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Research Article / Araştırma

Is It Possible to Use Prognostic Nutrition Index to Predict Mortality of ICU COVID-19 Patients?

Yoğun Bakım Ünitelerinde COVID-19 Hastalarının Mortalitesini Öngörmek İçin Prognostik Beslenme İndeksini Kullanmak Mümkün mü?

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ABSTRACT

Objectives: The prognostic nutrition index (PNI), as an indicator of inflammation and immunity, is calculated by "serum albumin (g/L)+5×lymphocyte count (109/L)." A lower PNI could determine a poor prognosis. Recent publications showed that lower albumin levels are correlated with an increased mortality to the coronavirus disease 2019 (COVID-19). This research aimed to determine the PNIs predictive value of mortality at intensive care units (ICUs) in patients with COVID-19.

Methods: In this retrospective one-centered research, 391 patients with COVID-19 followed up at ICU included in the study. Demographic data, comorbidities, thorax computed tomography, polymerase chain reaction results, length of stay, and laboratory results were collected and statistically analyzed.

Results: Data from 306 patients were analyzed. Older age (>65-years-old), hypertension, and cardiac diseases were found to be risk factors. Higher Acute Physiologic Assessment and Chronic Health Evaluation II scores were associated with increased mortality. Increased procalcitonin, creatinine, aspartate aminotransferases, lactate dehydrogenases, white blood cell count, D-dimer, fibrinogen, ferritin, brain-natriüretic peptide, and calcitonin-related peptide were related to mortality. Lower PNI scores were noted as indicators of mortality and prognosis.

Conclusion: Lower PNI scores indicate increased mortality and the length of stay in patients in the ICU. PNI scores could be useful in predicting the prognosis of patients with COVID-19.

Keywords: Biomarkers, COVID-19, prognosis, prognostic nutritional index

ÖZ

Amaç: Bağışıklık ve inflamatuvar durumun ortak belirteci olan prognostik beslenme indeksi (PNI), "serum albumini (g/L)+5×lenfosit sayısı (109/L)" formülü ile hesaplanır. PNI düşüklüğü hastaların kötü prognozuna işaret edebilir. Koronavirüs hastalığı (COVID-19) olan hastalarla yapılan çalışmalarda da düşük serum albumin düzeylerinin artmış mortalite ile ilişkili olduğu bulunmuştur. Bu çalışmada, PNI skorlarının yoğun bakım ünitelerinde yatan COVID-19 hastalarının mortalitesini takip etme etkinliği araştırılmaktır.

Yöntem: Tek merkezli ve retrospektif olarak yapılan bu çalışmaya yoğun bakımda tedavi edilmiş 391 COVID-19 hastası dahil edildi. Hastaların demografik verileri, komorbiditeleri, toraks bilgisayarlı tomografi değerlendirmeleri, polimeraz zincir reaksiyonu sonuçları, yatış süreleri ve laboratuvar değerleri kaydedildi.

Bulgular: Çalışmada 306 hastanın verileri değerlendirildi. İleri yaş (>65 yaş), hipertansiyon ve kalp hastalığı risk faktörü olarak anlamlı bulundu. APACHE II skorlarının yüksekliği artmış mortalite ile ilişkili değerlendirildi. Prokalsitonin, kreatinin, aspartat aminotransferaz, laktat dehidrogenaz, beyaz küre, D-dimer, ferritin, fibrinojen, beyin natriüretik peptidi (BNP) ve C-reaktif protein (CRP) yüksekliği artmış mortalite ile ilişkilendirildi. PNI skorlarının düşüklüğü mortalite açısından prognostik faktör olarak değerlendirildi.

Sonuç: Düşük PNI skorları, yoğun bakımdaki hastalarda mortalite ve kalış süresinin arttığını gösterir. PNI skorları, COVID-19 hastalarının prognozunu tahmin etmede faydalı olabilir.

Anahtar sözcükler: Biyobelirteçler, COVID-19, prognostik beslenme indeksi, prognoz

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Introduction

The coronavirus disease (COVID-19) occurs across the world on a large scale and can cause an asymptomatic infection, respiratory failure, and even death.[1] The agent pathogen of the disease is SARS-CoV-2, and mortality rates of its clinical presentation have ranged from 1% to 28.3% in different studies.[2] It has been shown that SARS-CoV-2 has the ability of human-to-human transmission, and its course is more severe in those with advanced age, hypertension (HT), diabetes mellitus (DM), cardiovascular disease (CVD), etc.[3]

Determining reliable and easily presumable predictors of COVID-19, which has become an important global public health problem, will be essential for planning follow-ups and treatment. In particular, albumin, lymphocyte, thrombocyte, aminotransferase, total bilirubin, D-dimer, C-reaktif protein (CRP), cardiac troponin, creatinine, prothrombin time (PT), and procalcitonin (PCT) values and the erythrocyte sedimentation rate stands out as markers to follow in terms of prognosis and determining the severity of the infection as well.[4]

The prognostic nutrition index (PNI), which evaluates nutritional and inflammatory statuses together, is calculated with the formula "serum albumin (g/L)+5×lymphocyte count (109/L)." The prognostic value of three PNIs has been proven for clinical conditions such as CVDs, infectious diseases, and cancer. A low PNI, which includes the effects of both lymphocytes and albumin, may indicate a poor prognosis in patients.

Studies of COVID-19 patients suggest that low serum albumin and lymphocyte levels are associated with an increased risk of mortality.[2]

In this study, our aim is to investigate whether some serological tests, especially the PNI, can be used to predict the length of stay and mortality of COVID-19 patients hospitalized in intensive care units (ICUs).

Methods

In the study, we examined 391 patients over the age of 18 with positive COVID-19 polymerase chain reaction (PCR) test results who were treated in Anesthesiology and Reanimation ICUs due to COVID-19 pneumonia between September 2020 and December 2020, and 85 of them were excluded because of missing data. The other 306 patients were evaluated as eligible for our study. The study was planned as a single-center registry study. Approval from the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee was obtained (Ethics Committee No: 30.11.2020, 99/11) for the study, and it was done in accordance with the Declaration of Helsinki.

The demographic data, clinical data, and laboratory results of the patients included for the study were scanned in the electronic medical record system, and those results were added to the cumulative data obtained from patient forms. It was recorded whether the patients had HT, cardiovascular system disease, chronic respiratory system disease, or cancer. Patients' chest X-ray/thorax CT evaluations, PCR results, length of stay, respiratory support requirements during hospitalization (O_2 need with mask, HFNO need, CPAP need, and IMV need), discharge status (discharged with cure/O_2 dependent/exitus), and the length of stay in the ICU were examined.

Laboratory test results were recorded on the patients' first admission and then weekly throughout their hospitalization. The PNI was calculated with the formula "serum albumin (g/L)+5×lymphocyte count (109/L)."

Statistical Analysis

In this study, the data were analyzed in the IBM SPSS 23.0 statistical program. Since continuous variables did not show normal distribution, the median and range of distribution and the number and percentage of patients for categorical variables were calculated as descriptive statistics. Continuous variables were compared according to the discharge type of patients (exitus, other [Discharged, O_2 dependent]) and the Mann-Whitney U-test, while categorical variables were compared using the Chi-square test. Variables that have an effect on hospitalization time and the patient discharge pattern were studied using Cox regression analysis, and survival probabilities were evaluated using the Kaplan-Meier method. Variables affecting the output pattern of patients were evaluated with the binary logistic regression model, and odds ratios were calculated. For the two-sided test, $p<0.05$ was considered statistically significant.

To predict the probability of mortality COVID-19 patients in ICUs, PNI values were examined according to the patients' discharge status from the ICU (exitus or service/home). According to the Mann-Whitney U-test, which was used to examine whether the PNI values were different, the effect size was 0.7632, the sample size ratio was 0.794, the type 1 error was 0.05, and the study's power under the two-sided test was 0.999.

Results

Initially, 391 patients were included in the study, but analyses were performed on 306 patients due to missing data. Of the patients included in the study, 167 (54.4%) were male and 139 (45.3%) were female. The ages of the patients ranged from 19 to 95 with a mean age of 69.68±12.69 standard deviation.

Table 1. Demographic parameters and comorbidities of the patients included in the study

Variables	All patients			Survival			Death			p□
	n	n	%	n	n	%	n	n	%	
Gender (Male)	306	167	54.6	136	73	53.7	170	94	55.3	0.778
Hypertension	305	200	65.6	136	81	59.6	169	119	70.4	0.047*
Diabetes	304	114	37.5	135	46	34.1	169	68	40.2	0.270
Cardiovascular disease	306	91	29.7	136	29	21.3	170	62	36.5	0.004*
Asthma	305	17	5.6	136	8	5.9	169	9	5.3	0.833
COPD	305	43	14.1	136	16	11.8	169	27	16.0	0.293
CKD	305	29	9.5	136	8	5.9	169	21	2.4	0.053
Rheumatic disease	305	10	3.3	135	3	2.2	170	7	4.1	0.356
Cerebrovascular disease	306	22	7.2	136	6	4.4	170	16	9.4	0.092
Malignancy	305	22	7.2	136	6	4.4	169	16	9.5	0.090
Other	306	1	0.3	136	1	0.7	170	0	0.0	-

COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; □: Chi-Square test, *: p<0.05.

Of the patients included in the study, 65.4% had HT, 37.3% had DM, 29.7% had cardiovascular system disease (CVS), 19.6% had respiratory system diseases, and 9.5% had end-stage renal disease (RF). HT and CVS diseases were found to be risk factors for mortality (Table 1).

The mean age of the 136 patients discharged from the ICU was 67.29±13.88, and the mean age of the 170 patients who died in the ICU was 71.57±11.36. The mean age of patients who died was statistically significantly older than those who were discharged (p<0.05).

There was a statistically significant difference between the two groups of patients in terms of the Acute Physiology and Chronic Health Evaluation II scores recorded within the first 24 hours after hospitalization in the ICU and the length of stay in the ICU (Table 2).

The mean ICU stay was 7 days (Table 2). In the Kaplan-Meier analysis, the median survival time of the patients was calculated as 11 days (95% CI: 9.55-12.45). Although there was a negative correlation between the length of stay in the ICU and the PNI, the difference was not statistically significant (Spearman rho=-0.065, p=0.261).

There was no statistically significant difference between the hemoglobin, alanine aminotransferase, and total protein values of the deceased and surviving patients (p>0.05). According to the laboratory results, there was a statistically significant difference between creatinine, aspartate aminotransferase, PCT, lactate dehydrogenase, white blood cell count, neutrophil count, lymphocyte count, platelet count, INR, PT, and activated partial thromboplastin time levels (p<0.001).

A statistically significant difference was found between the two groups of patients in terms of albumin and lymphocyte values, and ferritin, C-reactive protein (CRP), brain-derived natriuretic peptide (BNP), and D-dimer values (p<0.001) (Table 2).

This study determined that mortality was higher in COVID-19 patients who had a low PNI value and were in the ICU. The cutoff point for the PNI was calculated as 34,075 (AUC=0.689, St. Error=0.030, p<0.001, and 95% CI: 0.63-0.75) (Fig. 1).

This study found a negative correlation between PNI value and mortality and a positive correlation between ferritin, BNP and D-dimer values, and mortality (Table 3).

Discussion

This study shows that the PNI can be used to predict the mortality of COVID-19 patients in the ICU. The cutoff point for the PNI was set at 34,075. Patients with low PNI levels in the ICU have increased mortality rates. Our study also found that certain laboratory findings, such as high levels of ferritin, BNP, and D-dimer, may indicate an increased risk of mortality. Those findings have a significant correlation with the previous studies.[2,3]

Since the beginning of the COVID-19 pandemic, markers such as age, comorbidities, lymphopenia, D-dimer, and troponin I have been used in the follow-up and prognosis of patients.[2] Other studies used different laboratory parameters and found that values such as the neutrophil/lymphocyte, CRP-pre-albumin, and CRP-albumin ratios could be used to determine the severity of the disease.[5]

The PNI is easily calculated with the formula "serum albumin (g/L)+5×lymphocyte count (109/L)" and is used as a prognostic marker for systemic inflammatory response syndrome, malignancies, and infectious diseases.[5]

Table 2. Age, APACHE score, length of stay in ICU and laboratory findings analyzes of the patients included in the study

Variables	All patients		Survival		Death		p□
	n	Median (Range)	n	Median (Range)	n	Median (Range)	
Age (years)	305	71 (76)	135	68 (76)	170	73 (58)	0.004*
APACHE score	276	16 (40)	123	14 (32)	153	18 (36)	<0.001*
ICU stay (day)	306	7 (40)	136	8 (40)	170	6 (36)	<0.001*
Laboratory findings							
Procalsitonin (mcg/L)	306	0.29 (77.98)	136	0.09 (41.63)	170	0.83 (77.97)	<0.001*
Creatinine serum (mg/L)	306	0.96 (21.05)	136	0.73 (4.68)	170	1.34 (21.05)	<0.001*
AST (U/L)	306	37 (1000)	136	28 (585)	170	43 (1000)	<0.001*
ALT (U/L)	305	33.20 (746)	136	37 (603)	169	30 (746)	0.258
LDH (U/L)	304	472.5 (3681)	136	327.5 (1299)	168	642.5(3662)	<0.001*
WBC ($\times10^9$ /L)	305	10.06 (54.37)	136	8.58 (51.25)	169	11.50 (46.32)	<0.001*
NEU ($\times10^9$ /L)	306	8.58 (42.48)	136	6.97 (19.52)	170	10.53 (42.48)	<0.001*
LYM ($\times10^9$ /L)	305	0.70 (4.38)	135	0.97 (3.49)	170	0.52 (4.38)	<0.001*
RDW (%)	306	14.60 (21.70)	136	14.03 (21.7)	170	15.10 (11.60)	<0.001*
MPV (fL)	304	10.75 (6.7)	135	10.40 (4.5)	169	11.10 (6.4)	<0.001*
Hemoglobin (g/L)	306	11.90 (10.2)	136	12.20 (9.0)	170	11.70 (10.2)	0.094
Platelet ($\times10^9$ /L)	306	224 (621.3)	136	269 (568)	170	203 (445.3)	<0.001*
INR	306	1.15 (8.89)	136	1.12 (8.89)	170	1.19 (7.16)	<0.001*
PT (s)	306	10.5 (83.82)	136	10.10 (66.52)	170	10.90 (76.36)	<0.001*
APTT (s)	305	34.60 (69.90)	135	30 (44.90)	170	37.85 (66.30)	<0.001*
D-dimer (ng/mL)	306	1.46 (20.74)	136	1.02 (11.87)	170	2.82 (20.64)	<0.001*
Ferritin (ng/mL)	304	621 (18173.3)	136	459.5 (2611.3)	168	880 (18149.2)	<0.001*
CRP (mg/L)	306	64.35 (394.64)	136	22.65 (273.42)	170	108.50 (394.02)	<0.001*
BNP (ng/L)	306	836 (34989.09)	136	348.4 (34989.09)	170	2059.50 (34988.05)	<0.001*
Total protein (g/L)	302	56.90 (45.3)	132	57 (31.8)	170	56 (45.3)	0.087
Albumin (g/L)	306	30 (27.5)	136	30.45 (21.0)	170	29 (25.8)	<0.001*
Fibrinogen (g/L)	306	469.5 (1149)	136	412.5 (679)	170	500 (1149)	<0.001*

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactic dehidrogenase; WBC: White blood cells; NEU: Neutrophil; LYM: Lymphocyte; RDW: Red cell volume distribution width; MPV: Mean platelet volüme; INR: International normalized ratio; PT: Prothrombin time; APTT: Activated partial thromboplastin times; CRP: C-reactive protein; BNP: B-type natriuretic peptide; □: Mann-Whitney U test, *: p<0.05.

Albumin, the first component of PNI is a polypeptide that makes up 55-60% of the total plasma protein. Albumin is mostly found in the intravascular compartment. In critical illness, albumin production decreases while albumin is destroyed at an increased rate, and the distribution of albumin in the intra- and extra-vascular spaces also changes.[6]

In addition to providing oncotic pressure and being a carrier protein, albumin has been shown in the previous studies to have antioxidant properties, ensure the stability of the microvascular bed, and have a heparin-like anticoagulant effect thanks to the negatively charged groups in its structure.[6] Low levels of albumin have been associated with increased mortality in studies.[7]

It has been shown that COVID-19 patients are predisposed to clinical conditions associated with hypercoagulability, such as arterial-venous thromboembolism, pulmonary thromboembolism (PTE), and cerebrovascular accident (CVA), due to the deterioration of microvascular structure and increased procoagulant activity.[8,9] Hypoalbuminemia observed in patients may also pave the way for undesirable conditions, such as PTE and CVA, and adversely affect the prognosis of the disease.

The lymphocyte count, the second component of the PNI, has been used to determine the prognosis of the disease with the neutrophil/lymphocyte score (NLR) since the beginning of the COVID-19 pandemic. The lymphopenia seen in COVID-19 patients originates mainly from T cells. The decrease in T-cell population may have occurred due to the release of inflammatory cytokines, T-cell exhaustion, the invasion of T cells by the virus, and decreased T-cell maturation and activity due to virus during the disease process. Although there are publications supporting

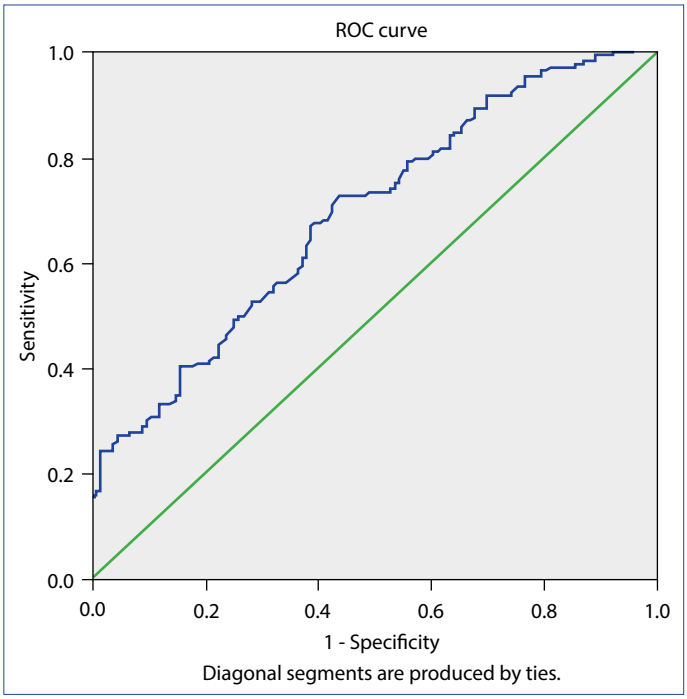

Figure 1. ROC curve calculated for PNI (AUC=0.689, St. error=0.030, p<0.001, [%95 CI: 063-0.75], Cutoff value for PNI 34.075).

ROC: Receiver operating characteristic; PNI: Prognostic nutrition index; AUC: Area under curve; CI: Confidence interval.

these hypotheses, future research can clarify the causes of lymphopenia.[10]

It has been shown that lymphopenia seen for any reason in COVID-19 patients causes poor prognosis, prolonged hospitalization, and an increased need for intensive care follow-up.[11] Therefore, the lymphocyte count can be used to determine disease severity and inflammatory status.

COVID-19 is a disease that concerns all systems in the body, and markers that evaluate nutritional, inflammatory, and coagulative statuses are needed to determine the prognosis.[5] The PNI provides information about both nutrition and inflammation status. The PNI is an easily calculated, fast, and cost-effective score that includes simple examinations that any center can perform.[3]

In COVID-19, where the virus invades the host's cells and causes disease, the immune and nutritional statuses of the host may affect the patient's response to the virus.[5] For this reason, the evaluation of the PNI at the onset of symptoms and the need for hospitalization and ICU stay, which are critical stages in the course of the disease, can indicate the patient's prognosis during the decision-making process. This study calculated the PNI value using the 1st day of hospitalization in the ICU, which is the day the general condition deteriorates and oxygen demand increases.

There are studies suggesting the follow-up of markers such as BNP, ferritin, and D-dimer in the prognosis follow-up of COVID-19 patients.[12-14] In this study, in addition to the PNI value, the predictive values of BNP, ferritin, and D-dimer on mortality and length of stay in ICU were found to be significant, supporting the previous studies.

This study has several limitations. The patient group and the patients' comorbidities are not homogeneous because the study was performed in a single center. In addition, some data could not be accessed during the process, and for this reason, a significant number of patients could not be included in the study. Another limitation of the study is that the PNI value was evaluated only on the day of hospitalization in the ICU. The patients' PNI values at the onset of symptoms and on the day of hospitalization were not

Table 3. Cox-Regression and Binary Logistic Regression Analysis for PNI, BNP, Ferritin and D-dimer

Cox regression analysis								
Variables	**B**	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95.0% CI for Exp(B)**	
							Lower	**Upper**
PNI	-.032	.015	4.657	1	.031	.968	.940	.997
BNP	.000	.000	1.537	1	.215	1.000	1.000	1.000
Ferritin	.000	.000	10.950	1	.001	1.000	1.000	1.000
D-dimer	.039	.016	6.102	1	.014	1.040	1.008	1.073
Binary logistic regression analysis								
PNI	-.097	.027	13.045	1	.000	.907	.861	.957
BNP	.000	.000	3.762	1	.052	1.000	1.000	1.000
Ferritin	.001	.000	11.067	1	.001	1.001	1.000	1.001
D-dimer	.230	.058	15.605	1	.000	1.259	1.123	1.411
Constant	2.120	.989	4.591	1	.032	8.332		

PNI: Prognostic nutrition index; BNP: Brain-derived natriuretic peptite; B: Unstandardized Beta; SE: Standart error; df: Degrees of freedom; Sig.: Significant.

recorded. In rate-based data such as NLR or PNI, a trend can be evaluated by recording data at different times instead of once. Monitoring as such may have more accurate results.

Future studies that use a prospective, multicenter, and homogeneous patient group and record PNI values more than once may provide more reliable results.

The PNI is a fast, easily accessible, and cost-effective score for estimating the intensive care length of stay and mortality of COVID-19 patients in ICUs. Considering the findings of this study, markers such as BNP, ferritin, and D-dimer, as well as the PNI follow-up, can be used to determine the prognosis of COVID-19 patients in ICUs.

Disclosures

Ethics Committee Approval: The study was approved by The University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Date: 30/11/2020, No: 99/11).

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