Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is prognostic nutritional index a predictive marker for estimating all-cause in-hospital mortality in COVID-19 patients with cardiovascular risk factors?

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ABSTRACT

Background: This study examined the possible association between the prognostic nutritional index (PNI) and in-hospital mortality rates in cases with a high cardiovascular risk burden and hospitalized with the diagnosis of coronavirus disease 2019 (COVID-19).
Material and Methods: This retrospective and cross-sectional study included 294 COVID-19 patients hospitalized in a tertiary referral pandemic center. The study cohort was grouped into tertiles based on the initial PNI values as T1, T2, and T3. The PNI was calculated for each case and the prognostic value of this index was compared to CURB-65 and 4C mortality risk scores in predicting in-hospital mortality.
Results: Patients stratified into the T1 tertile had a lower lymphocyte count, serum albumin level, and PNI values. In a multivariate analysis, the PNI (OR: 0.688,%95CI: 0.586−0.808, $p < 0.001$) was an independent predictor for all-cause in-hospital death. After adjusting for confounding independent parameters, patients included in the T1 tertile were found to have 11.2 times higher rates of in-hospital mortality compared to the T3 group, which was presumed as the reference group. In addition, we found that the area under curve (AUC) value of PNI was significantly elevated than that of serum albumin level and total lymphocyte counts alone. [(AUC):0.79 vs AUC:0.75 vs AUC:0.69; respectively).
Conclusion: This study demonstrated that the PNI is independently related with in-hospital mortality in patient with COVID-19 and cardiovascular risk factors. The power of the PNI was also validated using well-accepted risk scores of COVID-19 such as CURB-65 and 4C mortality risk scores.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) infection, has been a global pandemic since December 31, 2019.[1] As date of September 22, 2020, the number of confirmed cases worldwide has been reported to be over 30 million people, while the total deaths worldwide have been reported to be approximately 1 million.[1,2] In the majority of cases COVID-19 infection is mild without necessitating hospitalization.[3] However, the disease tends to appear in its more severe form in those with cardiovascular risk factors, including hypertension, diabetes, and smoking.[4] In addition, those patients usually have weakened immunity response and poor nutritional status, which are deemed as important risk factors for acute viral infections, including COVID-19.[5] Thus, early risk stratification using a simple and easily calculated parameter is crucial to reduce the mortality in such kind of patients.

Prognostic nutritional index (PNI) is a derivative of total lymphocyte count and serum albumin that can be accepted as an indicator of nutritional and immune status of patients.[6] Previous studies have shown that lower PNI was related with poor survival in cancer cases following surgery.[7,8] Moreover, the prognostic value of this index has been clearly documented in patients with cardiovascular disease, pulmonary embolism, and stroke.[9–11] However, in the current literature, there is a little data whether the PNI has a prognostic value on in-hospital mortality rates in COVID-19 cases with cardiovascular risk factors. Moreover, there is a lack of data in the literature on the comparison of PNI with other accepted prognostic scores such as CURB-65 and 4C mortality risk scores in predicting in-hospital mortality in COVID-19 patients.[12,13] Thus, in this study, we examined the association between PNI and in-hospital mortality in cases who were

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hospitalized with COVID-19 with a high cardiovascular risk factor burden.

Material and method

Study cohort

The present study was designed cross-sectionally and retrospectively. Firstly, patients who were diagnosed with COVID-19 by real-time PCR testing and hospitalized due to COVID-19 pneumonia between March 2020 and August 2020 were screened from our hospital electronic database. Then, patients with end-stage renal disease requiring peritoneal dialysis or haemodialysis and those who were diagnosed with acute hepatic failure and nephropathy were excluded from the research. In addition, patients with known cardiovascular and peripheral artery disease and those with unknown clinical and laboratory data were not included in the study. After excluding such patients, 294 COVID-19 cases were enrolled in the present study (Fig. 1). Risk factors, such as hypertension, diabetes, and hyperlipidemia, as well as laboratory data were obtained from the hospital's medical database. All of the cases enrolled in our study were managed according to the COVID 19 treatment protocol of Turkish Health Ministry. The research was first registered in the data of Turkish Health Ministry Scientific Research Committee, which was then reviewed and approved by the Local Ethics Committee (approval number: 2020/KK/170−2844). Our study followed the "Good Clinical Practice" guidelines of the Declaration of Helsinki. Since the research had a retrospective design, inform consent was not obtained.

Laboratory analysis

In all of the cases, blood samples were obtained from the antecubital vein on the first day of hospitalization. Immediately after sampling, complete blood count parameters were determined by a hematology analyser (ABX Pentra DX 120). Biochemical parameters were measured by the Roche Cobas Integra 800 (Roche Diagnostic Limited, Switzerland) device. Serum albumin level was determined using the bromocresolgreen method. For each case, the PNI was calculated based on the following formula; PNI = [10xalbumin (mg/dL)] + [0.005xlymphocyte count (per mm^3)].[6]

Study outcome

In this research, the primary outcome was defined as the all-cause in-hospital death during the hospitalization. For each subject, a trained study coordinator evaluated all of the medical electronic files and confirmed the in-hospital death.

Statistical analysis

Initially, the study cohort was grouped into tertiles based on the PNI values as T1, T2, and T3. Each tertile included 98 patients. After

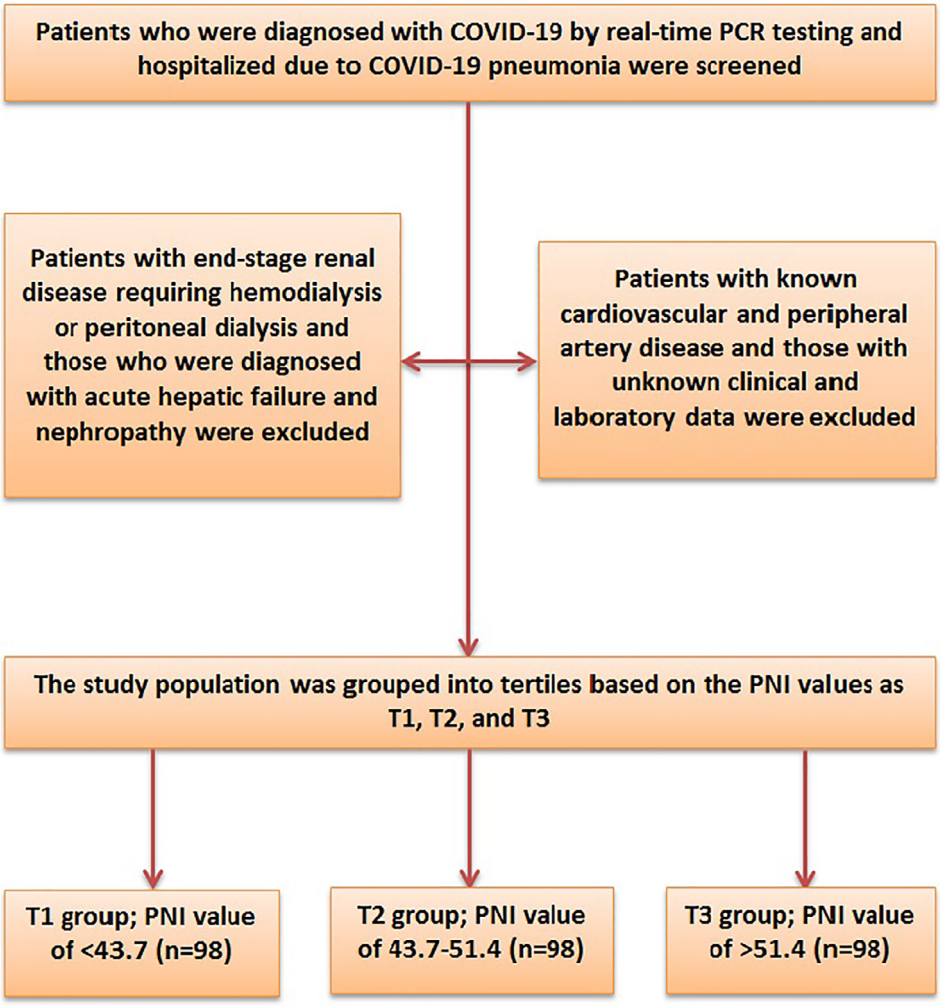

Fig. 1. Flowchart of the enrolled patients.

dividing into tertiles, baseline data and laboratory findings were compared. Mean value ± standard deviation was utilized to present the quantitative variables. Variables demonstrating skewed distributions were analyzed using the Kruskal-Wallis test. Numbers and percentages were utilized to demonstrate all categorical variables. By using Pearson's chi-square test, all categorical parameters were analysed. To determine the predictors of in-hospital death, both univariate and multivariate logistic regression analyses were performed. Parameters that could be a predictor of in-hospital mortality and with a significant p value in Table 1 and Table 2 were included in the univariate analysis. After then, variables with a p value <0.05 in univariate regression were included in the binary logistic regression analysis. Two multivariate models were used: model I; unadjusted and model II; adjusted. The parameters co-variated in the model II were: age, white blood cells count, and D-dimer. Cut-off values of CURB-65, 4C mortality risk score, albumin, lymphocyte count, and PNI with a highest sensitivity and specificity for in-hospital mortality were determined and were analysed by nonparametric receiver-operating characteristics (ROC) curve analysis. Statistical Package for Social Sciences software version 20.0 (SPSS; IBM, Armonk, New York, USA) was used to analyze the data. The goodness of fit of our multivariate analysis model was determined using the Hosmer-Lemeshow test ($\chi 2$ = 8.44, p = 0.184). The power value ($1-\beta$) and effect size (Cohen's d) for PNI, compared between survivors and non-survivors, were calculated using G*Power software (version 3.1.9.2.) The power value and effect size were 0.942 and 0.692, respectively.

Results

The mean age of the study cohort was 55.4 ± 12.8 years. A total of 157 (53.4%) cases were female. The in-hospital death was 10.2% (n = 30 patients) in the study. Patients with a PNI value of < 43.7 (n = 98) were stratified into the T1 group, patients with a PNI value of 43.7–51.4 (n = 98) were stratified into the T2 group, and patients with a PNI value of > 51.4 (n = 98) were stratified into the T3 group.

The baseline demographic properties of all cases are depicted in Table 1. Patients in the T1 tertile were older and most of them were smokers ($p < 0.05$ for each). Also, male gender was more prevalent when compared to those in the T2 and T3 tertiles ($p < 0.05$). Other baseline properties were not different between the tertiles ($p > 0.05$ for each). Regarding the admission symptoms, fever and dyspnea were more frequently observed in patients stratified into the T1 tertile compared to those stratified into the T2 and T3 tertiles ($p < 0.05$ for each). Besides that, patients in the T1 tertile were less likely to be asymptomatic at arrival. Both CURB-65 and 4C mortality risk scores were significantly higher in patients stratified into T1 group.

Table 2 depicts the laboratory findings and infiltrations in the lungs of all of the included cases. Patients stratified into the T1 tertile had a lower lymphocyte count, serum albumin level, and PNI values ($p < 0.05$ for each). However, those patients had higher lactate dehydrogenase (LDH), creatinine, D-dimer and C-reactive protein (CRP) levels ($p < 0.05$ for each). Other laboratory findings were indifferent between the tertiles. In regard to infiltrations in the lungs, patients included in the T1 tertile had a significantly higher chance of having bilateral infiltrations.

According to the univariate analysis, we found that age, male gender, diabetes, chronic obstructive lung disease, chronic renal failure, white blood cell (WBC) count, LDH, creatinine, D-dimer, CRP, and PNI values were associated with the in-hospital mortality (Table 3). These variables were included into the multivariate analysis for determining the independent predictors of in-hospital death. Age (odds ratio [OR]: 1.068,%95, confidence interval [CI]: 1.001–1.140, p = 0.047), WBC count (OR: 1.222,%95, CI: 1.003–1.490, p = 0.047), D-dimer (OR: 1.000,%95, CI: 1.000–1.001, p = 0.041), and PNI (OR: 0.688,%95, CI: 0.586–0.808, $p < 0.001$) were found to be the independent predictors of in-hospital mortality based on the multivariate examination.

In a different analysis using initial PNI values, the patients included in the T1 tertile had 17.2 times higher rates of in-hospital mortality than those in the T3 tertile, which was presumed as a reference group. After adjusting for confounding independent parameters, including age, WBC, and D-dimer, it was found that patients included

Table 1
Baseline clinical characteristics, admission symptoms and mortality risk scores of all cases.

	Prognostic nutritional index			
	T1 (<43.7), (n = 98)	T2 (43.7–51.4), (n = 98)	T3 (>51.4), (n = 98)	P value
Baseline characteristics				
Age, y	62.1 ± 13.2	54.5 ± 12.2	49.7 ± 9.6	<0.001
Male gender, n (%)	66 (67.3)	41 (41.8)	50 (51.0)	0.001
Hypertension, n (%)	70 (71.4)	63 (64.3)	62 (63.3)	0.420
Diabetes mellitus, n (%)	29 (29.6)	25 (25.5)	18 (18.4)	0.181
Insulin dependency, n (%)	8 (8.2)	4 (4.1)	5 (5.1)	0.455
Hyperlipidemia, n (%)	29 (29.6)	18 (18.4)	28 (28.6)	0.137
COPD, n (%)	16 (16.3)	6 (6.3)	12 (12.4)	0.077
CRF, n (%)	7 (7.1)	1 (1.0)	4 (4.1)	0.072
Atrial fibrillation, n (%)	4 (4.1)	3 (3.1)	1 (1.0)	0.367
Dementia, n (%)	4 (4.1)	2 (2.0)	2 (2.0)	0.607
Cancer, n (%)	6 (6.2)	3 (3.1)	1 (1.0)	0.122
Smoking, n (%)	22 (22.4)	22 (22.4)	40 (40.8)	0.005
Alcohol, n (%)	22 (22.4)	10 (10.2)	16 (16.3)	0.064
Admission symptoms				
Fever, n (%)	70 (72.2)	52 (53.1)	42 (42.9)	<0.001
Cough, n (%)	51 (52.6)	54 (55.1)	64 (65.3)	0.162
Dyspnea, n (%)	26 (26.5)	21 (21.4)	10 (10.2)	0.009
Diarrhea, n (%)	5 (5.1)	7 (7.1)	5 (5.1)	0.785
Myalgia, n (%)	33 (33.7)	26 (26.5)	36 (37.1)	0.273
Weakness, n (%)	35 (35.7)	30 (30.6)	25 (25.5)	0.301
Asymptomatic, n (%)	1 (1.0)	11 (11.2)	10 (10.2)	0.003
Mortality risk scores				
CURB-65	3.0 (2.0 – 4.0)	3.0 (2.0 – 4.0)	2.0 (1.0 –3.0)	<0.001
4C mortality risk score	10.0 (7.0 – 13.0)	9.0 (6.0 – 12.0)	5.0 (3.0 – 9.0)	<0.001

Continuous parameters were presented as mean±SD, categorical parameters as number (%).
Abbreviations: COPD indicates chronic obstructive pulmonary disease; CRF indicates chronic renal failure.

Table 2
Laboratory parameters and pneumonia location in the lung of all cases.

	Prognostic nutritional index			
	T1 (<43.7), (*n* = 98)	T2 (43.7–51.4), (*n* = 98)	T3 (>51.4), (*n* = 98)	P value
Laboratory parameters				
White blood cells, cells/μL	7.1 ± 4.1	5.7 ± 2.4	6.1 ± 2.4	0.132
Lymphocytes, cells/μL	0.9 ± 0.5	1.4 ± 0.4	2.0 ± 0.7	<0.001
Platelets, cells/μL	196.9 ± 70.1	201.7 ± 64.5	203.3 ± 64.3	0.434
Hemoglobin, g/dL	12.8 ± 1.8	12.9 ± 1.6	13.0 ± 1.6	0.827
Glucose, mg/dL	116.8 ± 51.1	115.5 ± 48.4	116.0 ± 38.4	0.305
Lactate dehydrogenase, U/L	632.0 ± 552.4	464.7 ± 208.9	419.9 ± 176.0	<0.001
ALT, U/L	36.5 ± 30.5	37.0 ± 40.2	30.6 ± 20.0	0.460
AST, U/L	29.9 ± 23.0	29.0 ± 22.3	24.9 ± 12.4	0.318
Creatinine, mg/dL	1.0 ± 0.4	0.9 ± 0.1	0.9 ± 0.2	0.002
Potassium, mEq/L	4.2 ± 0.4	4.2 ± 0.3	4.2 ± 0.4	0.790
Sodium, mEq/L	136.7 ± 3.6	136.6 ± 3.8	137.1 ± 4.0	0.432
D-dimer, μg/L	1089.9 ± 1579.5	432.8 ± 433.7	360.6 ± 698.2	<0.001
C-reactive protein, mg/dL	5.9 ± 1.1	5.5 ± 1.6	3.4 ± 1.2	<0.001
Albumin, mg/dL	3.2 ± 0.4	4.0 ± 0.3	4.5 ± 0.3	<0.001
Prognostic nutritional index	36.9 ± 5.7	47.2 ± 2.2	55.9 ± 3.8	<0.001
Pneumonia location, n (%)				
Bilateral	77 (78.6)	77 (78.6)	68 (69.4)	0.233
Left	11 (11.2)	6 (6.2)	9 (9.2)	0.451
Right	10 (10.2)	15 (15.3)	21 (21.4)	0.094

Continuous parameters were presented as mean±SD, categorical parameters as number (%).
Abbreviations: ALT indicates alanine aminotransferase; AST indicates aspartate aminotransferase.

Table 3
Univariate predictors and multivariate model for in-hospital mortality.

	Univariate analysis			Multivariate analysis		
	P value	OR	95% CI	P value	OR	95% CI
Age	<0.001	1.119	1.077 – 1.162	0.047	1.068	1.001 – 1.140
Male gender	0.004	3.940	1.560 – 9.951	–	–	–
Diabetes mellitus	<0.001	4.245	1.954 – 9.219	–	–	–
COPD	<0.001	4.958	2.083 – 11.805	–	–	–
CRF	0.001	7.343	2.170 – 24.844	–	–	–
White blood cells	<0.001	1.389	1.248 – 1.545	0.047	1.222	1.003 – 1.490
Lactate dehydrogenase	0.001	1.002	1.001 – 1.004	–	–	–
Creatinine	0.002	6.407	2.005 – 20.479	–	–	–
D-dimer	<0.001	1.001	1.000 – 1.001	0.041	1.000	1.000 – 1.001
C-reactive protein	0.005	1.008	1.002 – 1.013	–	–	–
Prognostic nutritional index	<0.001	0.656	0.571 – 0.754	<0.001	0.688	0.586 – 0.808

CI=confidence interval; OR=odds ratio.
*All clinical relevant parameters were included in the model.
Only parameters that reached statistical significance at univariable analysis were given in the leftmost column.
Abbreviations: COPD indicates chronic obstructive pulmonary disease; CRF indicates chronic renal failure.

in the T1 tertile had 11.2 times higher rates of in-hospital mortality compared to the T3 group. The results of logistic regression models of in-hospital mortality based on PNI values are shown in Table 4.

In ROC analyses, the optimal cut-off value of the PNI in predicting in-hospital survival was > 42.1 with a 81.8% sensitivity and 72% specificity (Area under curve (AUC): 0.79; 95%CI: 0.70–0.88; $p < 0.001$), the optimal cut-off value of serum albumin in predicting in-hospital survival was > 3.55 mg/dL with a 80% sensitivity and 71% specificity (AUC: 0.75; 95%CI: 0.66–0.84; $p < 0.001$), and the optimal cut-off value of lymphocyte count in predicting in-hospital survival was > 0.99 with a 72.5% sensitivity and 65% specificity (AUC: 0.69; 95%CI: 0.61–0.77; $p < 0.001$). It was found that the AUC value of PNI was significantly higher than that of serum albumin level and also lymphocyte counts (Fig. 2). Considering predictive scores, ROC analysis revealed that the optimal value of CURB-65 to predict in-hospital death was >3 with a 70% sensitivity and 80% specificity (AUC: 0.83; 95% CI: 0.76–0.90; $p < 0.001$) and the optimal value of the 4C mortality score to predict in-hospital mortality was >11 with a 83% sensitivity and 78% specificity (AUC: 0.89; 95% CI: 0.84–0.94; $p < 0.001$) (Fig. 3).

Table 4
Logistic regression models for in-hospital mortality by prognostic nutritional index tertiles.

	Prognostic nutritional index		
	T1, (*n* = 98)	T2, (*n* = 98)	T3, (*n* = 98)
In-hospital mortality			
Number of patients	25	4	1
Case rate,%	25.5	4.1	1.0
In-hospital mortality, OR (95% CI)			
Model 1:unadjusted	18.2 (10.2 – 64.1)	3.3 (1.5 – 6.9)	1[Reference]
Model 2: adjusted for all covariates[a]	12.2 (4.4 – 28.1)	1.5 (1.1 – 4.2)	1[Reference]

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Only parameters that reached statistical significance at multivariate analysis were; age, white blood cells and D-dimer.

Discussion

The present study was designed to evaluate the possible relationship between the PNI and all-cause in-hospital mortality in patients hospitalized with COVID-19 disease and who also had multiple cardiovascular risk factors. Our results clearly demonstrated that the PNI

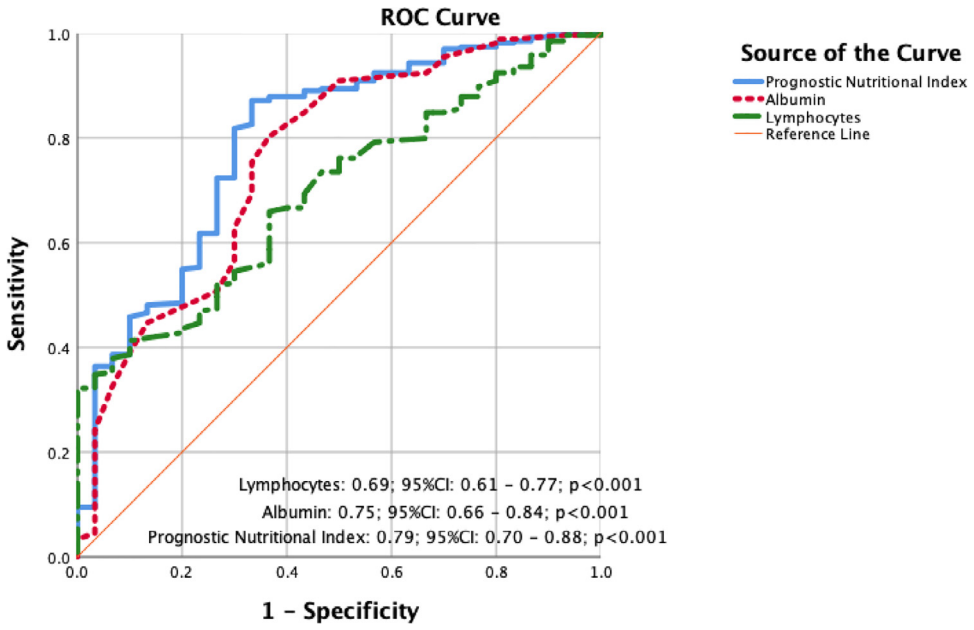

Fig. 2. A receiver operating curve analysis comparison for area under curve values of prognostic nutritional index (PNI), serum albumin, and lymphocytes count.

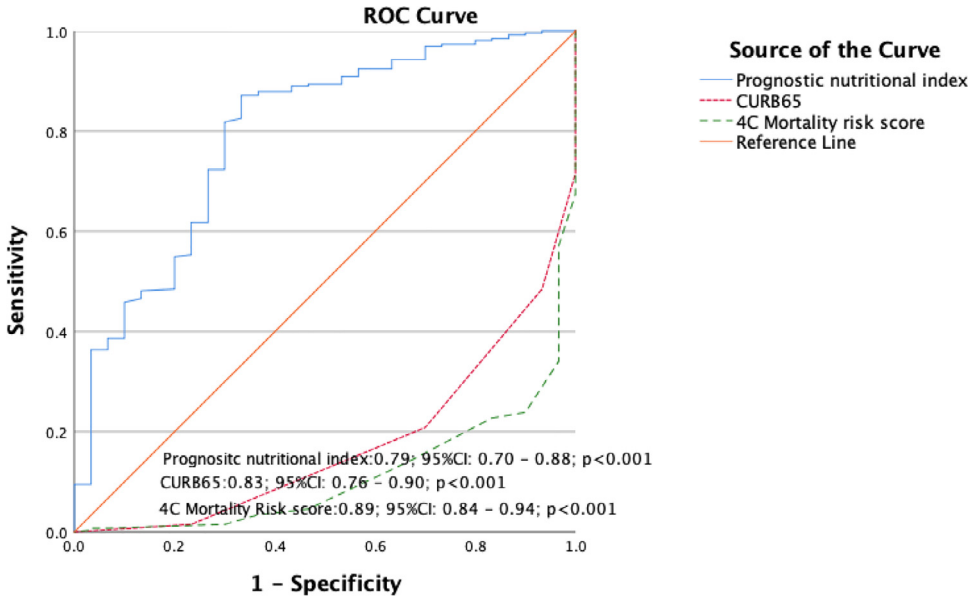

Fig. 3. A receiver operating curve analysis for the comparison of the area under curve values of prognostic nutritional index (PNI), CURB-65 and 4C mortality risk scores.

was an independent predictor of all-cause in-hospital death in such kind of patients. Although only laboratory parameters were included, PNI was found to have a comparable in-hospital prognostic power in COVID-19 patients when compared to the well-designed scores of CURB65 and 4C mortality risk scores.

The COVID-19 disease caused by the SARS-CoV-2 is an ongoing lethal pandemic since the identification of the first cases in Wuhan, China.[1] The COVID-19 disease is usually self-limited in most of the infected patients.[14] However, the infection can rapidly progress to acute respiratory failure, sepsis, and eventually to death, especially in those having cardiovascular disease and poor nutritional status.[3,4] Thus, risk assessment using a simple, useful, and easily accessible parameter plays a key role for not only reducing the mortality but also for appropriate management.

The PNI is measured based on the serum albumin level and lymphocyte counts in the patient population.[6] Serum albumin level is accepted to be a reliable indicator of the liver synthesis function.[15] It also indicates both an increased metabolism rate and nutritional deficiency, particularly in critically ill patients.[15] Studies have clearly shown that lower serum albumin levels were related with higher rates of acute respiratory distress syndrome (ARDS) which was proven to be the most common cause of mortality in COVID-19 cases.[16] Moreover, a recent study has shown that decreased serum albumin levels were related with a more severe disease progression in COVID-19 cases.[17] In addition to serum albumin levels lymphocytes also play a vital role in SARS-CoV-2 infection. Various studies have also demonstrated that lymphocyte counts were closely correlated with the disease progression in patients with COVID-19.[18,19] Several mechanisms have been proposed for the occurrence of lower lymphocyte counts in patients infected with COVID-19 disease. It has been reported that the cytokine storm might have led to a rise in the levels of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), thereby leading in a lymphocyte apoptosis.[20] Moreover, SARS-CoV-2 can directly attack the T lymphocytes with an unknown

mechanism.[21] And lastly, COVID-19 disease may result in the down-regulation of the genes associated with T-cell proliferation.[22] Since lower serum albumin levels and lymphocyte counts are related with higher death rates in COVID-19 patients, the combination of both of these parameters in a single index was assumed to be promising, which was nicely confirmed by the results of our study clearly showing that the PNI had a higher AUC value than that of the serum albumin or lymphocyte counts alone.

The PNI, which can be used as a reflecting marker of the immune and nutritional profile of the patients, has been frequently utilized for the prognostic evaluation of patients with various cancer types who have undergone surgery.[7,8] The predictive power of this index has also been proved to be high in predicting poor prognosis in subjects with coronary artery disease, acute coronary syndrome, and also stroke.[8,11,23] However, in the current literature, there is a gap in evidence whether the PNI has an independent predictive power on determining the in-hospital death in COVID-19 cases with cardiovascular risk factors. Our data clearly yielded that after controlling for confounding factors, the PNI was independently related with in-hospital death in such kind of cases. In the current study, we classified the cases into groups from lower to higher tertiles according to the PNI values. We found that those cases included in the lower tertile had 11.2 times higher rates of in-hospital death compared to those in the higher tertiles.

We believe that our results will have an important clinical impact on the management of such cases. In COVID-19 patients carrying various cardiovascular risk factors, a risk stratification index based on the PNI values can be easily performed at the first medical contact. Moreover, low PNI values detected early may promptly help the clinician to guide and improve the nutritional status of the patients, which will surely lead to a lower mortality due to an improved immune response. Also, patients with various cardiovascular risk factors and lower PNI values on admission may require more aggressive treatment protocols including interleukin alfa inhibitors and immunomodulators for improving the survival rate. Thus, this simple indicator may result in good clinical outcomes when used immediately upon arrival of the patients and should be kept in mind and applied promptly by the brave heart clinicians requiring salute for their hard work.

Limitations

The current study has some limitations. First the data regarding the weight and height of the patients could not be obtained as most of the patients were followed either in the isolation wards or intensive care units. Hence, body mass index (BMI) could not be calculated, and a correlation analysis between the PNI and BMI could not be performed. Second, our dataset was obtained from a single institution; thus, it might not be applicable to other regions. Third, although consecutive patients with the recordings of COVID-19 disease diagnosis were enrolled in the study, there might have been the possibility of selection bias due to the retrospective design of the study. Fourth, subclinical atherosclerotic cardiovascular diseases might have coexisted in some of the COVID-19 cases that might have resulted in poor prognosis. Fifth, relatively small sample size and the lack of ethnic characterization of the study population appeared to be another limitation. As a result, we believe that multi-center studies enrolling more patients are necessary to confirm the results of our research.

Conclusion

The current study has clearly shown that the PNI had an independent prognostic value in predicting in-hospital death in COVID-19 patients with various cardiovascular risk factors. This simple index can easily be utilized for risk assessment and may guide the clinician for appropriate management of such patients.

Declaration of Competing Interest

All authors declare that they do not have conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This article does not contain any studies with animal subjects performed by any of the authors.

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