



ARAŞTIRMA / RESEARCH

The impact of objective nutritional indexes on in-hospital mortality in Covid-19 infection

Covid-19 enfeksiyonunda objektif nutrisyonel indekslerin hastane içi mortaliteye etkisi

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Abstract

Purpose: The effect of nutritional status on in-hospital mortality in patients with coronavirus disease 2019 (COVID-19) is unclear. We aimed to analyze the relationship between nutritional status score (CONUT) and prognostic nutritional index (PNI) and in-hospital mortality in COVID-19 infection.

Materials and Methods: We included 187 patients with COVID-19 between 11 March-10 May 2020. The CONUT and PNI scores were calculated using the laboratory results. The groups were divided into survival and in-hospital mortality

Results: The mean age of the patients was 66.2±15.8 years (55.3% male). The mortality rate was 20.8% (n=39). The median PNI scores was significantly lower and the median CONUT score was significantly higher in the mortality group. Multivariate regression analysis showed that PNI and CONUT were independent predictors of mortality. ROC curve analyses showed that CONUT had a better performance than PNI to predict in-hospital mortality.

Conclusion: In COVID-19 patients, CONUT and PNI scores were independently associated with in-hospital mortality, with CONUT presenting a better performance than PNI.

Keywords: Coronavirus disease 2019, CONUT, PNI

Öz

Amaç: Koronavirüs hastalığı 2019 (COVID-19) tanısı nedeniyle yoğun bakım ünitelerinde yatan hastaların beslenme durumunun hastane içi mortaliteye etkisi belirsizdir. Çalışma, COVID-19 enfeksiyonu hastalarında iki objektif nutrisyonel indeksler olan controlling nutritional status score (CONUT) ve prognostic nutritional index (PNI) nin hastane içi mortalite ilişkisini analiz etmeyi amaçladı.

Gereç ve Yöntem: Çalışmaya 11 Mart-10 Mayıs 2020 tarihleri arasında yoğun bakım ünitelerinde yatan 187 COVID-19 hastası dahil edildi. Demografik ve klinik verileri kaydedildi. CONUT ve PNI skorları laboratuvar sonuçlarından hesaplandı. Hastalar mortalite grup ve ve non-mortalite grup olmak üzere iki gruba ayrıldı.

Bulgular: Hastaların ortalama yaşı 66.2±15.8 yıl (% 55,3 erkek), ölüm oranı % 20,8 (n = 39) idi. Mortalite grubunda Medyan PNI skorları anlamlı olarak daha düşük ve medyan CONUT skorları anlamlı olarak daha yüksek belirlendi. Çok değişkenli regresyon analizinde, PNI ve CONUT un mortalite ile bağımsız olarak ilişkili olduğunu belirlendi. Ayrıca ROC eğrisi analizlerinde, CONUT un hastane içi mortaliteyi tahmin etmede, PNI'den daha iyi bir performansa sahip olduğunu belirlendi.

Sonuç: COVID-19 hastalarında, CONUT ve PNI skorlarının hastane içi mortalitede bağımsız prediktörler olduğunu ve CONUT'un PNI'dan daha iyi bir performansa sahip olduğu belirlenmiştir.

Anahtar kelimeler: Koronavirüs hastalığı 2019, CONUT, PNI

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease affecting humans caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^{1,2}. Most cases experience the virus with no (asymptomatic) or mild symptoms, including fever, coughing, and dyspnea^{3,4}. However, in some cases, the disease progresses into a severe form and result in pneumonia and multiple organ failure⁵. The initial data from China, where the disease was believed to be originated, showed that 6% of the cases required intensive care unit (ICU), whereas Europe and the USA data is higher^{5,6}. The studies indicated that in COVID-19 cases, the male gender, older age, coronary heart disease, hypertension (HT), and diabetes mellitus (DM) were associated with mortality^{2,4}. The risk of mortality was shown to increase with age. The mortality rate for people younger than 50 years was 0.5%, and the rate was shown to rise to 8% for those aged 70 and over⁷.

Up to date, many laboratory parameters, including high sensitivity cardiac troponin I (hs-cTnI), brain natriuretic peptide (BNP), lactate dehydrogenase (LDH), myoglobin, creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin was shown to be related with mortality in patients with COVID-19⁸⁻¹¹. Also, increased D-dimer, CRP, ferritin levels, and lymphopenia have emerged as independent risk factors for poor outcomes, including death^{12,13}. Additional laboratory markers and blood count parameters have also been associated with poor prognosis due to possible links with the thrombosis mechanism¹³.

In many studies, the nutritional condition of patients with different diseases was associated with mortality¹⁴⁻¹⁷. Therefore, in addition to the laboratory parameters and clinical risk factors, the nutritional condition of the COVID-19 patients might be used to predict mortality.

Yet, to the best of our knowledge, there are no studies available that evaluated the relationship between the nutritional condition of COVID-19 patients and in-hospital mortality. Thus, the study aimed to analyze the association of the two objective nutritional indexes, controlling nutritional status score (CONUT) and prognostic nutritional index (PNI) with in-hospital mortality of COVID-19 cases. Besides, the two indexes were compared for superiority in predicting mortality.

MATERIALS AND METHODS

The study was approved by the Ministry of Health Clinical Research Ethics Committee of our country and our hospital Adana City Training and Research Hospital local Clinical Research Ethics Committee (873-57 / 20.05.2020). For the study, the data of all patients who were hospitalized with symptoms and laboratory or radiological findings of COVID-19 at our tertiary center serving as a pandemic hospital between 11 March 2020 and 10 May 2020 were recorded from the hospital digital recording system and patient files. In the study of Ai et al. published in August, chest CT findings were more sensitive than PCR positivity¹⁷.

Venous blood samples of the patients were taken when they were admitted to the intensive care unit. Baseline blood sample results and the routine examination data, including arterial blood gas, respiration rate, systolic and diastolic blood pressure, temperature, heart rate, were recorded. Also radiologic findings, ongoing treatment and clinical outcomes were noted. Patients with missing blood parameters or demographic characteristics like height, weight, respiratory rate, and blood gas measurement in the patient files were excluded from the study.

Table 1. CONUT score calculation

Parameters	Normal	Light	Modera te	Severe
Serum albumin (g/dL)	≥3.50	3.00–3.49	2.50–2.99	<2.50
Score	0	2	4	6
Total lymphocyte count	≥1600	1200–1599	800–1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	>180	140–180	100–139	<100
Score	0	1	2	3
CONUT score (total)	0-1	2-4	5-8	9-12
Assessment	Normal	Light	Modera te	Severe

CONUT: controlling nutritional status

In addition, patients with hematological disease or malignancy, chronic liver failure, autoimmune disease, and rheumatological disease history were excluded from the study because they could label objective nutritional indexes. The drugs used by patients were recorded from the national insurance

system. Those who had a history of using steroid or anti-lipidemic drugs were also excluded from the study. 280 patients were evaluated for the study and 187 patients who met the inclusion criteria were included.

The CONUT and PNI scores were calculated using the laboratory results. The analyses were based on survival and in-hospital mortality; therefore, the cases were dichotomized into mortality and non-mortality groups accordingly.

Heart failure was defined as having left ventricular ejection fraction < 40%. HT was defined as having a previous diagnosis of HT, systolic and diastolic blood pressure > 140/90 mmHg, or being on anti-hypertensive medication. DM was defined as having a previous DM diagnosis, using an anti-diabetic medication, fasting blood glucose \geq 126mg / dL or HbA1c > 6.5%. Smoking was defined as having one or more cigarettes a day continuously in the last twelve months. The body mass index (BMI) was calculated by the weight/height (m²) formula with the weight and height measurements taken on the day of hospitalization. The eGFR was calculated using the Cockcroft-Gault formula with the laboratory data results obtained from the samples taken on the day of hospitalization.

Evaluation of the nutrition status of patients

The nutritional status of the patients was determined of the objective nutritional indexes CONUT and PNI. The parameters of the CONUT score and the formula of the PNI was shown below.

1. Prognostic nutritional index

The PNI was calculated as an indicator of nutritional status using the formula: $PNI = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ ¹⁸.

2. Controlling the nutritional status score

CONUT scores were determined according to the Table 1¹⁹.

Statistical analysis

Levene test was used to determine whether continuous variables were homogeneously distributed. Variable with normal distribution were expressed as mean \pm standard deviation, compared with Student's t-test. Also, variable with non-normal distribution were expressed as median and interquartile range (IQR) and compared with Mann-Whitney U test.

Categorical variables were presented as total number and percentages and compared using the Chi-square test or Fisher exact test. Multivariate analysis using logistic regression models tested variables with $p \leq 0.05$ in univariate analysis. For each objective nutritional index two different multivariate logistic regression analysis models were established.

To demonstrate sensitivity and specificity of the PNI and CONUT scores and their cut-off values for predicting in hospital mortality Receiver Operating Characteristics (ROC) curves were used. The area under the curve (AUC) comparison of PNI and CONUT was performed by the DeLong method²⁰. A two-tailed p-value <0.05 was considered as statistically significant, and 95% confidence interval (95 % CIs) were presented for all odds ratios. All statistical analyses were performed using SPSS Windows software (ver. 16.0; IBM, NY, USA).

RESULTS

The study included 187 patients (mean age 66.2 ± 1.8 years (55.3% male) included to the study. There were 39 deaths (mortality group), and the remaining 148 patients were discharged from the hospital (non-mortality group). Baseline clinical and demographic characteristics of patients were summarized in Table-2. There were no significant differences between groups in terms of baseline characteristics, excluding the respiratory rate per minute, significantly higher in the mortality group. The laboratory parameters at the time of hospitalization were presented in Table-2. The mortality group had higher median AST, LDH, D-dimer, ferritin, procalcitonin, troponin, INR, and prothrombin time values, with lower serum albumin and lymphocyte count (for all $p < 0.05$). The median PNI was significantly lower and the median CONUT score was significantly higher in the mortality group (Table-2). Figure 1 shows the ROC curve analysis of the objective nutritional indexes. To predict mortality; the cut-off value of the PNI was ≤ 33 , with 97.4% sensitivity and 58.1% specificity (AUC: 0.845; 95% CI: 0.785–0.894; $p < 0.001$) and the cut-off value of the CONUT score was > 8 , with 79.4% sensitivity and 86.4% specificity (AUC: 0.889; 95% CI: 0.835–0.930; $p < 0.001$). Pairwise comparison of the ROC curve analyses has shown that the CONUT score had a better performance than PNI to predict in-hospital mortality.

Table 2. Basal demographic, clinical characteristics, laboratory parameters and nutritional status indexes of the study groups

Variables	Non-mortality (n=148)	Mortality (n=39)	P value
Age, years	65.5 ± 16.3	69.0 ± 13.7	0.226
Weight, kg	76.0 ± 16.0	76.8 ± 19.6	0.779
Height, cm	167.1 ± 7.8	168.8 ± 8.3	0.248
Body mass index (kg/m ²)	27.0 ± 5.6	27.5 ± 7.8	0.673
Gender, male, n (%)	81 (54.3)	23 (58.9)	0.606
Hypertension, n (%)	43 (28.8)	10 (25.6)	0.830
Diabetes mellitus, n (%)	43 (28.8)	8 (20.5)	0.590
Heart failure, n (%)	35 (23.4)	8 (20.5)	0.895
Coronary artery disease, n (%)	41 (27.5)	12 (30.7)	0.273
Chronic kidney disease, n (%)	27 (18.1)	5 (12.8)	0.169
Chronic obstructive pulmonary disease, n (%)	32 (21.4)	7 (17.9)	0.983
Cerebrovascular disease, n (%)	13 (8.7)	3 (7.6)	0.930
Malignancy, n (%)	14 (9.3)	5 (12.8)	0.340
Smoker, n (%)	31 (20.8)	9 (23.0)	0.384
Heart rate, bpm	80.4 ± 14.3	79.4 ± 17.1	0.752
Systolic blood pressure, mm Hg	118.0 ± 18.5	124.2 ± 20.0	0.118
Diastolic blood pressure, mm Hg	72.0 ± 13.0	73.0 ± 12.1	0.715
O ₂ saturation, %	84.5 ± 9.0	83.2 ± 9.1	0.498
Respiratory rate, rpm	18.4 ± 3.7	19.9 ± 3.3	0.045
Body temperature, °C	36.9 ± 0.8	37.4 ± 1.2	0.075
Glucose, mg/dL	123 (97)	151 (82,5)	0.545
Creatinine, mg/dL	1.63 ± 1.86	1.63 ± 0.91	0.992
Uric acid, mg/dL	5.71 ± 2.50	5.92 ± 2.53	0.677
eGFR, ml /m /1.73	66 (53)	58 (52,5)	0.054
Albumin, g/dL	30.30 ± 7.61	22.14 ± 5.33	<0.001
Total protein, g/dL	6.48 ± 1.25	5.42 ± 1.38	<0.001
AST, U/L	22 (26)	48 (92)	<0.001
ALT, U/L	22 (15)	35 (67.5)	<0.001
LDH, U/L	260 (175)	444 (442)	<0.001
Total cholesterol, mg/dL	181 (63.4)	157.5 (40)	0.024
LDL, mg/dL	118 (52)	110 (38)	0.197
HDL, mg/dL	36 (16)	33 (15.2)	0.040
WBC, 10 ³ /μL	10.4 (5.6)	11.5 (9.2)	0.077
Platelets, 10 ³ /mL	237 (163)	216 (146)	0.924
Lymphocyte, 10 ³ /μL	1000 (900)	300 (300)	<0.001
Neutrophil, 10 ³ /μL	7.2 (0.5)	9.7 (0.9)	0.006
CRP, mg/L	3.3 (99.9)	11.9 (190)	0.002
D-DIMER, ng/mL	1240 (2467)	3765 (17200)	<0.001
Ferritin, μg /L	164 (376.8)	378.9 (1910.1)	0.001
Procalcitonin, μg/L	0.26 (0.8)	2.9 (4.3)	0.004
Troponin I, ng/L	70 (165)	285 (1666)	<0.001
INR	1.1 (0.3)	1.4 (0.7)	0.003
Prothrombin time, s	14 (4.9)	18.4 (8.9)	0.004
Fibrinogen, mg/dL	400 (224)	432 (392)	0.359
BNP, μg/L	1500 (6983)	21250 (18600)	0.217
PNI, median (IQR)	36.05 (15.42)	23.50 (8.25)	<0.001
CONUT, median (IQR)	4.0 (5.0)	9.0 (1.0)	<0.001

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; WBC: white blood cell; INR: international normalized ratio; CONUT: controlling nutritional status; PNI: prognostic nutritional index; BNP: brain natriuretic peptide; CRP: C reactive protein; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

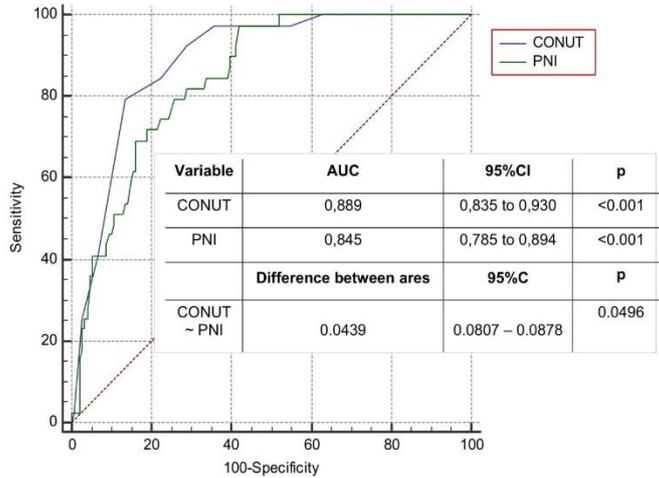


Figure 1. Comparison of the ROC curves of CONUT and PNI for in-hospital mortality

ROC: receiver operating characteristic, CONUT: controlling nutritional status PNI: prognostic nutritional index, AUC: area under curve, CI: confidence interval

Table 3. Univariate and multivariate logistic regression analysis for mortality

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	95 % CIs (confidence interval)	p value	OR	95 % CIs (confidence interval)	p value
Albumin	0.179	0.092-0.347	<0.001			
Total protein	0.540	0.381-0.766	0.001			
AST	1.008	1.003-1.013	0.002			
ALT	1.006	1.000-1.011	0.041			
LDH	1.003	1.001-1.005	0.001	1.003	1.001-1.006	0.010
Total cholesterol	0.991	0.983-0.999	0.026			
HDL	0.965	0.931-0.999	0.043			
Lymphocyte	0.997	0.996-0.998	<0.001	0.997	0.995-0.999	<0.001
Neutrophil	1.000	1.000-1.000	0.009			
CRP	1.008	1.004-1.013	<0.001			
Procalcitonin	1.172	1.042-1.318	0.008			
D-Dimer	1.000	1.000-1.000	0.004			
Ferritin	1.000	1.000-1.001	0.007			
Troponin	1.000	1.000-1.000	0.030			
INR	2.060	1.110 -3.824	0.022			
Pro-thrombin time	1.039	1.003- 1.077	0.034			
Respiratory rate	1.119	1.001-1.250	0.048			
CONUT*	1.849	1.493-2.290	<0.001	2.361	1.351-4.128	0.003
PNI**	0.832	0.779-0.890	<0.001	0.829	0.703- 0.979	0.027

*Model-1 included AST, ALT, LDH, HDL-C, Neutrophil, Lymphocyte, CRP, Procalcitonin, D-Dimer, Ferritin, Troponin, Pro-thrombin time, Respiratory rate.

**Model-2 included, AST, ALT, LDH,, HDL-C, Neutrophil, , Lymphocyte, CRP, Procalcitonin, D-Dimer, Total cholesterol, Ferritin, Troponin, Pro-thrombin time , Respiratory rate.

Two different multivariate regression analysis models have shown that both PNI (OR: 0.829; 95% CI: 0.703- 0.979; $p=0.027$) and CONUT score (OR: 2.361; 95% CI:1.351-4.128; $p=0.003$) were independently associated with in-hospital mortality. Other independent predictors of in-hospital mortality were LDH and lymphocyte count (Table-3).

DISCUSSION

The study revealed a significant association of the nutritional condition of the COVID-19 patients hospitalized in ICUs with in-hospital mortality. The results indicated that CONUT and PNI scores were independent predictors for in-hospital mortality, with CONUT presenting a better performance than PNI.

To our knowledge, there are no studies available that have evaluated the association of the nutritional condition of COVID-19 patients with in-hospital mortality.

Acute respiratory failure and multiple organ failure are the most common causes of ICU admissions in COVID-19 patients. Due to the lack of specific treatment, treatment in COVID-19 patients consists of relief of symptoms and support of the deteriorating organ. Although many risk factors and laboratory parameters have been shown in the prediction of patients in need of ICU, it is still not possible to predict which patients may have ICU and may be mortal. In this respect, it is important that we show that poor nutritional status of patients is a predictor of mortality in our study.

Malnutrition is a significant health problem observed in hospitalized patients²¹. The incidence varies between 13-86% in acute care patients, 42-91% in elderly patients, and 4-90% in special patient groups such as acute myocardial infarction, chronic kidney failure, malignancies, and patients with acute respiratory distress syndrome²².

The objective nutritional indexes are calculated using simple formulas and associated with mortality in various diseases, including cardiac and liver failure, hypertension, and malignancies²³.

Numerous laboratory parameters and risk factors have been determined in COVID-19 patients for mortality remaining a lot more waiting to be uncovered. Determination of the poor nutritional status of a COVID-19 patient on hospitalization might help to predict undesired outcomes. The study showed that the PNI score, easy to use, calculated by

lymphocyte count and serum albumin level, performed well in predicting the in-hospital mortality rates of ICU patients with COVID-19. The low PNI scores, indicating a poor nutritional status, were associated with high mortality in COVID-19 patients, similar to the associations computed in other diseases. In previous studies, the components of the PNI, low lymphocyte count, and low serum albumin levels were shown to be associated with worse outcomes separately²⁴. In this study, we have shown that the PNI index, which includes both parameters in the calculation, was associated with worse outcomes. The multivariate regression analyses have shown that PNI independently associated with in-hospital mortality. Moreover, our results revealed that the CONUT score was an independent predictor of in-hospital mortality for ICU patients with COVID-19. Besides, compared to PNI, CONUT presented a better performance in predicting in-hospital mortality. CONUT score can accurately reflect the nutritional status and immune function of the body. As the CONUT score increases, the severity of malnutrition also increases, indicating a poor prognosis for most chronic diseases. The parameters used to determine the CONUT score, similar to the PNI, include the lymphocyte count and serum albumin levels. The difference is that the serum cholesterol levels exist in the calculation of the CONUT score. The low mean cholesterol level contributes to the better performance of the CONUT score over PNI in predicting mortality. Parallel to a study conducted in China, suggesting that COVID-19 patients had lower serum cholesterol levels than healthy controls²⁵. Moreover, a recent study from Spain showed that low serum cholesterol levels are associated with 30-day mortality in COVID-19 patients²⁶.

As shown in previous studies, in our study, it was shown that lymphocyte count was significantly low and independently associated with mortality. In addition, parameters such as CRP, ferritin and D dimer, Troponin, AST, ALT, fibrinogen and prothrombin time, which were shown to be mortality predictors in many previous studies, lost their significance in multivariate analysis, although they were different between the groups in our study. This may be due to the fact that all of the patients included in our study were high-risk patients. In addition, it can be interpreted that the importance of these parameters decreases when nutritional indexes are used together with laboratory parameters in these patients. However, larger studies will guide this.

In our study, surprisingly, LDH was identified as an independent risk factor for mortality. In previous studies, it has been shown that increased LDH is associated with severe lung involvement in lung involvement secondary to viral diseases^{27,28}. Our study also supports that the increased LDH in the patient group who died can be used as an indicator of a more serious lung injury.

One major limitation was the small sample size. Also, it was a single-center study. The study included severe ICU patients with COVID-19 diagnosis. Thus, the study results should not be generalized for all COVID-19 patients. Studies with larger samples are required to confirm our results.

The study revealed a significant association of the nutritional condition of the COVID-19 patients hospitalized in ICUs with in-hospital mortality. The results indicated that CONUT and PNI scores were independent predictors of in-hospital mortality, with CONUT presenting a better performance than PNI. To the best of our knowledge, our study is the first to evaluate PNI and CONUT indexes and compare among patients with COVID-19.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AY; Veri toplama: MCB; Veri analizi ve yorumlama: AY; Yazı taslağı: AY; İçeriğin eleştirel incelenmesi: MCB; Son onay ve sorumluluk: AY, ÖÖA, MCB; Teknik ve malzeme desteği: ÖA; Süpervizyon: MCB; Fon sağlama (mevcut ise): yok.

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