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CLINICAL RESEARCH

Clinical significance of prognostic nutrition index in hospitalized patients with COVID-19: Results from single-center experience with systematic review and meta-analysis

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Abstract

Background: We aimed to ascertain risk indicators of in-hospital mortality and severity as well as to provide a comprehensive systematic review and meta-analysis to investigate the prognostic significance of the prognostic nutrition index (PNI) as a predictor of adverse outcomes in hospitalized coronavirus disease 2019 (COVID-19) patients.

Methods: In this cross-sectional study, we studied patients with COVID-19 who were referred to our hospital from February 16 to November 1, 2020. Patients with either a real-time reverse-transcriptase polymerase chain reaction test that was positive for COVID-19 or high clinical suspicion based on the World Health Organization (WHO) interim guidance were enrolled. A parallel systematic review/meta-analysis (in PubMed, Embase, and Web of Science) was performed.

Results: A total of 504 hospitalized COVID-19 patients were included in this study, among which 101 (20.04%) patients died during hospitalization, and 372

(73.81%) patients were categorized as severe cases. At a multivariable level, lower PNI, higher lactate dehydrogenase (LDH), and higher D-dimer levels were independent risk indicators of in-hospital mortality. Additionally, patients with a history of diabetes, lower PNI, and higher LDH levels had a higher tendency to develop severe disease. The meta-analysis indicated the PNI as an independent predictor of in-hospital mortality (odds ratio [OR] = 0.80; $P < .001$) and disease severity (OR = 0.78; $P = .009$).

Conclusion: Our results emphasized the predictive value of the PNI in the prognosis of patients with COVID-19, necessitating the implementation of a risk stratification index based on PNI values in hospitalized patients with COVID-19.

KEYWORDS
COVID-19, inflammation, meta-analysis, mortality, patient outcomes, risk indicators

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) has posed tremendous challenges and threats to public health.[1] By May 13, 2021, COVID-19 had affected 161,611,299 people worldwide, resulting in 3,352,944 deaths.[2] From a diagnostic point of view, the complex interplay between the pathogen and the host's immune system, possibly originating from the alterations of both adaptive and innate immune responses, could affect the severity and mortality of COVID-19[3] In this regard, practical prognostication of critically ill patients with COVID-19 may result in optimizing the allocation of healthcare resources.[4,5] However, there still exists a huge gap to achieve the aspirational targets, owing to the lack of standardized methods for early identification of those at higher risk of disease progression.[6] Hence, it is imperative to develop simple and robust methods to stratify the prognosis of patients with COVID-19.

The prognostic nutrition index (PNI) has been proposed as a criterion method for quantifying the immune status, as it consists of easily accessible parameters, including serum albumin level and total lymphocyte count.[7–9] So far, an accumulated number of studies have illustrated the critical role of PNI in predicting clinical outcomes of patients with chronic underlying diseases[7,10,11] In critically ill patients, a low serum albumin concentration is associated with poor outcomes, although this correlation is mostly attributed to the propagated inflammatory state rather than to the nutrition condition.[12] Likewise, lower serum lymphocyte count and hypoalbuminemia are represented as pivotal indicators of detrimental inflammation status and unfavorable outcomes in COVID-19 patients.[13–15] When integrating the effects of both albumin and lymphocyte, it can be intuitive to hypothesize that the PNI could serve as a simplified means of rapid prognosis assessment in COVID-19 patients.[16,17] Consistent with this concept, a recent study demonstrated that the PNI was an essential discrimination indicator for the severity of COVID-19.[16] Additionally, in a study conducted by Çınar et al,[17] the PNI was an independent predictor for in-hospital mortality in patients with COVID-19. Thus, integrating the PNI into the overall therapeutic strategy is of utmost importance given that effective management of patients with COVID-19 necessitates an accurate risk assessment.

Owing to the findings of previous efforts, early risk stratification with an accurate and easily calculated parameter is crucial to prevent the progression of COVID-19.[16,17] However, it seems difficult to arrive at the best evidence-based decision with respect to the current literature, as no prior study had been conducted systematically regarding the impact of the PNI on outcomes and prognosis among COVID-19 patients. In this study, first, we report the results of our patients to investigate the indicators of in-hospital mortality and severity in patients with COVID-19. In addition, a supporting analysis consisting of a systematic review and meta-analysis of studies was performed to ascertain the prognostic effect of the PNI as a predictor of adverse outcomes in COVID-19 patients.

MATERIALS AND METHODS

Ethical considerations

The research complied with the principles of the 1975 Declaration of Helsinki. All participants or their legal guardians gave written informed consent before inclusion in the study. The protocol of this study was approved by

the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.005).

Study design and participants

In this cross-sectional study, we enrolled patients with confirmed or clinically suspected COVID-19 who were admitted to our hospital from February 16 to November 1, 2020. We performed a retrospective study of 504 patients above 18 years of age with confirmed or clinically suspected COVID-19 who fulfilled one of the following criteria: (1) participants with a real-time reverse-transcriptase polymerase chain reaction (PCR) test of endotracheal or oropharyngeal swab that was positive for specimens for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or (2) patients who were highly suspected to have COVID-19 based on the World Health Organization (WHO) interim guidance, encompassing those who had a history compatible with COVID-19 and had ground-glass opacity accompanied by consolidation in chest computed tomography or ground-glass opacity alone, not perfectly elucidated by nodules, lobar collapse, or volume overload.[18]

To ascertain the risk indicators of in-hospital outcomes, patients were accurately divided into two groups for both the severity and in-hospital mortality of COVID-19. It is noteworthy to mention that all patients were treated based on the WHO interim guidance.[18] The demographics and clinical data of patients enrolled in this study were derived from patients' electronic medical records. Patients were appraised regarding demographics, past medical history, admission vital signs, laboratory data, and in-hospital outcomes. Patients' laboratory measurements were examined accurately in the laboratory of our hospital.

Definitions

We measured body mass index (BMI) as weight divided by height squared (kg/m^2). Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a history of antihypertensive treatment.[19] Diabetes mellitus (DM) was determined as one of the following: (1) fasting blood glucose ≥126 mg/dl (7.0 mmol/L) on two occasions, (2) 2-h plasma glucose ≥200 mg/dl (11.1 mmol/L) during the oral glucose tolerance test on two occasions, (3) glycated hemoglobin A_{1c} ≥6.5% (47.5 mmol/mol), (4) a random test of plasma glucose ≥200 mg/dl (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or (5) positive history of antidiabetic medication use, according to the latest American Diabetic Association guidelines.[20] We designated cardiovascular disease as a history of coronary artery disease (stenosis of coronary artery ≥50%), heart failure, or receiving treatment for any of these conditions.

A history of asthma, chronic obstructive pulmonary disease, or interstitial lung disease was characterized as chronic respiratory disease. We characterized chronic kidney disease (CKD) as a renal replacement requirement or a glomerular filtration rate below 30 ml/h. Rheumatologic disease was diagnosed according to the Nomenclature and Classification Committee of the American Rheumatism Association.[21] Malignancy was described as a history of treated neoplasm. Cerebrovascular disease (CVA) was specified as a history of stroke or transient ischemic attack. Current smoking was defined according to the National Health Interview Survey (NHIS) criteria.[22]

We ascertained acute respiratory distress syndrome (ARDS) based on the Berlin definition criteria.[23] Acute kidney injury (AKI) was defined as patients who met one of the following features (except for those with end-stage renal disease): (1) urine volume <0.5 ml/kg/h for 6 h, (2) an increase in serum creatinine to ≥1.5 times baseline within the prior 7 days, or (3) an increase in serum creatinine by ≥0.3 mg/dl (>26.5 μmol/L) within 48 h.[24] We denoted acute liver injury (ALI) as an increase in serum levels of alkaline phosphatase, as total bilirubin more than two units above the upper limit of normal (ULN), or as alanine aminotransferase or aspartate aminotransferase (AST) at least three times the ULN.[25] Acute cardiac injury (ACI) was determined if the serum level of highly sensitive (hs) cardiac troponin I was above the 99th percentile upper reference limit (11 pg/ml for women and 26 pg/ml for men).[26]

Multiple organ dysfunction was diagnosed as patients with at least two complications, encompassing ACI, AKI, ALI, and ARDS. Severe disease was ascertained as patients with one of the following criteria: dyspnea, septic shock, respiratory failure, oxygen saturation ≤93% or >50% lung involvement on imaging, or multiple organ dysfunction/failure. The remaining patients were considered to have nonsevere COVID-19. The aforementioned criteria were determined similar to those in the study by Wu et al and were modified to compare patients with severe vs nonsevere COVID-19.[26] The PNI was calculated according to the following formula: PNI = 10 × serum albumin level (g/dl) + 0.005 × peripheral lymphocyte count (10^9/L).[7]

Systematic review and meta-analysis

The review was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[27] The literature search

was performed in PubMed, Embase, and Web of Science from the date of inception until February 2, 2021, without language or study type restriction, using the keywords ["COVID-19" OR "SARS-CoV-2"] AND ["Prognostic Nutritional Index"]. The detailed search strategy in each electronic database is described in the supplementary material. Secondary source investigations were identified by screening the bibliography of eligible studies, as well as a manual search in Google Scholar.

After removing the duplicate records and irrelevant studies based on title and abstract review, full texts of all the remaining studies were assessed against the eligibility criteria, defined as studies (regardless of language or publication status) in hospitalized COVID-19 patients that assessed the prognostic significance of PNI on at least one of the two main outcomes under the study: (1) in-hospital mortality or (2) disease severity. The severity of COVID-19 was assumed as the definition mentioned earlier or any similar definition.

The following data were extracted from the included studies: study design (retrospective vs prospective), number of centers involved (single-center vs multicenter), number of participants and their demographic features (age, sex, and BMI), PNI categories, and the results regarding the impact of PNI on the in-hospital mortality and severity of COVID-19. The quality of the included studies was evaluated by using the Newcastle-Ottawa scale (NOS).[28] The process of study selection, data extraction, and quality assessment was independently performed by two investigators, and discrepancies were solved by a meeting/discussion.

Statistical analysis

All statistical analyses were conducted using Stata (version 14.2; Stata Corp, College Station, TX, USA), and $P <$ .05 was considered significant. Continuous variables were expressed as mean ± standard deviation and compared using the independent-samples *t*-test. Categorical variables were summarized as counts and percentages and compared by using the chi-squared test. Baseline characteristics, including demographic features, comorbidities, and laboratory variables, alongside PNI were included in the univariate logistic regression to evaluate their association with the mortality and severity of COVID-19. The variables that were significantly correlated with the mortality or severity of COVID-19 were then analyzed in multivariate logistic regression, and the adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated. Ultimately, two prediction models for mortality and severity of COVID-19 were derived based on the parameters independently linked with the predefined outcomes in multivariate analyses. The prediction performance of the derived models, as well as the PNI, was investigated by receiver operating characteristic (ROC) curves and calculation of the sensitivity, specificity, and area under the curve (AUC). The optimal cutoff values of the PNI for predicting mortality and severity of COVID-19 were determined based on the largest Youden index. Based on these cutoff values, the unadjusted and adjusted (for all the covariates previously included in the multivariate analyses) PNI prediction models regarding in-hospital mortality and disease severity were also proposed.

Concerning the meta-analysis, the pooled ORs of the PNI, as a continuous variable adjusted for the main confounding parameters, regarding the in-hospital mortality and severity of COVID-19 were calculated using the random-effects models. The statistical heterogeneity was evaluated by two tests: (1) the Cochran *Q* test, with a *P*-value of <.05 signaling heterogeneity[29] and (2) the Higgins I^2 test (results interpreted as follows: 0%–40%, not important heterogeneity; 30%–60%, moderate heterogeneity; 50%–90%, moderate heterogeneity; 75%–100%, substantial heterogeneity).[30] Publication bias was explored with visual assessment of funnel plots and statistical calculation of Begg test, with a *P*-value of <.05 signifying the presence of publication bias.[31]

RESULTS

Patient characteristics

A total of 504 hospitalized COVID-19 patients were included in this study, among which 101 (20.04%) patients died during the hospitalization, and 372 (73.81%) patients were categorized as severe cases. The diagnosis of COVID-19 was confirmed by PCR test in 339 (67.26%) patients. Table 1 summarizes the demographic characteristics, comorbidities, laboratory data, and clinical outcomes of the study cohort. The mean age of the participants was 60.61 ± 16.92 years, and males accounted for 61.51% (310 of 504) of the patients.

Compared with the survivors, the deceased patients were older (68.86 vs 58.53 years; $P <$ .001), and a higher percentage had hypertension (62.38% vs 45.16%; $P =$ .002), CVA (11.88% vs 4.22%; $P =$ .003), and cardiovascular disease (33.66% vs 23.57%; $P =$ .038). These patients had higher serum levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), AST, creatinine, blood urea nitrogen (BUN), hs-troponin I, and D-dimer and lower levels of lymphocyte count, hemoglobin, and serum albumin. The PNI was significantly lower in the deceased patients (33.99 vs 40.11; $P <$ .001). As expected, adverse clinical outcomes (for example, ARDS, AKI, ACI, intensive care unit [ICU]

TABLE 1 Clinical characteristics of the study population stratified by in-hospital mortality and disease severity

		In-hospital mortality			Disease severity		
	Total patients (n = 504)	**Deceased (n = 101)**	**Nondeceased (n = 403)**	***P*-value**	**Severe (n = 372)**	**Nonsevere (n = 132)**	***P*-value**
Age, years	60.61 ± 16.92	68.86 ± 14.02	58.53 ± 16.96	<.001	61.37 ± 16.24	58.46 ± 18.59	.090
Male sex	310 (61.51%)	67 (66.34%)	243 (60.30%)	.265	219 (58.87%)	91 (68.94%)	.041
BMI, kg/m^2	27.43 ± 4.72	27.70 ± 5.18	27.39 ± 4.65	.668	27.74 ± 4.88	26.57 ± 4.16	.042
Comorbidities							
Hypertension	245 (48.61%)	63 (62.38%)	182 (45.16%)	.002	187 (50.27%)	58 (43.94%)	.211
DM	157 (31.15%)	37 (36.63%)	120 (29.78%)	.183	126 (33.87%)	31 (23.48%)	.027
Cardiovascular disease	129 (25.60%)	34 (33.66%)	95 (23.57%)	.038	98 (26.34%)	31 (23.48%)	.518
Chronic respiratory disease	26 (5.16%)	8 (7.92%)	18 (4.47%)	.160	21 (5.65%)	5 (3.79%)	.407
CKD	29 (5.75%)	6 (5.94%)	23 (5.71%)	.928	22 (5.91%)	7 (5.30%)	.796
Rheumatologic disease	11 (2.18%)	3 (2.97%)	8 (1.99%)	.545	9 (1.42%)	2 (1.52%)	.541
Malignancy	19 (3.77%)	4 (3.96%)	15 (3.72%)	.910	14 (3.76%)	5 (3.79%)	.990
CVA	29 (5.75%)	12 (11.88%)	17 (4.22%)	.003	23 (6.18%)	6 (4.55%)	.488
Current smoking	51 (10.12%)	9 (8.73%)	42 (10.42%)	.653	36 (9.68%)	15 (11.36%)	.581
Laboratory tests							
Leukocytes, ×10^9/L	8.43 ± 5.17	9.06 ± 5.25	8.28 ± 5.14	.175	8.47 ± 4.67	8.32 ± 6.39	.779
Lymphocytes, ×10^9/L	1.20 ± 0.81	1.24 ± 0.81	1.42 ± 0.82	.027	1.16 ± 0.84	1.32 ± 0.72	.055
Hemoglobin, g/dl	13.04 ± 2.38	12.55 ± 2.82	13.16 ± 2.25	.022	13.12 ± 2.32	12.79 ± 2.55	.164
LDH, U/L	713.27 ± 342.11	877.55 ± 466.33	673.40 ± 291.56	<.001	745.28 ± 340.94	621.70 ± 329.96	<.001
CRP, mg/L	76.10 ± 51.11	96.93 ± 50.79	70.91 ± 49.92	<.001	80.29 ± 50.42	64.29 ± 51.40	.002
ESR-1h, mm	58.64 ± 30.88	62.00 ± 31.01	57.79 ± 30.56	.226	60.19 ± 30.47	54.18 ± 31.71	.059
AST, U/L	64.32 ± 43.81	79.62 ± 62.45	60.52 ± 36.93	<.001	67.92 ± 46.24	54.32 ± 34.46	.002
ALT, U/L	52.18 ± 42.26	55.27 ± 55.08	51.41 ± 39.49	.417	54.19 ± 43.47	46.60 ± 38.33	.076
Creatinine, mg/dl	1.50 ± 1.56	1.79 ± 1.81	1.43 ± 1.48	.035	1.50 ± 1.58	1.51 ± 1.50	.961
BUN, mg/dl	24.20 ± 19.36	32.21 ± 24.30	22.19 ± 17.37	<.001	24.43 ± 18.27	23.54 ± 22.19	.650
hs-troponin I, pg/ml	102.97 ± 1055.89	423.39 ± 2421.56	29.92 ± 125.83	.001	130.39 ± 1232.14	28.06 ± 93.29	.350

(Continues)

TABLE 1 (Continued)

	Total patients (n = 504)	In-hospital mortality			Disease severity		
		Deceased (n = 101)	Nondeceased (n = 403)	*P*-value	Severe (n = 372)	Nonsevere (n = 132)	*P*-value
D-dimer, mg/L	1570.46 ± 2099.78	1997.94 ± 3032.35	1348.09 ± 1826.87	<.001	1685.41 ± 2212.87	1244.77 ± 1714.92	.162
Serum albumin level, g/dl	3.28 ± 0.62	2.87 ± 0.71	3.38 ± 0.55	<.001	3.22 ± 0.58	3.45 ± 0.70	<.001
PNI	38.89 ± 7.72	33.99 ± 8.23	40.11 ± 7.05	<.001	38.09 ± 7.40	41.13 ± 8.09	<.001
Clinical outcomes							
ARDS	150 (29.76%)	74 (73.27%)	76 (18.86%)	<.001	146 (39.25%)	4 (3.03%)	<.001
AKI	92 (18.25%)	55 (54.46%)	37 (9.18%)	<.001	78 (20.97%)	14 (10.61%)	.008
ALI	81 (16.07%)	21 (20.79%)	60 (14.89%)	.149	55 (14.78%)	26 (19.70%)	.187
ACI	166 (32.94%)	63 (62.38%)	103 (25.56%)	<.001	135 (36.29%)	31 (23.48%)	.007
ICU admission	104 (20.63%)	74 (73.27%)	30 (7.44%)	<.001	98 (26.34%)	6 (4.55%)	<.001
Mechanical ventilation	72 (14.29%)	63 (62.38%)	9 (2.23%)	<.001	68 (18.28%)	4 (3.03%)	<.001
Length of stay, days	7.85 ± 7.13	10.23 ± 10.58	7.22 ± 5.58	<.001	8.25 ± 7.08	6.64 ± 7.16	.037

Note: Continuous variables are presented as mean ± standard deviation, categorical variables as number (%).

Abbreviations: ACI, acute cardiac injury; AKI, acute kidney injury; ALI, acute liver injury; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, C-reactive protein; CVA, cerebrovascular accident; DM, diabetes mellitus; ESR-1h, erythrocyte sedimentation rate over 1 h; hs-troponin I, highly sensitive troponin I; ICU, intensive care unit; LDH, lactate dehydrogenase; PNI, prognostic nutrition index.

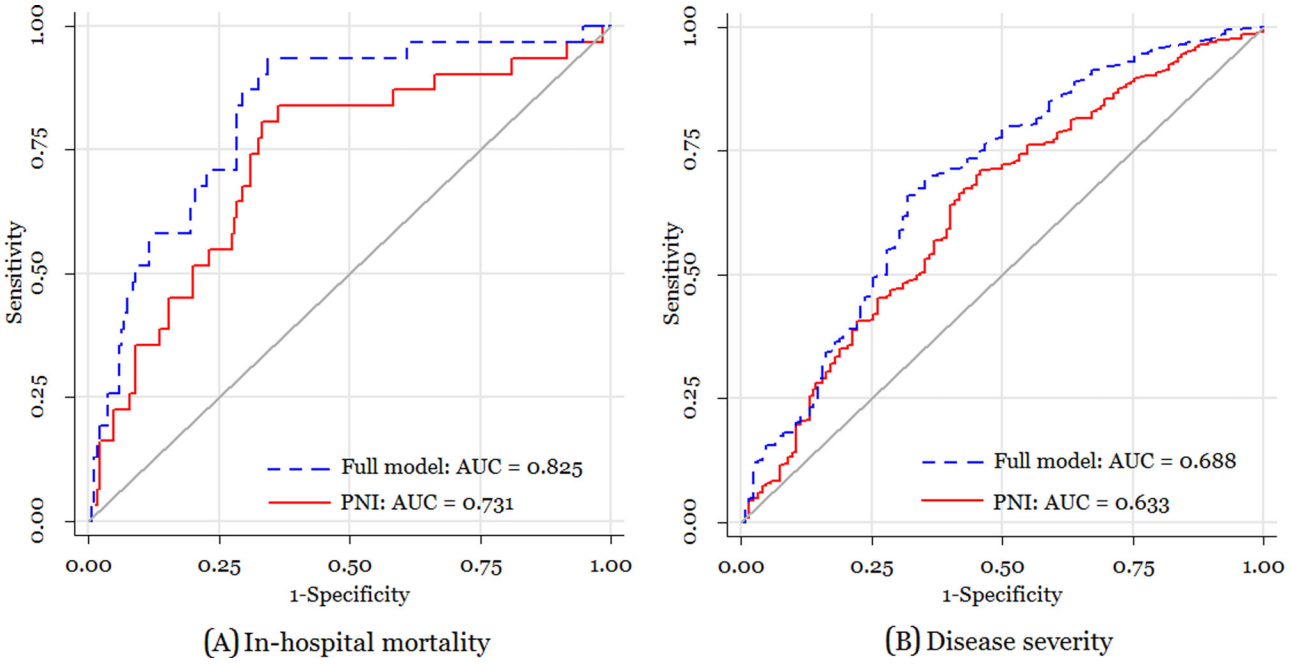

FIGURE 1 Receiver operating characteristic curves for the prediction models and prognostic nutrition index (PNI) regarding (A) in-hospital mortality and (B) disease severity. AUC, area under the curve

admission, and mechanical ventilation) occurred more frequently in the mortality group, and the length of stay was significantly higher in this group (10.23 vs 7.22 days; $P <$ .001) (Table 1).

Regarding disease severity, patients with severe cases had a higher BMI (27.74 vs 26.57 kg/m^2; $P = .042$), and a higher percentage had diabetes (33.87% vs 23.48%; $P =$ .027). These patients included fewer males (58.87% vs 68.94%; $P = .041$) and were more likely to develop ARDS, AKI, and ACI. Moreover, these patients required more ICU admissions, more mechanical ventilation, and a longer duration of hospital stay. Higher levels of LDH, CRP, and AST and lower serum albumin levels were detected in patients with the severe course of the disease. The PNI was significantly lower in the severe cases (38.09 vs 41.13; $P <$ .001).

Prediction models

Twelve variables were significantly associated with in-hospital mortality in univariate analysis: PNI (OR = 0.887, $P < .001$), age (OR = 1.041, $P < .001$), hypertension (OR = 2.013, $P = .002$), cardiovascular disease (OR = 1.645, $P = .039$), CVA (OR = 3.061, $P = .005$), hemoglobin (OR = 0.901, $P = .023$), LDH (OR = 1.001, $P < .001$), CRP (OR = 1.009, $P < .001$), AST (OR = 1.008, $P = .001$), BUN (OR = 1.021, $P < .001$), hs-troponin I (OR = 1.002, $P = .002$), and D-dimer (OR = 1.0002, $P < .001$). Among these variables, three parameters remained significant in multivariate analysis and were included in the final prediction model: PNI (OR = 0.891; 95% CI, 0.822–0.967; $P = .006$), LDH (OR = 1.0017; 95% CI, 1.0003–1.0031; $P = .017$), and D-dimer (OR = 1.0002; 95% CI, 1.0001–1.0004; $P = .044$) (Table 2). This model reached an AUC of 0.825 (Figure 1A).

Concerning the severity of COVID-19, seven predictors were identified in univariate analysis: PNI (OR = 0.948, $P <$ .001), male sex (OR = 0.645, $P = .042$), BMI (OR = 1.059, $P = .043$), DM (OR = 1.668, $P = .028$), LDH (OR = 1.0014, $P = .001$), CRP (OR = 1.006, $P = .002$), and AST (OR = 1.012, $P = .003$). Ultimately, the prediction model for COVID-19 severity consisted of four independent predictors in multivariate analysis: PNI (OR = 0.938; 95% CI, 0.902–0.975; $P =$ .001), male sex (OR = 0.530; 95% CI, 0.291–0.964; $P = .038$), DM (OR = 1.984; 95% CI, 1.067–3.689; $P = .030$), and LDH (OR = 1.0021; 95% CI, 1.0008–1.0035; $P = .002$) (Table 2). The AUC of this prediction model was 0.688 (Figure 1B).

Based on the ROC curve analyses, optimal PNI cutoff values for in-hospital mortality and disease severity were determined as 36.85 and 41.61, respectively. The prediction performance of PNI regarding these two end points is described in Table 3. After adjusting for all the covariates in multivariate analyses, PNI below these cutoff values was significantly correlated with in-hospital mortality (OR = 5.16; 95% CI, 1.69–15.73; $P = .004$) and disease severity (OR = 2.72; 95% CI, 1.54–4.81; $P = .001$).

TABLE 2 Univariate and multivariate logistic regression analysis for the in-hospital mortality and disease severity of COVID-19

	In-hospital mortality						Disease severity					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
PNI	0.887	0.857–0.918	<.001	0.891*	0.822–0.967*	.006*	0.948	0.923–0.974	<.001	0.938*	0.902–0.975*	.001*
Age	1.041	1.026–1.057	<.001	1.018	0.983–1.054	.307	1.010	0.998–1.022	.091	–	–	–
Male sex	1.297	0.820–2.052	.265	–	–	–	0.645	0.422–0.984	.042	0.530*	0.291–0.964*	.038*
BMI	1.014	0.951–1.080	.430	–	–	–	1.059	1.002–1.120	.043	1.031	0.965–1.103	.355
Hypertension	2.013	1.286–3.150	.002	0.758	0.232–2.473	.646	1.289	0.865–1.922	.212	–	–	–
DM	1.363	0.862–2.154	.184	–	–	–	1.668	1.057–2.633	.028	1.984*	1.067–3.689*	.030*
Cardiovascular disease	1.645	1.025–2.639	.039	1.228	0.371–4.056	.736	1.165	0.732–1.853	.518	–	–	–
Chronic respiratory disease	1.840	0.776–4.361	.166	–	–	–	1.519	0.561–4.115	.410	–	–	–
CKD	1.043	0.413–2.634	.928	–	–	–	1.122	0.468–2.691	.796	–	–	–
Rheumatologic disease	1.511	0.393–5.802	.547	–	–	–	1.611	0.343–7.556	.545	–	–	–
Malignancy	1.067	0.346–3.286	.910	–	–	–	0.993	0.350–2.813	.990	–	–	–
CVA	3.061	1.411–6.639	.005	2.102	0.249–17.701	.494	1.384	0.550–3.477	.489	–	–	–
Current smoking	0.840	0.395–1.790	.653	–	–	–	0.835	0.441–1.581	.581	–	–	–
Leukocyte count	1.026	0.987–1.066	.182	–	–	–	1.005	0.966–1.046	.779	–	–	–
Hemoglobin	0.901	0.823–0.985	.023	1.046	0.847–1.293	.671	1.060	0.976–1.151	.165	–	–	–
LDH	1.0010	1.0008–1.0020	<.001	1.0017*	1.0003–1.0031*	.017*	1.0014	1.0006–1.0022	.001	1.0021*	1.0008–1.0035*	.002*
CRP	1.009	1.005–1.014	<.001	1.001	0.992–1.009	.800	1.006	1.002–1.010	.002	1.002	0.996–1.008	.487
ESR-1h	1.004	0.997–1.011	.226	–	–	–	1.006	0.999–1.013	.060	–	–	–
AST	1.008	1.003–1.012	.001	0.999	0.990–1.008	.897	1.012	1.004–1.020	.003	1.008	0.995–1.021	.218
ALT	1.002	0.997–1.006	.420	–	–	–	1.005	0.999–1.011	.083	–	–	–
Creatinine	1.126	0.996–1.273	.057	–	–	–	0.996	0.878–1.131	.962	–	–	–
BUN	1.023	1.012–1.034	<.001	1.027	0.997–1.058	.071	1.002	0.991–1.013	.650	–	–	–
hs-troponin I	1.0020	1.0003–1.0030	.019	0.999	0.997–1.002	.934	1.001	0.999–1.003	.321	–	–	–
D-dimer	1.0002	1.0001–1.0004	<.001	1.0002*	1.0001–1.0004*	.044*	1.0001	0.9999–1.0002	.171	–	–	–

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CVA, cerebrovascular accident; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate over 1 h; hs-troponin I, highly sensitive troponin I; LDH, lactate dehydrogenase; OR, odds ratio; PNI, prognostic nutrition index.
*$P < 0.05$.

TABLE 3 Prediction performance and logistic regression models for in-hospital mortality and disease severity based on PNI cutoff values

	PNI cutoff	AUC	Sensitivity	Specificity	Patients with PNI below the cutoff	PNI prediction models
In-hospital mortality	36.85	0.731	70.29%	69.23%	195 (38.69%)	OR* = 5.32 (95% CI, 3.30–8.57); $P < .001$
						OR** = 5.16 (95% CI, 1.69–15.73); $P = .004$
Disease severity	41.61	0.633	72.31%	53.03%	331 (65.67%)	OR* = 2.94 (95% CI, 1.95–4.44); $P < .001$
						OR** = 2.72 (95% CI, 1.54–4.81); $P = .001$

Abbreviations: AUC, area under the curve; CI, confidence interval; OR, odds ratio; PNI, prognostic nutrition index.
*Unadjusted.
**Adjusted for all the covariates included in the multivariate analyses.

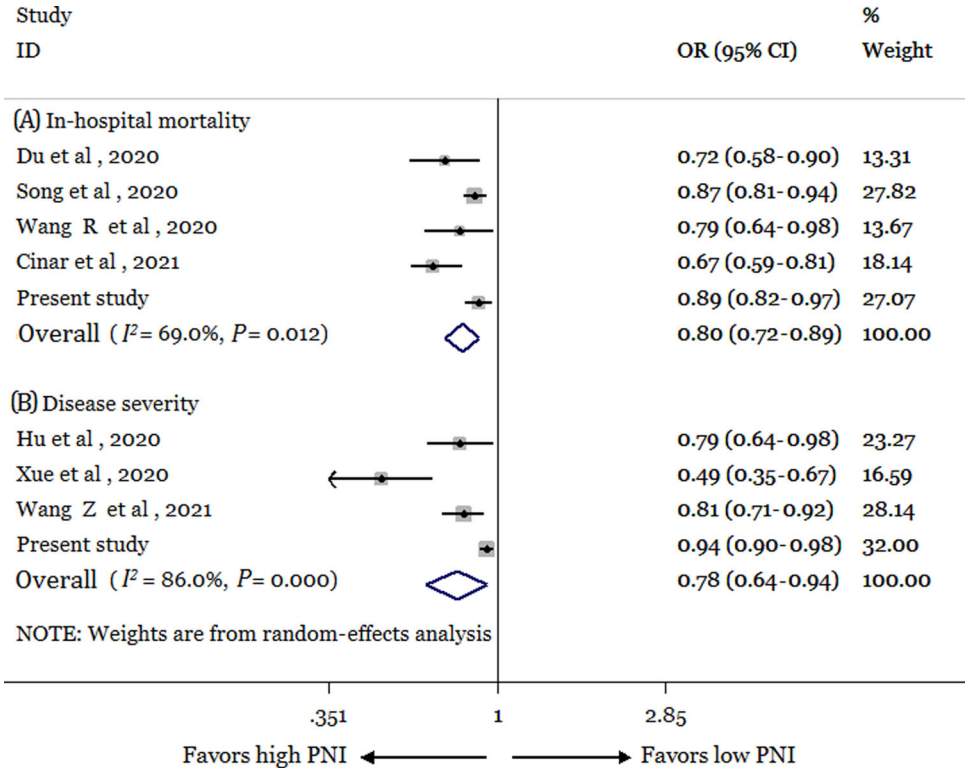

FIGURE 2 Forest plots for pooled odds ratios (ORs) for the prognostic nutrition index (PNI) in the multivariate analysis regarding (A) in-hospital mortality and (B) disease severity

Systematic review and meta-analysis

The search strategy in electronic databases yielded 18 records, and two studies were identified by manual search. After removing the duplicate records and irrelevant studies, nine full-text studies were assessed for eligibility. One study did not provide any data regarding mortality or severity of COVID-19 and therefore was excluded.[32] Finally, eight observational studies, with a total of 2002 patients, were included.[8,16,17,33–37] However, one study did not report the adjusted OR of PNI as a continuous variable[33] and thus was not included in the meta-analysis (Figure S1).

All of the included studies had a retrospective design, and except for one study,[35] all were conducted as single-center investigations. Males accounted for 49.30% (987 of 2002) of the patients. Table S1 presents the characteristics of these studies. Regarding the quality of included studies, the NOS scores were in the range of 6–9 (out of a total of 9 points) (Figure S2).

Alongside our study, four other studies determined the PNI as an independent predictor of in-hospital mortality in COVID-19 patients (n = 1772; pooled OR = 0.80; 95% CI, 0.72–0.89; $P < .001$), with moderate heterogeneity (I^2 = 69.0%, P = .012) (Figure 2A).[8,17,35,36] Similar to our

results, three other studies detected significant association between PNI and severity of COVID-19 after adjusting for major confounding variables (n = 831; pooled OR = 0.78; 95% CI, 0.64–0.94; $P = .009$), with considerable heterogeneity ($I^2 = 86.0\%$, $P < .001$) (Figure 2B).[16,34,37] No significant publication bias was detected regarding in-hospital mortality ($P = .462$) or disease severity ($P = .308$) according to the Begg test (Figure S3).

DISCUSSION

To the best of our knowledge, this is the first study that ascertains risk indicators of in-hospital mortality and severity, as well as providing a comprehensive systematic review and meta-analysis, to investigate the prognostic effect of the PNI as a predictor of adverse outcomes in COVID-19 patients. As we hypothesized, patient groups with higher percentages of comorbidities were at increased risk of mortality and developed more severe COVID-19. After adjusting for possible confounders, lower PNI, higher LDH, and higher D-dimer levels were independent risk indicators of in-hospital mortality. In addition, patients with a history of DM, lower PNI, and higher LDH levels had a higher tendency to develop severe disease. Interpretation of the ROC analysis revealed that the PNI had valuable screening power to determine the prognosis of COVID-19 patients. Moreover, the results of the performed meta-analysis confirmed our findings, representing the PNI as an independent predictor of in-hospital mortality and severity in COVID-19 patients.

Given the significant burden of COVID-19 on healthcare systems, developing efficient strategies for equitably allocating the resources is of utmost importance.[5] In this regard, several clinical models have been designed to stratify the prognosis of patients with COVID-19.[4,5] Knight and colleagues[4] developed the 4C mortality risk score to determine the risk of in-hospital prognosis in patients with COVID-19. Similarly, by applying detailed clinical, biochemical, and radiological parameters, Liang et al[5] created a clinical risk prediction score to stratify the prognosis of critically ill patients with COVID-19. Furthermore, in a recent study on 492 COVID-19 patients, Mei et al[38] designed a validated prognostic model based on age advancing and laboratory biomarkers to determine the clinical prognosis of the disease. Dissecting the described models by previous investigations indicates that most of the included components are based on radiological information or complex laboratory biomarkers, which could limit their applicability. By contrast, the PNI highly relies on two easily measurable parameters without the need for complex parameters.[36] Therefore, it seems that the PNI could serve as a valuable clinical prediction tool, which could facilitate guiding high-risk patients with COVID-19 more effectively.

The first component of the PNI, serum albumin level, is a well-known indicator of protein status in noninflamed patients, but it is not nutritionally informative in an ICU setting, because of its status as a negative acute-phase protein.[12] Although there exists a legitimate debate regarding the accurate function of circulating albumin in critically ill patients, several studies have indicated the essential role of low serum albumin levels in predicting poor outcomes.[39,40] A previous study by Yin et al[39] on patients in the ICU of a tertiary hospital indicated that low serum albumin level was an independent predictor of mortality. Another study by Villota and colleagues[40] on 214 ICU-admitted patients illustrated that lower serum albumin levels were associated with increased risk of mortality ($P < .05$). Of note, studies have represented that correcting hypoalbuminemia could not improve the outcome of those with critical illness.[12,41] Therefore, these findings indicate that hypoalbuminemia can act as a prognostic rather than a therapeutic factor in critically ill patients.

In parallel with other infectious diseases, the propagation of cytokine storm has been blamed as the essential culprit for the disease progression in COVID-19 patients.[3] In this respect, hypoalbuminemia is a indicator of detrimental inflammation status and unfavorable outcomes in these patients.[13] In our study, the serum albumin level was significantly lower in deceased patients as well as in those with severe disease. Our observation agrees with a previous meta-analysis study that indicated an increased risk of severe COVID-19 in patients with hypoalbuminemia (OR = 12.6; $P < .001$).[13] Similarly, according to a study conducted by Wong et al,[42] the pooled risk of hypoalbuminemia was higher in patients with severe and critical COVID-19 compared with others. The pathophysiology of low serum albumin levels in patients with COVID-19 could be justified as follows. First, SARS-CoV-2 gains entry to human cells by binding its spike to the angiotensin-converting enzyme 2 (ACE2) receptor, leading to a subsequent response of the immune system. With the production of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), the virus inhibits the transcription rate of albumin messenger ribonucleic acid (mRNA) and the synthesis ability of hepatocytes, leading to a decrease in serum albumin level.[12,15] In addition, the albumin distribution between extravascular and intravascular compartments is changed during the acute phase of critical diseases.[12] Investigating the essential contributors to the altered distribution pattern reveals that releasing a large amount of cytokines, arachidonic acid metabolites, complement components, chemokines, and other vasoactive peptides

could cause an increase in capillary leakage, leading to a decrease in circulating serum albumin concentrations.[12] Consequently, lower serum albumin levels are linked with the development of ARDS and pulmonary edema, indicating a necessity for more precise care toward the serum albumin levels among patients with COVID-19.[36]

As another essential component of PNI, we found a remarkably lower lymphocyte count in the deceased group compared with surviving patients. In support of this concept, in a meta-analysis on 22 studies, severe lymphopenia was associated with 12-fold increased odds of in-hospital mortality in COVID-19 patients.[14] Likewise, Zhao et al[43] indicated that patients with lymphopenia tended to have higher risks of severe COVID-19 (OR = 2.99; 95% CI, 1.31–6.82). It has been postulated that SARS-CoV-2 mediates its effects on the immune system through multiple pathways. First, the direct invasion of the virus to lymphocytes, along with the excessive release of cytokines, could induce apoptosis of lymphocytes.[44] Second, the induced pyroptosis of hematological stem cells could result in a decrease in lymphocyte count.[44] In addition, by triggering autophagy- and antibody-mediated death of infected lymphocytes, COVID-19 could lower the peripheral lymphocyte count.[44] Hence, these findings suggest that decreased lymphocyte count might have an essential prognostic value in patients with COVID-19. Taken together, as a combination of both serum albumin levels and peripheral lymphocyte count, the PNI illustrates the immune-inflammatory status of COVID-19 patients more comprehensively.

To more accurately ascertain the impact of the PNI per se on the prognosis of COVID-19, the effects of confounder factors were eliminated, representing that the PNI was an independent indicator of in-hospital mortality and severity in COVID-19 patients. Consistent with this concept, Doganci and colleagues[33] divided COVID-19 patients into two groups regarding the median of the PNI, indicating that patients in the low-risk group were at increased risk of in-hospital mortality (unadjusted OR = 18.57; $P < .05$). Identically, in the study by Wang et al,[36] the PNI was an independent risk factor for in-hospital mortality in patients with COVID-19 (OR = 0.79; $P = .029$). In light of COVID-19 severity, a recent study on 101 COVID-19 patients demonstrated the PNI as an independent risk factor for critical disease (OR = 0.81; $P = .002$).[16] Likewise, Hu and colleagues[34] indicated that the PNI was inversely associated with the severity of COVID-19 (OR = 0.797; $P = .030$). Of note, the most challenging part of these findings could be the diversity that exists among different studies with respect to the definition of COVID-19 severity, although these results still provide comprehensive evidence that the PNI exerts a pivotal role in the prognosis of COVID-19.

As a key insight from this study, the ROC analysis revealed that the PNI could serve as an insightful predictor of in-hospital mortality and disease severity in COVID-19 patients. Additionally, we found that the PNI below these cutoff values was remarkably associated with in-hospital mortality and disease severity. Similar to our findings, Cınar and colleagues[17] divided COVID-19 patients into three groups regarding the PNI tertiles and indicated 11.2 times higher rates of in-hospital mortality in the lowest tertile compared with the highest tertile. In addition, they reported notably higher screening power of PNI in predicting in-hospital survival compared with serum albumin level and lymphocyte counts alone. Overall, even though this is an observational study with its inherent biases, it supports the statement that the PNI measurement could be integrated into the overall therapeutic strategy to more accurately guide COVID-19 management.

Most notably, a distinctive feature of this study is that we conducted a systematic review and meta-analysis of studies to substantiate our analysis. Our findings provide robust evidence that the PNI serves as an independent predictor of in-hospital mortality and disease severity in patients with COVID-19. Indeed, the interpretation of the meta-analysis revealed that a per-point increase in the PNI was associated with a 22% and 20% decrease in the risk of in-hospital mortality and disease severity, respectively. Accordingly, these results indicate that the PNI should be applied promptly by clinicians to achieve the aspirational goals in the management of hospitalized patients with COVID-19.

Drawing from the results of the multivariate logistic regression analysis, we found that LDH, D-dimer, and DM were other significant indicators of in-hospital mortality and severity. The increased level of LDH is a reflection of tissue injury, which in turn contributes to human immunosuppression.[45] We found that higher levels of LDH were independently associated with both in-hospital mortality and severity, which is in line with a recent pooled analysis indicating that an elevated level of LDH is associated with 6- and 16-fold increased odds of disease severity and mortality of COVID-19.[45] In terms of D-dimer levels, our results are in agreement with those of Gungor et al,[46] who found that elevated D-dimer level was associated with higher risks of mortality and severity. Possible explanations for the hypercoagulable state in COVID-19 could be the excess production of inflammatory cytokines, stimulation of cell-death mechanisms, and vascular endothelial damages.[46] So far, several studies have narrowed the path, linking DM with COVID-19 progression.[47,48] The significant association of DM with COVID-19 severity in our study is similar to the results of a pooled analysis, which demonstrated that patients with DM had significantly higher risks of disease

severity and mortality.[47] Across sex disparity, Galbadage and colleagues[49] indicated male sex as an essential risk factor for COVID-19 progression. By contrast, we found that the male group had notably lower severe disease compared with the female group. The finding of our study could be due to the higher rates of CKD in the female group compared with the male group (8.25% vs 4.19%, $P = .057$), although other characteristics and comorbidities were almost similar between the females and males in our cohort of patients. Taken together, our prognostic model regarding the susceptibility for developing severe disease and in-hospital mortality could objectively reflect the inflammatory status of patients with COVID-19. Strikingly, our model is nearly consistent with the findings of Violi et al,[50] who found an association between hypoalbuminemia and hypercoagulability in patients with COVID-19. Given that fostering an effective strategy to mitigate the burden of COVID-19 necessitates a suitable adjustment of effective strategies, our findings could have an important clinical impact on the management of patients with COVID-19.

Strengths and limitations

We would like to emphasize the essential strengths of our study. To the best of our knowledge, this is the first study that provides a comprehensive systematic review and meta-analysis to investigate the prognostic effect of the PNI in patients with COVID-19. In addition, compared with previous studies that have evaluated the impact of PNI on the prognosis of COVID-19 patients, we included a higher number of patients, providing a robust metric for applying the PNI as a risk stratification index. Furthermore, our prognostic model regarding the susceptibility for developing severe disease and in-hospital mortality could comprehensively reflect the inflammatory status of patients with COVID-19. The present study was subject to a number of potential limitations. First, we could not accurately assess the causal association between the PNI and COVID-19 progression, because of the cross-sectional design of the study, although a supporting meta-analysis could provide some additional information in this regard. Second, it is a single-center observational study; thus, further longitudinal multicenter studies should be performed to confirm these results more accurately. Third, as serum albumin level might be affected by other pathological conditions rather than COVID-19, serum albumin level as a prognostic indicator should be used with caution. Also, the meta-analysis might have some limitations. Because of the diversity in the nutrition assessment methods, we were able to include a limited number of investigations focusing on this topic. Therefore, interpretation of the meta-analysis findings should be considered carefully in light of possible bias.

CONCLUSIONS

All in all, owing to the huge burden of COVID-19 on healthcare systems, it seems crucial to endorse an early pragmatic strategy for stratifying the prognosis of COVID-19 patients. We revealed that lower PNI, higher LDH, and higher D-dimer levels were independent risk indicators of in-hospital mortality. Furthermore, patients with a history of diabetes, lower PNI, and higher LDH levels had a higher tendency to develop severe disease. Noticeably, results of the meta-analysis illustrated that the PNI was an independent predictor of in-hospital mortality and disease severity. Without the need to employ complex parameters, our analysis, along with the result of the meta-analysis, emphasized the predictive value of the PNI in the prognosis of patients with COVID-19. Hence, we urge clinicians to implement a risk stratification index based on PNI values to appraise prognosis in hospitalized patients with COVID-19.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Sina Rashedi, Mohammad Keykhaei, Marzieh Pazoki, Haleh Ashraf, and Mahnaz Montazeri equally contributed to the conception and design of the research; Marzieh Pazoki, Haleh Ashraf, and Atabak Najafi contributed to the design of the research; Samira Kafan, Niloufar Peirovi, and Farhad Najmeddin contributed to the acquisition and analysis of the data; Seyed Aboozar Jazayeri, Mehdi Kashani, and Reza Shariat Moharari contributed to the interpretation of the data; and Sina Rashedi, Mohammad Keykhaei, Marzieh Pazoki, Haleh Ashraf, Atabak Najafi, Samira Kafan, Niloofar Peirovi, Farhad Najmeddin, Seyed Aboozar Jazayeri, Mehdi Kashani, Reza Shariat Moharari, and Mahnaz Montazeri drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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