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RESEARCH ARTICLE

The Relationship Between OR-PNI Score and Disease Course in Coronavirus-19 Infection

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ABSTRACT

Objective: Prognostic nutritional index (PNI), fibrinogen/albumin ratio index (FARI), and OR-PNI scores (obtained by using the PNI score, oxygen saturation, and computed tomography findings) were examined.

Materials and Methods: This study was conducted with 486 patients.

Results: : A FARI score of >18.08 predicted mortality with a sensitivity of 71.8% and a specificity of 71.1%. In the receiver operating characteristic analysis for PNI and OR-PNI scores, p-values were <0.001, but the area under the curve values were found to be 0.151 and 0.072, respectively.

Conclusion: FARI score is a parameter that predicts mortality; PNI and OR-PNI failed to predict mortality. In addition, PNI and OR-PNI values were found to be closely related to the course of the disease.

Keywords: Coronavirus-19, fibrinogen-albumin index, mortality, OR-PNI, prognostic nutritional index

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, in late 2019 and rapidly disseminated globally, resulting in a pandemic.[1,2] It has been reported that most of the patients with COVID-19 are asymptomatic throughout the disease, whereas approximately 5% are critically ill. The mortality rate of COVID-19 is 2–3%.[3,4] Many studies have examined the risk factors for mortality in patients with COVID-19 and found advanced age, male gender, presence of comorbid diseases, elevated levels of inflammation and coagulation markers, lymphopenia, and presence of organ dysfunction at the time of admission to be the major risk factors.[5]

Fibrinogen is an acute-phase reactant synthesized in the liver. It participates in the coagulation and inflammatory pathways and stimulates the release of pro-inflammatory cytokines.[6] Albumin, a plasma protein, is a negative acute phase reactant synthesized in the liver, and its low levels have been associated with an increased risk of cardiovascular disease.[7] Numerous studies have reported that the fibrinogen-albumin ratio is closely associated with the disease course and mortality in COVID-19 cases.[8–11]

The immune system and nutritional level are closely linked to an individual's susceptibility to infections. Although hypoalbuminemia occurs in cases of inflammation and malnu-

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trition, lymphopenia is one of the most common laboratory findings in acute viral infections.[12] The prognostic nutritional index (PNI) is an objective index calculated using albumin level and lymphocyte count, indicating the prognosis of various diseases.[13,14] In a previous study, we reported that the PNI score was correlated with many disease-related laboratory parameters in COVID-19 patients. The PNI values were worse in patients older than 65 years, and a higher mortality rate was seen in patients with low PNI scores.[14] OR-PNI is a newly developed score by our hospital, and it can be calculated by combining the PNI score with oxygen saturation percentage and radiological findings in PCR-positive COVID-19-infected patients. Details on OR-PNI scoring are described in the methods section. The aim of this study was to examine the relationship between OR-PNI score and disease course, clinical findings, laboratory parameters, and mortality in COVID-19 patients and compare the efficiency of OR-PNI to indices such as PNI and fibrinogen/albumin ratio index (FARI), which have been previously shown to be closely associated with mortality and disease course in patients with COVID-19.

MATERIALS and METHODS

Patient Selection

This retrospective observational study was approved by the Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital with the protocol number KAEK/2021.10.271. This study was carried out in accordance with the Helsinki Declaration. Patients who were hospitalized in isolation wards and had moderate-to-severe COVID-19 infection were included in the study. Physical examination findings, demographic data, thoracic computed tomography (CT) data, and laboratory parameters including glucose, aspartate transaminase (AST), alanine transaminase (ALT), urea, creatinine, high-sensitivity C-reactive protein (CRP), ferritin, albumin, fibrinogen, D-dimer, international normalized ratio (INR), interleukin 6 (IL-6), and complete blood count levels were recorded for each patient. Blood pressure, peak heart rate, and oxygen saturation were also noted. Comorbid diseases and medications used for COVID-19 treatment were noted. Participants were added in groups based on their clinical endpoints: discharge, referral to the intensive care unit (ICU), and exitus. PNI, FARI, and OR-PNI scores were calculated, and their relationships with patient endpoints were evaluated. Patients younger than 18 years of age or older than 85 years of age, patients with solid organ malignancies and active autoimmune disease, and patients with a defined focus of infection other than COVID-19 infection were excluded from the study.

PNI: The score was calculated using the following formula: 10 × serum albumin value (g/dL) + 0.005 × total lymphocyte count in the peripheral blood (mm^3). The malnutrition status was assigned according to the obtained PNI score:

- PNI score ≥50: normal malnutrition
- PNI scores ≥45 and <50: mild malnutrition
- PNI scores ≥40 and <45: moderate-to-severe malnutrition
- PNI score <40: severe malnutrition

FARI is calculated as fibrinogen concentration (g/L)/albumin concentration (g/L).

OR-PNI index: OR-PNI is a new index that we created by combining oxygen saturation and radiologic data with the PNI. While calculating OR-PNI, 20 points were added to the PNI score if oxygen saturation was >95% or if there were no findings for COVID-19 on thoracic CT. Ten points were added if oxygen saturation was 85–95% or if there was mild involvement or an atypical involvement pattern for COVID-19 on thoracic CT. Zero points were added to the PNI if there were typical findings for COVID-19 and severe involvement on thoracic CT or if oxygen saturation was <85%.

Statistical Analysis

The statistical Package for the Social Sciences 21.0 program for Windows (IBM Corporation, Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were presented as numbers and percentages for categorical variables. Numerical variables were expressed as mean, standard deviation, minimum, maximum, median, and interquartile range. Independent multiple-group comparisons of numerical variables were performed using one-way analysis of variance and Kruskal-Wallis tests when parametric assumptions were met and not met, respectively. Subgroup analyses were performed using the Mann–Whitney U test and interpreted with the Bonferroni correction. Risk effects were analyzed using logistic regression analysis. Cutoff value analysis was performed by receiver operating characteristic curve analysis. $p<0.05$ was accepted as statistically significant in all analyses.

RESULTS

Of the patients included in the study, 52% were male (n=256), and the mean age of all participants was 59.9±16.7 years (min-max: 19–103). Comorbid diseases, radiological findings, treatment regimens, and disease outcome data of the patients are presented in Table 1. Hypertension (HT) and diabetes mellitus (DM) were the most common comorbid condi-

Table 1. Demographic parameters of the patients

	n	%		n	%
Gender			Oxygen saturation, %		
Male	256	52.7	<85	130	26.7
Female	230	47.3	Therapy		
Age, mean±SD (min-max)	59.9±16.7 (19–103)		Favipiravir	357	73.5
Comorbid diseases			Chloroquine	157	32.3
DM	118	24.3	Steroid	202	41.6
HT	165	34.0	Antibiotics	284	58.4
Heart failure	65	13.4	Colchicine	7	1.4
CKD	35	7.2	Acetil salycilic acid	46	9.5
COPD-asthma	57	11.7	LMWH	427	87.9
Thorax CT			Paracetamol	155	31.9
No pulmonary involvement	25	5.1	Vitamins	6	1.2
Atypical involvement	62	12.8	TNF alfa inhibitors	5	1.0
Typical pulmonary involvement	399	82.1	Outcome		
Oxygen saturation, %			Discharged	365	75.1
>95	129	26.5	Referred to Intensive care unit	43	8.9
85–95	227	46.7	Exitus	78	16.0

SD: Standard deviation; DM: Diabetes mellitus; HT: Hypertension; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; LMWH: Low molecular weight heparin; TNF: Tumor necrosis factor

Table 2. Laboratory parameters of the patients

	Mean±SD (min-max)	Median (IQR)
Glucose (mg/dL)	144.4±70.4 (40–414)	120 (98–170.5)
AST (U/L)	97.5±530.0 (4–7285)	30 (22–46)
ALT (U/L)	66.6±368.8 (2–7526)	25 (16–42)
Urea (mg/dL)	47.4±44.1 (2.34–445)	35 (24–51.9)
Creatinine (mg/dL)	1.05±0.98 (0.27–11.1)	0.835 (0.67–1.06)
Ferritin (mcg/L)	1020.8±3450.6 (4.3–40000)	360 (174.9–785.1)
CRP (mg/L)	84.0±84.8 (0.39–437)	53 (19.9–127.6)
IL–6 (pg/mL)	4524.5±14644.9 (2.8–100000)	128 (27.1–1185)
Albumin (g/L)	34.9±5.8 (15.9–48.6)	35.4 (31.9–39)
D–dimer (mcg/mL)	3.0±7.0 (0.01–80)	0.915 (0.53–1.9)
Fibrinogen (mg/dL)	549.2±201.1 (6.3–1200)	537.5 (400.75–673.25)
INR	1.16±0.43 (0.84–5.34)	1.06 (0.99–1.18)
WBC (10^3/mcL)	8.3±4.8 (0.51–45.4)	7 (5.5–10)
NEU (10^3/mcL)	6.5±4.6 (0.1–44.1)	5.2 (3.5–8.3)
Lym (10^3/mcL)	1.18±0.84 (0.01–13)	1 (0.7–1.5)
MPV (fL)	10.5±1.4 (0.4–15.2)	10.5 (9.7–11.3)

IQR: Inter quartile range; AST: Aspartate transaminase; ALT: Alanine transaminase; CRP: C-reactive protein; IL-6: Interleukin 6; INR: International normalized ratio; WBC: White blood cell; Neu: Neutrophil; Lym: Lymphocyte; MPV: Mean platelet volume

Table 3. Evaluation of the demographic parameters of the patients groups

	Discharged		Referred to ICU		Exitus		p
	n	%	n	%	n	%	
Gender							
Male	183	51.8	28	65.1	39	50	0.224
Female	170	48.2	15	34.9	39	50	
Age, mean±SD (min-max)	59.9±16.7 (19–103)		65.4±12.8 (34–89)		69.5±14.6 (32–92)		**<0.001**
Comorbidities							
DM	61	17.3	20	46.5	34	43.6	**<0.001**
HT	111	31.4	17	39.5	36	46.2	**0.037**
Heart failure	39	11.0	9	20.9	16	20.5	**0.028**
CKD	19	5.4	5	11.6	9	11.5	0.070
COPD-asthma	40	11.3	8	18.6	9	11.5	0.380
Thorax CT							
No pulmonary involvement	22	6.2	2	4.7	1	1.3	0.484
Atypical involvement	43	12.2	6	14.0	11	14.1	
Typical pulmonary involvement	288	81.6	35	81.4	66	84.6	
O_2 Saturation, %							
>95	125	35.4	1	2.3	1	1.3	**<0.001**
85–95	206	58.4	10	23.3	3	3.8	
<85	22	6.2	32	74.4	74	94.9	
Treatment agents							
Favipiravir	241	68.3	34	79.1	70	89.7	**<0.001**
Chloroquine	141	39.9	9	20.9	7	9.0	**<0.001**
Steroid	110	31.2	28	65.1	59	75.6	**<0.001**
Antibiotics	199	56.4	25	58.1	56	71.8	**0.043**
Colchicine	1	0.3	1	2.3	5	6.4	**0.001**
Acetil salycilic acid	25	7.1	4	9.3	17	21.8	**<0.001**
LMWH	301	85.3	38	88.4	76	97.4	**0.013**
Paracetamol	96	27.2	15	34.9	39	50	**<0.001**
Vitamins	3	0.8	1	2.3	2	2.6	0.210
TNF alfa inh	1	0.3	1	2.3	3	3.8	**0.023**

ICU: Intensive Care Unit; HF: Heart failure

tions. Most patients had typical pulmonary involvement and were receiving favipiravir treatment. Although 34 patients were discharged, 78 had a mortal course.

Oxygen saturation values of the patients revealed that saturation was >95%, 85–95%, and <85% in 26.5%, 26.7%, and 46.8% of patients, respectively.

Laboratory results of all patients are presented in Table 2. Patients were grouped according to COVID-19 infection outcomes, and the results were compared in terms of demographic data, comorbidities, treatment modalities, and imaging findings (Table 3). There was a statistically significant difference in outcomes except for age, DM, HT, heart failure, oxygen saturation, and vitamin use ($p<0.05$) (Table 3). The mean age of the patients in the ICU and exitus groups was significantly higher compared to the discharged group. The prevalence of DM was higher in both the ICU and the exitus group compared to the discharged group. The prevalence of HT was higher in the ICU and exitus groups compared to the discharged group. In terms of treatment agents, the frequency of use of fa-

Table 4. Comparison of the patient groups in terms of laboratory parameters, PNI score, OR-PNI score and FARI

	Discharged	Referred to ICU	Exitus	Discharged versus referred to ICU	Discharged versus exitus	Referred to ICU versus exitus
	Median (IQR)	Median (IQR)	Median (IQR)	p	p	p
Glucose (mg/dL)	116 (97–153)	139 (108–191)	146 (97.5–211.25)	0.013	0.019	0.873
AST (U/L)	28 (21–41)	39 (25–58)	44.5 (25.5–108.25)	0.003	<0.001	0.144
ALT (U/L)	25 (15.5–39)	38 (21–47)	25.5 (16–48.25)	0.016	0.254	0.301
Urea (mg/dL)	31 (23–43)	48 (33–61.6)	55.5 (33.3 –108)	<0.001	<0.001	0.100
Creatinine (mg/dL)	0.81 (0.67–1)	0.99 (0.81–1.35)	0.92 (0.68–1.70)	<0.001	0.003	0.667
Ferritin (mcg/L)	308.2 (138–582.5)	597 (345.7–1138)	941 (361.25–3011)	<0.001	<0.001	0.090
CRP (mg/L)	38 (12.9–97.3)	80 (34–143)	154.5 (81.4–234)	<0.001	<0.001	<0.001
IL–6 (pg/mL)	26 (8–53.2)	34.8 (17.5–205.5)	850 (129–4886)	0.197	<0.001	0.002
Albumin (g/L)	36.9 (33.8–40)	32.8 (28.1–35.7)	28.4 (23.55–33)	<0.001	<0.001	0.002
D–dimer (mcg/mL)	0.78 (0.44–1.3)	1.18 (0.75–2.9)	3.36 (1.3–11.7)	<0.001	<0.001	0.001
Fibrinogen (mg/dL)	496 (383–637)	580 (452–736)	660 (474.75–764)	0.005	<0.001	0.226
INR	1.02 (0.98–1.11)	1.14 (1.03–1.21)	1.25 (1.11–1.59)	<0.001	<0.001	0.001
WBC (10^3/mcL)	6.62 (5.23–8.33)	7.49 (6.1–11.48)	11.16 (7.18–14.72)	0.020	<0.001	0.004
NEU (10^3/mcL)	4.64 (3.33–6.46)	5.87 (4.2–9.91)	9.84 (6.33–13.21)	<0.001	<0.001	0.002
LYM (10^3/mcL)	1.10 (0.80–1.60)	0.80 (0.50–1.20)	0.70 (0.50–1)	<0.001	<0.001	0.436
MPV (fL)	10.3 (9.6–11.3)	10.4 (9.8–11.1)	10.9 (10.15–11.7)	0.983	0.001	0.018
PNI	43.2 (39–47.05)	36 (32.8–40.5)	33.45 (28.1–37.5)	<0.001	<0.001	0.007
OR–PNI	57.1 (50.8–66.5)	37.7 (34.2–45.9)	35.2 (28.85–39)	<0.001	<0.001	0.001
FARI	14 (9.87–18.27)	19.5 (15.3–22.5)	22.39 (15.9–30.7)	<0.001	<0.001	0.010

PNI: Prognostic Nutritional Index; FARI: Fibrinogen–Albumin Ratio

vipiravir, chloroquine, colchicine, acetylsalicylic acid, low molecular weight heparin, and paracetamol was significantly higher in the exitus group compared to the ICU and discharged groups. Similarly, the rate of antibiotic and tumor necrosis factor (TNF) alpha inhibitor use for the treatment was higher in the exitus group compared to the discharged group (Table 3).

Intergroup analyses examining laboratory findings; PNI, OR-PNI, and FARI scores; and post-hoc subgroup analyses are presented in Table 4. Glucose and ALT levels were significantly higher in the ICU group compared to the discharged group. AST, urea, creatinine, ferritin, and fibrinogen levels were significantly higher, and lymphocyte count was significantly lower in the ICU and exitus groups compared to the discharged patients. CRP, D-dimer, INR, and neutrophil levels were significantly higher in the exitus group compared to the ICU and discharge groups, and in the ICU group compared to the discharge group. The white blood cell level was higher in the exitus group compared to the ICU and discharge groups. PNI and OR-PNI indexes were significantly higher, and the FARI index was significantly lower in the exitus group compared to the ICU and discharge groups and in the ICU group compared to discharged patients (Fig. 1).

In the receiver operating characteristic analysis, a PNI score of <37.05 predicted exitus with 78.9% sensitivity and 73.1% specificity, an OR-PNI score of <41.3 predicted exits with 89% sensitivity and 84.6% specificity, and a FARI score of >18.08 predicted exits with 71.8% sensitivity and 71.1% specificity (Fig. 2). Although the p-value was significant for all three parameters in the receiver operating characteristic analysis, the area under the curve value was found to be statistically significant only for FARI.

DISCUSSION

The results obtained in the present study showed that PNI, OR-PNI, and FARI scores can give an idea about the disease course. The results indicated that PNI and OR-PNI scores

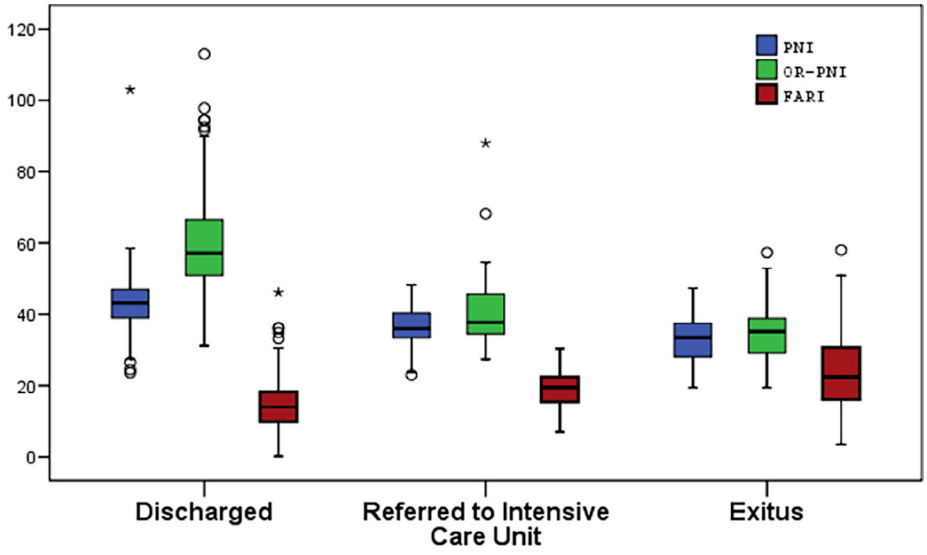
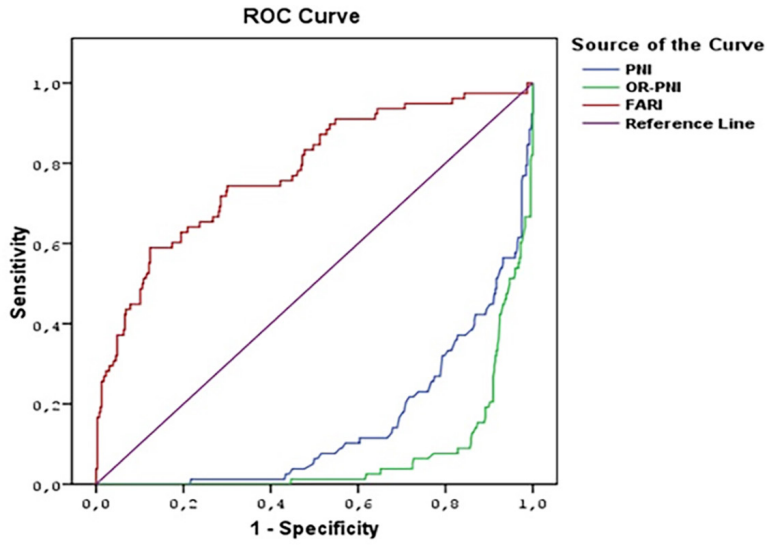


Figure 1. Prognostic nutritional index (PNI), OR-PNI and fibrinogen/albumin ratio index scores of the patients groups



Variable	Area Under the Curve	p	Asymptotic 95% Confidence Interval	
PNI	0,151	<0,001	0,108	0,194
OR-PNI	0,072	<0,001	0,046	0,098
FARI	0,776	<0,001	0,716	0,837

Figure 2. Receiver operating characteristic Curve analysis for prognostic nutritional index (PNI), OR-PNI and fibrinogen/albumin ratio index in Covid-19 patients

ROC: Receiver operating characteristics; FARI: Fibrinogen–Albumin Ratio

decreased and FARI scores increased as the disease endpoint worsened. While the FARI value was a good predictive parameter for mortality, it was observed that PNI and ORPNI did not predict mortality to the same extent.

Due to the high mortality of patients with COVID-19, its diagnosis, treatment, follow-up, and vaccination studies are being conducted rapidly worldwide. It has been found that mortality rates can be reduced by timely identification of high-risk

patients with COVID-19, appropriate patient management, and effective resource utilization. This study aimed to categorize hospitalized patients with COVID-19 according to mortality risk using an inexpensive and noninvasive scoring system.

The importance of nutritional parameters has been known since the early stages of the COVID-19 pandemic.[15] PNI has previously been used in clinical practice to predict postoperative complications.[16] IL-6, IL-8, and TNF alpha, which are cytokines released in acute and chronic inflammatory processes, cause acute respiratory distress syndrome development and progression by decreasing albumin levels.[17] It is known that lymphocytes generate the immune response against viral infection in the host.[18] The 2 years of clinical experience have shown us that cytokine storms are observed in COVID-19 cases, with the mortal course in some cases. Mazzoni et al.[19] found that a cytokine storm occurred and levels of TNF alpha and IL-6 increased in severe COVID-19 cases, resulting in the development of lymphocyte apoptosis. PNI scores obtained from albumin and lymphocyte levels are associated with COVID-19 progression and mortality.[20] In our previous study, we categorized our patients as having normal or mild malnutrition and moderate-to-severe or serious malnutrition using the PNI score and concluded that mortality was higher in patients with severe malnutrition.[14] The results obtained in the present study are in accordance with the data we presented in our previous study.

In the present study, age, comorbid conditions, drugs other than vitamin groups used in pharmacotherapy, and oxygen saturation levels were found to be effective in determining COVID-19 endpoints. Furthermore, the OR-PNI score, which we created by combining clinical data, oxygen saturation percentage, and thoracic CT findings with the PNI score, could provide information about the course of the disease, although it was not directly related to mortality. Xie et al.[21] reported that low oxygen saturation with a cutoff value of 90.5% was associated with mortality in patients who were hospitalized due to COVID-19 infection alone. In a multicenter study involving 3,927 patients diagnosed with COVID-19, it was found that low oxygen saturation and high CRP and creatinine levels were strongly associated with mortality.[22] Algorithms and artificial intelligence models created using COVID-19 thoracic CT imaging data provide valuable insights into the diagnosis and prognosis of the disease.[23,24] The COVID-19 Reporting and Data System were established in 2020 with the aim of standardizing COVID-19 CT findings.[25]

Microthrombi and the coagulation cascade are important in the pathophysiology of COVID-19 infection. FARI has been presented as a marker of thrombosis risk, inflammation, and nutritional status.[23] In the present study, we compared OR-PNI with FARI and PNI, as they are considered predictors of mortality in intense inflammatory processes such as COVID-19. The results showed that the FARI value is effective in predicting mortality rather than PNI and OR-PNI. The difference in OR-PNI from the other scores was that it included COVID-19-related clinical and radiological data in addition to nutritional parameters. Both PNI and FARI can be associated with all inflammatory processes and, therefore, provide the clinician with generalized data on the patient. In contrast, the OR-PNI score is specifically adjusted to include the COVID-19 clinical picture. Therefore, it can be suggested that categorizing COVID-19 cases based on the OR-PNI is valuable in predicting progression but not mortality of COVID-19.

The main limitation of this study was its retrospective design, as the prognosis of the patients who did not have a mortal course was not followed in the post-COVID period. Therefore, further prospective observational studies should be conducted to support our results. Oxygen saturation is a parameter that can vary in a short time and can slightly decrease the reliability of the OR-PNI score. On the other hand, pulmonary involvement in COVID-19 infection may be evident and severe in certain periods of the disease; however, there may not yet be any evidence of pulmonary involvement in the early stages, leading to misinterpretation of the index scores. However, as seen in this study, we believe that it will be more useful to apply this index in clinical practice when the clinical picture is established, the disease is symptomatic, and patients require hospitalization and follow-up. Based on this, we propose that the OR-PNI index may not be appropriate for use in outpatients with COVID-19 but may provide reliable information about the course of the disease in inpatients.

CONCLUSION

In this retrospective study we found that FARI score is a reliable parameter to predict the mortality in patients with COVID-19. On the other hand, although PNI and OR-PNI scores were closely related to the course of the disease, they failed to predict mortality.

Disclosures

Ethics Committee Approval: The study was approved by the Kanuni Sultan Suleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2021.10.271, Date: 13/10/2021).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions: Concept: M.T., İ.E., M.A., A.Ç., Y.Ö., H.Ö., B.T., İ.K.U.; Design: M.T., İ.E., M.A., A.Ç., Y.Ö., H.Ö., B.T., İ.K.U. G.A., Ö.T.; Supervision: M.A., İ.E., Ö.T.; Materials: M.T., H.Ö., Y.Ö., G.A., İ.K.U., A.Ç.; Data Collection or Processing: M.T., İ.E., Y.Ö., H.Ö., İ.K.U., A.Ç., G.A.; Analysis or Interpretation: M.A., İ.E., Ö.T.; Literature Search: M.T., İ.E., M.A., Ö.T., A.Ç., Y.Ö., İ.K.U., H.Ö.; Writing: M.T., İ.E., M.A.; Critical review: M.T., İ.E., M.A., A.Ç., Y.Ö., Ö.T., İ.K.U., H.Ö., G.A.

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