ORIGINAL ARTICLE

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The Use of Neutrophil/Lymphocyte Ratio and Prognostic Nutritional Index for Predicting Mortality in COVID-19 Patients: A Retrospective Study

COVID-19 Hastalarında Nötrofil/Lenfosit Oranının ve Prognostik Nutrisyonel İndeksinin Mortalite Öngördürücülüğü: Retrospektif Bir Çalışma

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ABSTRACT

Aim: Various prognostic risk-scoring systems and parameters have been investigated to predict mortality in patients with coronavirus disease-2019 (COVID-19). In this study, we aimed to evaluate the neutrophil/lymphocyte ratio (NLR) and prognostic nutritional index (PNI) scores to evaluate their predictive value on COVID-19-related mortality.

Materials and Methods: A total of 1239 patients were admitted in the study. Patients were followed up for 34 months. Specific variables and biochemical parameters were recorded. NLR and PNI values of the participants were calculated and divided into three equal groups from smallest to largest according to these values (NLR and PNI incrementally from 1 to 3). The terciles of NLR and PNI levels were compared between the survival and non-survival groups.

Results: The study included 1.239 patients. The patients were followed up for an average of 22 months (range, 0-34 months). Compared to surviving patients in the mortality group, NLR was also significantly higher and the PNI score was significantly lower ($p<0.001$).

Conclusion: Lower PNI and higher score NLR were found to be independent risk factors for mortality in hospitalized COVID-19 patients.

Keywords: Prognostic nutritional index, neutrophil/lymphocyte ratio, mortality, COVID-19

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) hastalarında mortaliteyi tahmin etmek için çeşitli prognostik skorlama sistemleri ve parametreleri üzerine araştırmalar yapılmıştır. Bu çalışmada nötrofil/lenfosit oranı (NLR) ve prognostik nutrisyonel indeks (PNI) skorlarının, COVID-19'a bağlı mortalite üzerindeki öngördürücülüğünün değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya toplam 1239 hasta dahil edildi. Hastalar taburculuk sonrası 34 ay boyunca takip edildi. Hastaların spesifik değişkenler ve biyokimyasal parametreleri kaydedildi. Tüm hastaların NLR ve PNI değerleri hesaplandı. Katılımcıların NLR ve PNI değerleri hesaplandı. Küçükten büyüğe sıralandı ve 1. gruptan 3. gruba artacak şekilde 3 eşit gruba ayrıldı (NLR ve PNI'nın 1. gruptan 3'e kadar artış gösteren üçte birlik dilimler halinde). NLR ve PNI düzeylerinin üçte birlik dilimleri hayatta kalan ve hayatta kalmayan gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya 1.239 hasta dahil edildi. Hastalar ortalama (minimum 0 - maksimum 34) 22 ay takip edildi. Mortalite grubunda hayatta kalan hastalarla karşılaştırıldığında, NLR düzeyleri anlamlı derecede yüksek ve PNI skoru anlamlı derecede düşük saptandı.

Sonuç: Hastanede yatan COVID-19 hastalarında daha düşük PNI ve daha yüksek NLR skoru mortalite için bağımsız risk faktörleri olarak bulundu.

Anahtar Kelimeler: Prognostik nutrisyonel indeks, nötrofil/lenfosit oranı, mortalite, COVID-19

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INTRODUCTION

Coronavirus disease-2019 (COVID-19), which the World Health Organization designated as a pandemic in March 2020, has maintained its importance, even though its effect has decreased recently, and it has been one of the causes of increased mortality[1]. One of the causes of increased mortality in coronavirus disease-19 (COVİD-19) disease is severe lung parenchyma disease and respiratory failure, which require hospitalization in the intensive care unit [2]. There is no standardized treatment and medication for those with COVID-19, therefore, determining the risk factors for prognosis and mortality is important[3]. Several prognosis and risk parameters have been investigated for their use in mortality prediction for those with COVID-19[4]. The aim of estimating mortality is the early detection and treatment of patients with a poor prognosis. In particular, markers of inflammation have frequently been used to make such predictions[5]. Inflammatory parameters in peripheral blood cell composition are important predictive inflammatory response indicators, and their use as mortality indicators is increasing[6]. This measurement method is inexpensive, easy, and cost-effective. The neutrophil and lymphocyte counts are hemogram parameters, and this study calculates the neutrophil/lymphocyte ratio (NLR). NLR is shown to be an important parameter in showing the inflammatory status of patients. NLR is a risk factor that increases mortality in infectious diseases, malignancy, and ischemic heart diseases[7-9]. Malnutrition refers to a chronic imbalance between the intake of consumed nutrients (protein, energy, and other nutrients) and meeting changing metabolic needs. Malnutrition causes some changes in the immune system. High degrees of malnutrition have been shown to be associated with increased inflammation[10]. Moreover, malnutrition suppresses the immune system response and increases susceptibility to COVID-19 and similar infections[11,12]. There is no specific screening method for nutrition in inpatients with COVID-19. Recently, researchers have proposed a prognostic nutritional index (PNI) for detecting malnutrition and calculated it based on the serum albumin value and lymphocyte count. Previous studies have reported that the PNI is significantly associated with increased mortality and morbidity in patients with various gastrointestinal malignancies[13,14]. Therefore, PNI may indicate nutrition and inflammation in COVID-19 patients. This study has the aim of determining the effects that the NLR and PNI score have on predicting COVID-19-related mortality.

MATERIALS AND METHODS

Data-Sources

This research was conducted using the data of patients hospitalized University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Internal Medicine Units for the Pandemic. The Ethics Committee of the University of Health Sciences, İstanbul Haseki Training and Research Hospital approved the study (decision no: 253-2023, date: 27.12.2023), which has been performed in line with guidelines from the National Institutes of Health and the Declaration of Helsinki principles regarding proper clinical practices. Patient data were all gathered without including any patient-identifying information and without permitting investigation of the patients' medical data. Consent was obtained from the inpatients as a matter of routine upon admission.

Population of the Study and Data Collection

Data were collected from all adult patients hospitalized in internal medicine pandemic services with a COVID-19 diagnosis between April 2020 and March 2021. The study had 1.239 enrolled patients. Only those with positive swab test results and clinical and/or radiological findings were considered to have COVID-19 disease and were included in this study. Patients who had fully recovered as well as those who had passed away were also included. Patients who had negative swab tests and/or serological tests, those hospitalized for other diagnoses, and re-admissions were excluded from the study. Patients were followed up for 34 months, including primary endpoints and all-cause mortality. The study obtained all follow-up data from the University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, IT Department, with death reports verified using the Turkish National Death Registry. The specific variables of age and gender, as well as glucose, white blood cell, neutrophil, lymphocyte, hemoglobin, platelet, uric acid, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase, C-reactive protein, procalcitonin, ferritin, thyroid stimulant hormone, and albumin levels were recorded. Blood samples were obtained immediately after hospitalization and before the treatment. The NLR and PNI / 10 × serum albumin [g/dL] + 0.005 × lymphocytes per µL were formulated for all participants. NLR and PNI values of the participants were calculated and divided into three equal groups from smallest to largest according to these values (NLR and PNI incrementally from 1 to 3). These terciles were then compared in terms of survival and non-survival groups.

Statistical Analysis

The study benefitted from IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA) for performing the statistical analyses, presenting continuous data as mean and standard deviation values regarding groups T1–T3, and all categorical variables as percentages. The study implemented the chi-square test to compare the groups' ratios and the Student's t-test to examine the normally distributed numerical data. The Mann-Whitney U test was used to compare the two groups

regarding their non-normally distributed numerical data and the Cox regression model was used to analyze the variables' effects on event-free survival. Moreover, the Cox regression was employed to assess the predictive performance of age, gender, hemoglobin and uric acid levels, NLR, and PNI. The study included parameters that were found to vary between the different outcomes (survivor or non-survivor) in the regression models to reveal which ones showed independent relationships with these outcomes. Statistical significance was set at $p<0.05$. The study used the Kaplan-Meier method to examine time-to-event data and the log rank test to determine differences between groups.

RESULTS

The study included 1.239 patients (565 women and 674 men) admitted to the clinic and given treatment. The patients were followed up for a median (minimum 0 - maximum 34) 22 months. The main characteristics of the surviving and non-surviving patient groups are shown in Table 1. When compared to the survivor group, the mortality risk for the non-surviving group was significantly higher among older patients and male gender ($p<0.001$). The PNI levels were less than 36.95 for tercile 1, between 36.95 and 42.5 for tercile 2, and greater than 42.5 for tercile 3. The NLR levels were less than 3.26 for tercile 1, between 3.26 and 7.4 for tercile 2, and greater than 7.4 for tercile 3.

In terms of the NLR, terciles 1 and 2 had fewer non-surviving patients than surviving patients, and a greater number of non-surviving patients from tercile 3. Regarding PNI, the rate of survival was lower for tercile 1 while it was higher for terciles 2 and 3 (Table 1). The study conducted a multivariable cox regression to assess the mortality risk between the groups, with Table 2 showing these results with regard to age, male sex, hemoglobin level, uric acid level, NLR, and PNI. The NLR tertiles 3 and 2 showed a very close relationship in terms of mortality risk. [NLR: (tercile 1 and tercile 2) odds ratio (OR): 1.63, 95% confidence interval (CI): 1.14-2.32, p=0.007; NLR:

Table 1. Patients' baseline clinical and laboratorial characteristics

	Survivor	Non-survival	p value
Gender Female: n (%) Male: n (%)	 416 (73.6%) 442 (65.5%)	 149 (26.4%) 232 (34.5%)	 0.002
Age (years)	57.5±15.1	70.9±13.1	0.001
Glucose (mg/dL)	160.9±82.3	173.6±101.8	0.021
White blood cell count $\times10^9$/L	7,6±4.9	10.1±22.2	0.02
Neutrophils $\times10^9$/L	5.4±3.6	7.7±5.4	0.001
Lymphocytes $\times10^9$/L	1.3±3.1	1.1±2.3	0.095
Hemoglobin (g/dL)	12.2±1.9	10.9±2.4	0.001
Platelet ($\times1000/mm^3$)	214.3±89.1	205.7±116.4	0.161
Uric acid (mg/dL)	4.9±2	6.5±2.7	0.001
ALT (U/L)	30.8±31.1	34.6±113.2	0.005
AST (U/L)	37.8±41.7	58.3±344.5	0.005
GGT (U/L)	52.3±73.8	72.52±145.4	0.001
ALP (U/L)	76.9±64.1	107.9±106.5	0.001
Albumin (g/dL)	3.4±6.4	3.1±6.1	0.001
Hs-CRP (mg/L)	74.3±70.9	110.6±92.3	0.001
Procalcitonin (ug/L)	0.9±6.7	8.8±53.3	0.001
Ferritin (ug/dL)	406.3±558.7	623.9±934.4	0.001
TSH (mU/L)	1.2±8.5	0.8±1.6	0.325
NLR tercile 1 (n)	354 (29%)	53 (4.3%)	
NLR tercile 2 (n)	295 (24.2%)	112 (9.2%)	0.001
NLR tercile 3 (n)	202 (16.5%)	205 (16.8%)	
PNI tercile 3 (n)	351 (28.9%)	55 (4.5%)	
PNI tercile 2 (n)	298 (24.5%)	107 (8.8%)	0.001
PNI tercile 1 (n)	199 (16.4%)	206 (16.9%)	

Statistically significant variables ($p<0.05$), ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein, TSH: Thyroid stimulant hormone, NLR: Neutrophil/lymphocyte ratio, PNI: Prognostic nutritional index

(tercile 1 and tercile 3)] OR: 2.21, 95% CI: 1.55-3.17, ≤0.001 (Table 2). PNI's first tertile indicates a close relationship with a mortality risk [PNI between terciles 3 and 1 OR: 1.51, 95% CI: (1.06, 2.17), p=0.022]. In addition, the mortality risk was higher in patients with high uric acid levels and low hemoglobin levels, and in those who were male and older in age (p≤0.001 for each).

The Kaplan-Meier curves illustrate the incidences for all-cause mortality as categorized by the NLR (Figure 1) and by PNI (Figure 2) in the COVID-19 patients. The long-term survival rates of inpatients with elevated NLR and lower PNI values were significantly worse than for patients with lower NLR and elevated PNI levels. All-cause mortality had a significantly higher cumulative incidence in patients with a lower PNI score (log rank=154.2; p<0.001) and higher NLR (log rank=149.1; p<0.001).

DISCUSSION

Blood tests and simple scoring systems provide the physician with information about the inflammatory process and may also provide important clues about the prognosis of the disease. This study has found higher NLR and lower PNI to be significantly associated with increased mortality. Moreover, the results indicate that low hemoglobin, uric acid level and male gender were independent predictors of mortality. Studies have shown that advanced age, male sex, and uric acid level are strongly associated with mortality, as in our study, apart from these known factors, various markers have been put forward to predict mortality[15,16].

Table 2. Cox regression anaysis for neutrophil/lymphocyte ratio and prognostic nutritional index

Factor	Hazard ratio 95% CI [lower, upper]	p value
Age	1.04 [1.03, 1.05]	0.001
Gender (male)	1.59 [1.27, 1.99]	0.001
Hemoglobin (g/dL)	0.89 [0.85, 0.94]	0.001
Uric acid (mg/dL)	1.10 [1.06, 1.15]	0.001
NLR (terciles 1 and 2)	1.63 [1.14, 2.32]	0.007
NLR (terciles 1 and 3)	2.21 (1.55-3.17)	0.001
PNI (terciles 3 and 2)	1.18 (0.83-1.67)	0.363
PNI (terciles 3 and 1)	1.51 (1.06-2.17)	0.022

Statistically significant variables (p<0.05), CI: Confidence interval, NLR: Neutrophil/lymphocyte ratio, PNI:Prognostic nutritional index

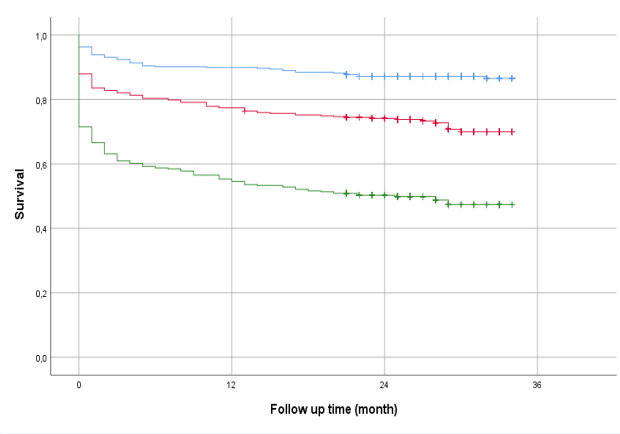

Figure 1. Kaplan-Meier curve for all-cause mortality by tercile with regard to NLR.

Blue line = tercile 1 of NLR (=407; NLR ≤3.26). Red line = tercile 2 of NLR (n=407; 3.26< NLR <7.40). Green line = tercile 3 of NLR (n=407 patients; 7.40 ≤ NLR)

NLR: Neutrophil/lymphocyte ratio

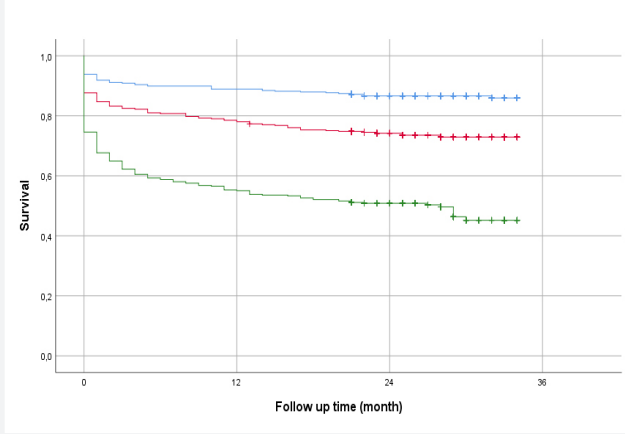

Figure 2. Kaplan-Meier curve for all-cause mortality by terciles with regard to PNI

Blue line = tercile 3 of PNI (n=406; 42.5≤ PNI). Red line = tercile 2 of PNI (n=405; 36.95< PNI <42.5). Green line = tercile 1 of PNI (n=405; PNI ≤36.95)

PNI: Prognostic nutritional index

The results also reveal PNI to be an independent predictor of COVID-19 patients' mortality. Malnutrition is known to be associated with increased morbidity and mortality[17]. Studies have shown PNI, being a simple and easily applied scoring system to determine malnutrition levels, to be associated with poor prognosis regarding various diseases, with a low PNI score having been reported as being significantly associated with poor prognosis and increased complications in patients with malignant gastrointestinal tumors[18].

Albumin, a PNI component, is synthesized by the liver and widely used as a nutritional indicator. Systemic inflammation resulting from acute or chronic diseases reduces albumin synthesis and increases its degradation. Studies have shown an increased cytokine storm occurring alongside COVID-19 to be associated with albumin depletion[19]. Previous studies have shown low albumin levels to be associated with poor outcomes in COVID-19 patients[20]. Additionally, decreased serum albumin levels that occur during an infection and systemic inflammation may be indicators of liver function due to inflammatory cytokines' ability to reduce hepatocytes' albumin synthesis capacity[21]. Moreover, Wei et al.[22] found in their study that PNI had the strongest relationship with COVID-19 inpatients' NLRs and lactate dehydrogenase levels. In parallel with all these findings, the current study found a low PNI to be closely related to mortality in COVID-19 patients. Therefore, PNI can be used as a new biomarker to predict mortality in COVID-19 patients.

NLR has been demonstrated as a new biomarker indicative of systemic inflammation. The inflammatory response stimulates neutrophil production and increases the apoptosis of lymphocytes. This causes an increase in NLR. Recent studies have shown that increased levels of inflammatory cytokines, chemokines, and NLRs in patients with infection correlate with disease severity due to cytokine storms[23]. Therefore, NLR can be used as a predictive indicator of mortality in diseases. In line with this information, the study has found high NLR to be an independent risk factor for COVID-19 mortality. However, research on this subject is new, and studies continue to be conducted in this field regarding COVID-19 and other diseases. When the literature was examined, studies on this subject have generally involved other diseases. The strong features that distinguish the current study from others are its long examination and follow-up periods, large number of cases, and case diversity. In addition, this study was conducted using data from patients managed by a team equipped and experienced in the treatment of COVID-19 in a reference pandemic hospital. This study has also found all-cause mortality to be significantly higher in patients with low PNI and high NLR. These findings may contribute to the development of new scoring systems for predicting mortality in the future.

Study Limitations

This study is found to have several limitations. Firstly, it is a retrospective study. Secondly, the hematological and biochemical markers examined limited the implications of the findings.

CONCLUSION

This study has found lower PNI and higher NLR values to be independent risk factors for COVID-19 mortality regarding hospitalized COVID-19 inpatients. As long as COVID-19 remains a part of life, research in line with it will continue to attract attention.

Ethics

Ethics Committee Approval: The study was conducted after obtaining the necessary permissions from University of Health Sciences, İstanbul Haseki Training and Research Hospital Ethics Committee (decision no: 253-2023, date: 27.12.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: B.Ç.T., E.H., E.Ç.Ö., F.T., H.E.A., Concept: E.H., Design: E.Ç.Ö., Data Collection or Processing: H.E.A., Analysis or Interpretation: H.E.A., Literature Search: F.T., Writing: B.Ç.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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