	n	%	n	%	
Disease severity (n=206)							0.01
Not severe	35	36.1	12	27.3	12	18.5	
Severe	31	32.0	14	31.8	14	21.5	
Critical	31	32.0	18	40.9	39	60.0	
Comorbidities Arterial hypertension (n=204)							0.94
No	55	57.3	25	56.8	35	54.7	
Yes	41	42.7	19	43.2	29	45.3	
Diabetes Mellitus (n=204)							0.61
No	64	66.7	29	65.9	38	59.4	
Yes	32	33.3	15	34.1	26	40.6	
Lung disease (n=204)							0.13
No	87	90.6	41	93.2	63	98.4	
Yes	9	9.4	3	6.8	1	1.6	
Obesity (n=204)							0.02
No	79	82.3	43	97.7	58	90.6	
Yes	17	17.7	1	2.3	6	9.4	
Cardiomyopathies (n=204)							0.01
No	94	97.9	38	86.4	55	85.9	
Yes	2	2.1	6	13.6	9	14.1	
Tobacco use (n=204)							0.79
No	88	91.7	39	88.6	57	89.1	
Yes	8	8.3	5	11.4	7	10.9	
Pregnancy (n = 204)							0.91
No	94	97.9	43	97.7	62	96.9	
Yes	2	2.1	1	2.3	2	3.1	
Immunodepression/neoplasia (n=204)							0.14
No	88	91.7	36	81.8	53	82.8	
Yes	8	8.3	8	18.2	11	17.2	
Outcome (n=203)							<0.01
Discharge	67	70.5	26	59.1	15	23.4	
Death	28	29.5	18	40.9	49	76.6	

Note: [1]*p*-value <0.05 for the chi-square test and Fisher's test when the expected frequencies were less than 5. COVID-19: Coronavirus Disease 2019; PNI: Prognostic Nutritional Index.

As shown in Table 1, a significant association was observed between COVID-19 disease severity and stratification by PNI (p=0.01). In the analysis of comorbidities, significant differences were observed for obesity (p=0.02) and cardiomyopathy (p=0.01). The prevalence of cardiomyopathy was higher in the PNI 2 group (14.1%) than in the PNI 1 (13.6%) and PNI 0 (2.1%) groups. Regarding obesity, the highest frequency occurred in the group with better nutritional status (PNI 0: 17.7%), with lower prevalence in the PNI 1 (2.3%) and PNI 2 (9.4%) groups. Regarding the clinical outcome, mortality was significantly higher in the PNI 2 group (76.6%) than in the PNI 1 (40.9%) and PNI 0 (29.5%) groups, as shown in Figure 1.

Figure 2 clearly shows the distribution of COVID-19 severity per the PNI classification. In the PNI 0 group (no/low nutritional risk), the distribution between severity levels is relatively balanced, with similar percentages among the non-severe (36.1%), severe (32.0%), and critical (32.0%) categories. The PNI 1 group reveals an increase in the proportion of critical patients (40.9%), while a significant portion remains in the non-severe (27.3%) and severe (31.8%) levels. The PNI 2 group displays a marked change in profile, with a higher frequency of critical cases (60.0%), while non-severe cases (18.5%) become proportionally much lower. These findings reinforce the association between nutritional impairment – reflected by the lower PNI – and the progression to more severe COVID-19 forms.

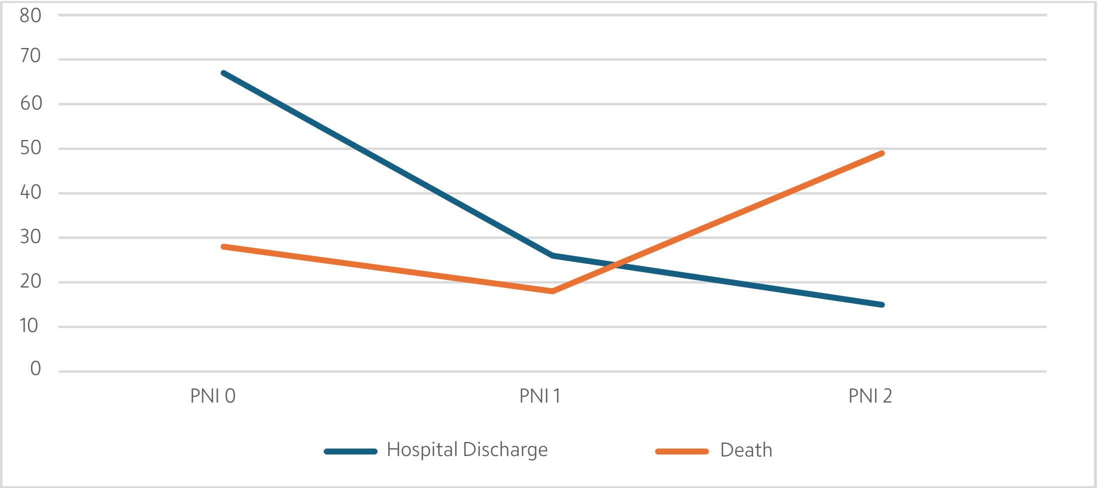

Figure 1 – Representation of mortality in patients with COVID-19, according to the Prognostic Nutritional Index classification.

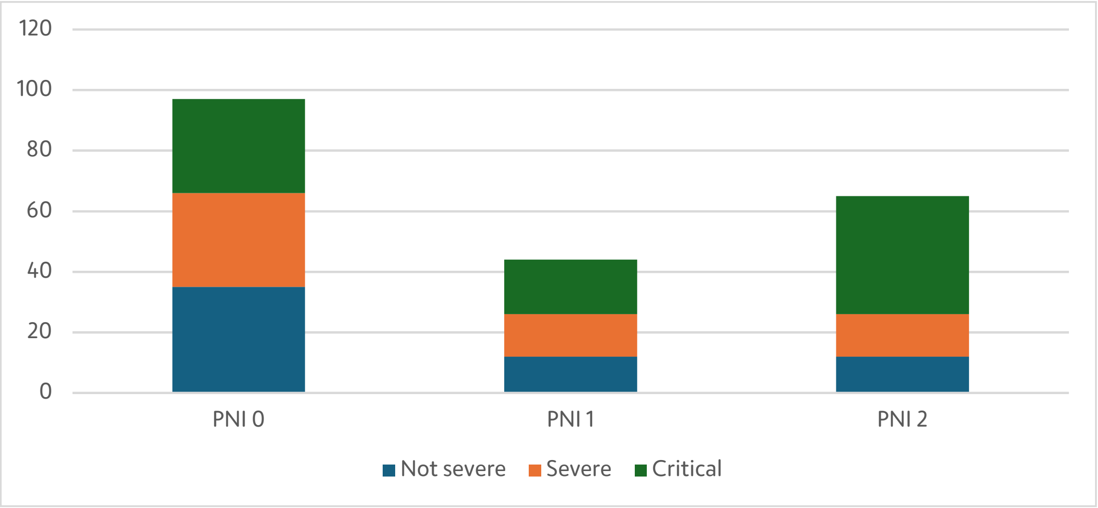

Figure 2 – Frequency of COVID-19 severity according to Prognostic Nutritional Index classification.

In the analysis of laboratory parameters (Table 2), we observed that patients classified in the PNI 2 group had worse nutritional and inflammatory profiles. The mean albumin levels were significantly lower in the PNI 2 group (2.54±0.46) than in the PNI 1 (3.21±0.20) and PNI 0 groups (3.50±0.41) (p<0.01). Likewise, we observed a progressive decline in hemoglobin (PNI 2: 11.19±2.57; PNI 1: 12.30±2.64; PNI 0: 13.15±1.99; p<0.01) and hematocrit values (p<0.01). Furthermore, more pronounced lymphopenia was observed in the PNI 2 group (790.43±460.95) than in the PNI 1 (915.56±398.54) and PNI 0 groups (2,377.27±5,614.96) (p=0.01). Urea levels were significantly higher in the PNI 2 group (87.25±80.35; p<0.01).

Univariate and multivariate linear regression

We performed univariate and multivariate regression between the variables PNI, laboratory test results, comorbidities, and clinical outcome to assess the probability of predictor variables and thus identify risk factors that could influence COVID-19's severity and mortality.

Table 2 – Laboratory test results, according to the Prognostic Nutritional Index classification, in patients with COVID-19 Triglycerides.

Features	PNI 0		PNI 1		PNI 2		*p*-value[1]
	M	SD	M	SD	M	SD	
Age (years, n=206)	53.02[a]	15.99	56.20[a,b]	19.06	61.09[a]	17.20	0.01
Hemoglobin (n=205)	13.15[a]	1.99	12.30[a,b]	2.64	11.19[b]	2.57	<0.01
Hematocrit (n=192)	38.06[a]	6.23	37.44[a]	6.73	33.45[b]	7.71	<0.01
Platelets (n=198)	247.673.68[a]	123.844.48	312.976.19[a]	511.261.11	205.901.64[a]	102.400.79	0.11
Leukocytes (n=205)	15.518.85[a]	23.403.43	10.963.64[a]	6.260.77	12.232.00[a]	6.867.71	0.25
Lymphocytes (n=206)	2.377.27[a]	5.614.96	915.56[a,b]	398.54	790.43[b]	460.95	0.01
Albumin (n=206)	3.50[a]	0.41	3.21[b]	0.20	2.54[c]	0.46	<0.01
Urea (n=195)	55.64[a]	49.03	58.18[a]	47.71	87.25[b]	80.35	<0.01
Creatinine (n=204)	1.42[a]	2.63	1.37[a]	1.32	2.22[a]	2.67	0.08
Blood glucose (n=129)	208.89[a]	143.11	191.12[a]	194.99	177.48[a]	122.46	0.57
Triglycerides (n=140)	217.43[a]	150.20	192.88[a]	93.57	227.97[a]	201.68	0.63

Note: [1]*p*-value <0.05 for the ANOVA test. [a,b,c]Different superscript letters indicate differences in means between groups. COVID-19: Coronavirus Disease 2019; M: Mean; SD: Standard Deviation; PNI: Prognostic Nutritional Index.

When analyzing the association between the PNI classification and its continuous values (Table 3), we observed a statistically significant association in the univariate and multivariate analyses. Compared to the reference group (PNI 0), patients classified as PNI 1 showed a mean reduction of 10.20 points in the PNI value (95% CI: -16.9 to -3.5; $p<0.01$) in the univariate analysis and 10.37 points (95% CI: -17.11 to -3.62; $p<0.01$) after adjustment for gender and age. Even more significantly, those classified as PNI 2 showed a mean decline of 17.50 points (95% CI: -23.4 to -11.6; $p<0.01$) in the univariate analysis and 17.82 points (95% CI: -23.90 to -11.73; $p<0.01$) in the multivariate model.

Still in Table 3, the regression analysis of laboratory tests showed that hemoglobin levels were negatively associated with worse PNI, with $\beta = -1.99$ (95% CI: -2.74 to -1.25; $p<0.01$) in the multivariate analysis. Albumin also showed a strong association, with $\beta = -0.92$ (95% CI: -1.05 to -0.79; $p<0.01$). Urea ($\beta = 22.73$; 95% CI: 3.25 to 42.22; $p=0.02$) and C-reactive protein ($\beta = 38.71$; 95% CI: 7.69 to 69.73; $p=0.01$) remained significantly associated with the worst PNI classification, reinforcing the relationship between inflammation, nutritional deterioration, and unfavorable clinical evolution.

Figure 3 shows the association between the PNI classification and comorbidities with the clinical outcome of death in patients with COVID-19, with data shown in Table 4. The outcome variable (death) evidences a statistically significant association with the PNI classification, with an OR of 2.54 (95% CI: 1.73-3.72), indicating that patients with worse PNI are more than twice as likely to evolve to death than others.

Cardiomyopathy stands out among the comorbidities analyzed, also showing a significant association, with an OR of 1.92 (95% CI: 1.00-3.69), suggesting a significant increase in the risk of death in these patients. Other comorbidities, such as hypertension, diabetes mellitus, lung disease, and obesity, did not show independent statistically significant associations, since their confidence intervals include the reference value (OR=1). The vertical dashed line at OR=1 represents "no effect". Thus, points to the right of this line indicate a higher risk, while those to the left indicate a lower risk. However, only cardiomyopathy and outcome (death) were significantly associated with PNI in this graph.

Table 3 – Results of univariate/multivariate analysis between comorbidities and clinical outcome, and Prognostic Nutritional Index in patients with COVID-19.

Features	Univariate analyses				Multivariate analyses			
	PNI 1	*p*-value	PNI 2	*p*-value	PNI 1	*p*-value	PNI 2	*p*-value
	β [95% CI]		β [95% CI]		β [95% CI]		β [95% CI]	
PNI (n=206)	-10.20 [-16.9; -3.5]	< 0.01	-17.50 [-23.4; -11.6]	<0.01	-10.37 [-17.11; -3.62]	<0.01	-17.82 [-23.90; -11.73]	<0.01
Hemoglobin (n=205)	-0.85 [-1.69; -0.01]	0.04	-1.95 [-2.70; -1.21]	<0.01	-0.82 [-1.64; 0.01]	0.05	-1.99 [-2.74; -1.25]	<0.01
Hematocrit (n=192)	-0.61 [-3.16; 1.93]	0.63	-4.60 [-6.84; -2.37]	<0.01	-0.60 [-3.11; 1.90]	0.63	-5.03 [-7.29; -2.77]	<0.01
Platelets (n=198)	65303.0 [-28282.0; 158887.0]	0.17	-41772.0 [-124636.0; 41092.0]	0.32	67923.0 [-25822.0; 161669.0]	0.15	-37470.0 [-122250.0; 47311.0]	0.38
Leukocytes (n=205)	-4555.0 [-10571.0; 1461.0]	0.13	-3287.0 [-8595.0; 2021.0]	0.22	-4515.6 [-10575.0; 1544.0]	0.14	-3092.1 [-8562.0; 2378.0]	0.26
Lymphocytes (n=206)	-1462.0 [-2850.0; -73.2]	0.03	-1587.0 [-2811.0; -362.3]	0.01	-1511.1 [-2906.8; -115.4]	0.03	-1692.5 [-2951.4; -433.6]	<0.01
Albumin (n=206)	-0.28 [-0.42; -0.14]	<0.01	-0.95 [-1.07; -0.82]	<0.01	-0.27 [-0.41; -0.13]	<0.01	-0.92 [-1.05; -0.79]	<0.01
Urea (n=195)	2.54 [-19.4; 24.4]	0.81	31.60 [11.9; 51.3]	<0.01	-0.54 [-21.69; 20.60]	0.95	22.73 [3.25; 42.22]	0.02
Creatinine (n=204)	-0.04 [-0.92; 0.83]	0.91	0.80 [0.02; 1.57]	0.04	-0.07 [-0.94; 0.80]	0.87	0.66 [-0.11; 0.09]	0.09
Blood glucose (n=129)	-17.8 [-87.2; 51.7]	0.61	-31.4 [-90.7; 27.9]	0.29	-16.65 [-85.97; 52.68]	0.63	-48.20 [-110.01; 13.61]	0.12

Note: *p*≤0.05. COVID-19: Coronavirus Disease 2019; CI: Confiance Interval; PNI: Prognostic Nutritional Index.

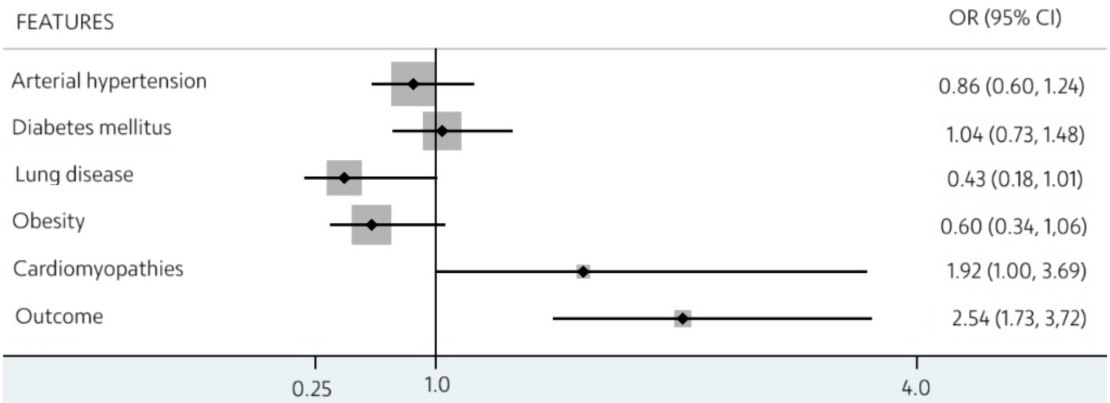

Figure 3 − Regression analysis (Forest Plot) between clinical outcome, comorbidities, and Prognostic Nutritional Index.

Table 4 - Results of univariate/multivariate analysis of laboratory test results, according to Prognostic Nutritional Index classification in patients with COVID-19.

Features	Univariate analyses		Multivariate analyses*	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Arterial hypertension	1.05 [0.76; 1.44]	0.75	0.86 [0.60; 1.24]	0.44
Diabetes mellitus	1.16 [0.83; 1.61]	0.36	1.04 [0.73; 1.48]	0.81
Lung disease	0.46 [0.20; 1.04]	0.06	0.43 [0.18; 1.00]	0.05
Obesity	0.61 [0.35; 1.05]	0.07	0.60 [0.34; 1.06]	0.07
Cardiomyopathies	2.31 [1.24; 4.32]	<0.01	1.92 [1.00; 3.69]	0.04
Clinical outcome	2.70 [1.89; 3.86]	<0.01	2.54 [1.73; 3.72]	<0.01

Note: *Adjustments for gender and age $p \leq 0.05$. COVID-19: Coronavirus Disease 2019; CI: Confiance Interval; OR: Oddis Ratio; PNI: Prognostic Nutritional Index.

DISCUSSION

Several studies have been conducted to evaluate the PNI as a predictor of prognosis in diseases. A study that evaluated the preoperative PNI in patients with gastric cancer undergoing curative gastrectomy revealed that the PNI was effective in predicting patient prognosis [18]. In a systematic review, the PNI was considered "a good tool for indicating the risk of death and complications in the postoperative period of heart surgeries (...)" [19, p. 1]. Miyasato et al. [20] affirm that the PNI predicted mortality better than serum albumin level or total lymphocyte count alone in patients undergoing hemodialysis. Dong Wang et al. [21] concluded that PNI can predict the prognosis of Hepatocellular Carcinoma in patients undergoing liver resection, where PNI is an independent risk factor for the overall survival of patients with HCC.

The present study aimed to detail the PNI in three classification levels (PNI 0 without malnutrition, PNI 1 with mild malnutrition, and PNI 2 with severe malnutrition), with results in agreement with Mei-Yu et al. [7]. We observed a statistically significant association ($p<0.01$) between the PNI groups in the univariate and multivariate analysis, with a lower PNI observed among patients in the PNI 2 group (severe malnutrition) than in the PNI 1 group [mean difference: −7.38, $p<0.001$], confirming that lower PNI values are strongly related to worse nutritional classifications.

Regarding COVID-19, studies have evaluated the PNI in general. Wang et al. [9] developed a prognostic nomogram using leukocytes, PNI, and lactate dehydrogenase values, concluding that the index was independently associated with patient mortality. In a meta-analysis of 14 articles, the authors concluded that the PNI could serve as an easily calculated bedside biomarker of "malnutrition-inflammation" and that a lower PNI was associated with a worse prognosis in patients with coronary insufficiency [10]. However, in another systematic review and meta-analysis with 13 articles (3 articles published in 2020 and the rest in 2021), the authors identified a negative association between PNI and COVID-19 prognosis. However, they considered in their conclusions that large-scale trials would still be necessary to confirm the findings [4].

When analyzing the PNI by stratification with clinical outcome, it was observed that the PNI classification was strongly associated with death (p<0.01). Patients with better nutritional status (PNI 0) had a higher hospital discharge rate (70.5%) and a lower death rate (29.5%). A significant mortality increase is observed with PNI deterioration (Figure 1): in patients classified as PNI 1, the death rate rises to 40.9%, while in the PNI 2 group, mortality reaches 76.6%, representing more than three-quarters of the patients in this group. These findings reveal a direct association between worse nutritional status, as reflected by the PNI, and worse clinical outcome, with a clear trend toward higher mortality in patients with lower nutritional reserves. In Figure 3, the robust association between the clinical outcome of death and PNI 2 (OR: 2.54; 95% CI: 1.73-3.72; p<0.01) is noteworthy, reinforcing the prognostic value of index stratification in predicting the risk of death.

However, Kaku et al. [22] concluded in a study of 70 patients with critically ill COVID-19 that the PNI might not be valid for use as a prognostic indicator. The authors stressed important study limitations, such as incomplete data, which could have led to discrepancies in the results with the PNI, in addition to the fact that their study was conducted in a population with fewer deaths for the primary outcome than in previous studies. Contrary to the authors' claims, the present study showed that patients with PNI 2 had high mortality when stratifying patients by nutritional status.

Regarding clinical severity, the results of this study demonstrated a significant association between PNI and the clinical severity of COVID-19, as well as with laboratory parameters and clinical outcomes. Patients with lower PNI evidenced higher disease severity, worse laboratory parameters – especially lower hemoglobin, hematocrit, albumin, and lymphocytes levels – and a higher mortality rate.

In a study that aimed to verify risk indicators of hospital mortality and severity, as well as to provide a comprehensive systematic review and meta-analysis to investigate the prognostic significance of PNI as a predictor of adverse outcomes in hospitalized patients with COVID-19, the authors concluded that PNI had predictive value in patient prognosis, but that there was a need for risk stratification based on PNI values [23]. This fact reinforces the results of the PNI risk stratification performed in this study for COVID-19 patients. Table 1 and Figure 3 clearly show the distribution of COVID-19 severity per the PNI classification. A clear trend is observed: the proportion of critical cases significantly increases with decreasing PNI (indicating worse nutritional status). Therefore, the PNI is a valuable tool in risk stratification, indicating that patients at higher nutritional risk tend to have more severe and critical cases of the disease.

In the analysis of laboratory parameters (Table 2), anemia and lymphopenia were observed from the initial phase of the disease, reducing further with the deterioration of the nutritional status, and a significant difference was identified between the groups (p<0.001). We also observed that patients classified in the PNI 2 group had worse nutritional and inflammatory profiles. The mean albumin levels were significantly lower in the PNI 2 group (2.54±0.46) than in the PNI 1 (3.21±0.20) and PNI 0 groups (3.50±0.41) (p<0.01). Similarly, we noted a progressive reduction in hemoglobin (PNI 2: 11.19±2.57; PNI 1: 12.30±2.64; PNI 0: 13.15±1.99; p<0.01) and hematocrit values (p<0.01). More pronounced lymphopenia was also found in the PNI 2 group (790.43±460.95) than PNI 1

(915.56±398.54) and PNI 0 groups (2,377.27±5,614.96) (p=0.01), as well as significantly higher urea levels in the PNI 2 group (87.25 ± 80.35; p<0.01).

In Coronavirus infections, including COVID-19, a direct attack by the virus occurs on lymphocytes, resulting in excessive release of inflammatory cytokines, which can result in declining T cells through cellular apoptosis and damage to antigen-presenting cells [24,25]. In a study that aimed to evaluate the association of T lymphocytes with the severity of COVID-19, the authors concluded that lymphopenia is the first indicator of impaired T cell-mediated immunity and that disease severity is inversely proportional to the number of these cells [26].

Serum albumin is considered the most abundant circulating plasma protein in human serum, synthesized by hepatocytes, negatively regulating the expression of ACE2, which is the target receptor of COVID-19 [27]. Hypoalbuminemia may also be associated with situations in which it is necessary to subject patients to long periods of orotracheal intubation with low nutritional intake, leading to malnutrition and liver dysfunction [6]. Furthermore, since albumin preserves osmotic regulation, when it drops, fluid leaks from the blood vessels, increasing the likelihood of pulmonary congestion, which contributes to a deterioration of the acute respiratory distress syndrome and leads to a poor prognosis [9]. Other pathophysiological mechanisms have also been identified in COVID-19, such as an exacerbated systemic inflammatory response and the release of excess inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, TNF-α, monocyte chemotactic protein 1, inducible protein-10 (IP-10), interferon-γ, and granulocyte colony-stimulating factor, which cause significant organ damage and can even inhibit the synthesis capacity of hepatocytes [28].

Hemoglobin, hematocrit, lymphocytes, and albumin (Table 3), in addition to the significant association, showed a negative beta value, suggesting an inverse relationship between hemoglobin levels and the PNI classification. In other words, for each declining unit of hemoglobin, hematocrit, lymphocytes, or albumin, the probability of progressing to severe malnutrition increases as many times as shown by the OR of the uni/multivariate analysis, while the confidence interval and p-value support the statistical significance of this association. Regarding urea, the results suggest that higher urea levels are strongly associated with an increased likelihood of progression to severe malnutrition (a one-unit increase in urea and C-reactive protein increases the likelihood of progress to severe malnutrition, as per the corresponding OR). Wang et al. [29] found similar results to the present study: the prevalence of critical illness was significantly higher in patients with lower PNI than in patients with higher PNI, and linear regression analysis showed that PNI in patients with COVID-19 was correlated with a drop in hemoglobin in 101 patients. The patients included were those with severe and critical illness, but PNI classification was not performed, as in this study.

Another meta-analysis study performed to evaluate laboratory test results found that platelet count, creatinine, albumin, and blood uremic nitrogen levels were associated with ICU admission, while lower levels of hemoglobin, lymphocytes, and albumin were associated with increased mortality in ICU patients. This meta-analysis did not use the PNI as a variable, showing that low-cost and rapid biochemical and hematological tests can be used to estimate the risk of mortality in patients with COVID-19. The present study expanded this perspective, adding the PNI as an important variable to estimate the importance of nutritional aspects in patient outcomes [30].

Data from the present study show that, among the comorbidities evaluated, cardiomyopathy had a statistically significant association with the worst PNI scores (Table 4 and Figure 3), indicating that patients with previous heart disease could be more susceptible to the impact of malnutrition and systemic inflammation, contributing to a deteriorated clinical condition and reinforcing the vulnerability of this population, especially in the context of systemic inflammation and endothelial dysfunction aggravated by COVID-19. Nascimento et al. [31] concluded in their study that myocardial injury, systemic arterial hypertension, and high body mass index were independent predictors of risk for COVID-19. In the present study, however, arterial hypertension, diabetes mellitus, and obesity did not show a statistically significant independent association with the PNI classification in the univariate and multivariate analyses, which may be related to the clinical variability of the sample or the small sample size of some subgroups.

Lung diseases showed a trend toward an association with COVID-19 risk in the multivariate analysis (OR: 0.43; 95% CI: 0.18-1.00; p=0.05), although the upper limit of the confidence interval was close to 1. This fact may reflect selectivity in the care and early monitoring of these chronic patients already followed in specialized services. In a study that evaluated the potential risks of severity and mortality caused by COVID-19 in patients with obstructive pulmonary disease, the authors concluded that COVID-19 infection was associated with substantial severity and mortality rates in this group of patients and that current smokers were at higher risk of severe complications and a higher mortality rate than former and non-smokers [32].

This study's main strength is the use of a sample composed of all patients hospitalized with COVID-19 in a reference center, which allows for a representative analysis of the population served, stratified by nutritional status. However, some limitations should be considered. The data shown are retrospective and were obtained from medical records and a sample of an isolated facility that, at the time of the pandemic, served as a reference center for critically ill patients, including patients from other Brazilian states who could not cope with the demand, arriving at HUPAA in severe conditions. This situation hinders medical interviews, potentially limiting the generalizability of the results to other populations and healthcare settings. Furthermore, the lack of specific nutritional data, such as anthropometric measurements or dietary assessment, limits the analysis of the direct impact of nutritional status on clinical outcomes.

CONCLUSION

This study's findings suggest that the PNI Index may represent a relevant marker for risk stratification in patients with COVID-19, being associated with greater clinical severity, unfavorable laboratory parameters, and increased in-hospital mortality. Calculated based on serum albumin levels and lymphocyte counts, the PNI is a practical, accessible, and easy-to-use tool that can aid in predicting outcomes and early identification of patients at higher risk. Its use in the initial assessment of patients can inform clinical decisions and guide the implementation of timely nutritional and therapeutic interventions. Although these results point to potential clinical relevance – reflecting not only nutritional status but also the interaction between malnutrition, inflammation, and immunosuppression, critical factors in the COVID-19 progression – further studies, preferably multicenter and with a greater sample size, are needed to validate these findings and establish their practical applicability.

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