Factors Associated with Intensive Care Hospitalization in Patients with Covid-19

Covid-19 Hastalarında Yoğun Bakım Yatışı ile İlişkili Faktörler

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Öz

Amaç: Bu çalışmada biyokimyasal parametreler, vital bulgular ve nötrofil-lenfosit oranı (NLR) değerlerinin COVID-19 hastalarında yoğun bakım yatış endikasyonunun belirlenmesinde kullanılabilir olup olmadığı amaçlandı.
Hastalar ve Yöntem: Bu retrospektif gözlemsel çalışma, bir üniversite hastanesinin acil servisinde gerçekleştirildi. 1-31 Temmuz 2020 tarihinde hastanemize başvurmuş SARS-CoV-2 PCR testi pozitif olan hastalar çalışmaya dahil edildi. Elektronik ortamda hastaların laboratuvar sonuçları, demografik bulguları ve klinik sonuçları toplandı. Hastalar taburcu edilmiş, servise veya yoğun bakıma yatışı yapılmış olarak 3 gruba ayrıldı. Gruplar arasında semptomların görülme sıklığı, şiddeti, ek hastalıklar, laboratuvar değerleri, NLR değerleri kıyaslandı.
Bulgular: Çalışmaya toplam 489 hasta dahil edildi. Dahil edilen hastaların ortalama yaşı 48.69 + 17.25 yıl iken bunların 260'ı (%53,16) kadındı. Bu hastaların 248'i (%50,9) taburcu edilirken, 207'si (%42,3) servislere, 33 (%6,7)'ü de yoğun bakım ünitelerine alındı. Yoğun bakıma yatış yapılan hastaların yaş, kalp hızı, üre, kreatinin, CRP, D-dimer ve NLR değerleri diğer gruplara kıyasla yüksekken, bu grupta oksijen saturasyonu ise istatiksel olarak anlamlı derecede düşüktü. Yoğun bakımı yatışı olanlarda Diabetes Mellitus, Esansiyel Hipertansiyon, Kronik Obstrüktif Akciğer hastalığı gibi eşlik eden sistemik rahatsızlıklar daha fazlaydı. Çok değişkenli analizde oksijen satürasyonu (OR:0.803) ve nötrofil-lenfosit oranı (OR:1.09) yoğun bakım ünitesinde yatış endikasyonunun bağımsız öngördürücüsü olarak bulundu.
Sonuç: Çalışmamızın sonucunda acil servise COVID-19 nedeni ile başvuran hastalarda özellikle düşük oksijen satürasyonu ve yüksek nötrofil-lenfosit oranının yoğun bakım yatış endikasyonun belirlenmesinde kullanılabileceklerini düşünüyoruz.

Anahtar Kelimeler: Acil servis, COVID-19, pandemi, NLR, yoğun bakım

Abstract

Aim: In this study, it was aimed whether biochemical parameters, vital signs and neutrophil-lymphocyte ratio (NLR) values could be used in determining the indication for intensive care hospitalization in COVID-19 patients.
Patients and Methods: This retrospective observational study was conducted in the emergency department of a university hospital. Patients with positive SARS-CoV-2 PCR test who applied to our hospital on 1-31 July 2020 were included in the study. Laboratory results, demographic findings and clinical results of the patients were collected electronically. The patients were divided into 3 groups as discharged, admitted to the service or intensive care unit. The incidence and severity of symptoms, comorbidities, laboratory values, and NLR values were compared between the groups.
Results: A total of 489 patients were included in the study. The mean age of the included patients was 48.69 + 17.25 years, of which 260 (53.16%) were female. While 248 (50.9%) of these patients were discharged, 207 (42.3%) were taken to the service and 33 (6.7%) to the intensive care units. Age, heart rate, urea, creatinine, CRP, D-dimer and NLR values of the patients admitted to the intensive care unit were higher than the other groups, while oxygen saturation was statistically significantly lower in this group. Concomitant systemic diseases such as Diabetes Mellitus, Essential Hypertension, Chronic Obstructive Pulmonary Disease were more common in those hospitalized in the intensive care unit. In multivariable analysis, oxygen saturation (OR:0.803) and neutrophil-lymphocyte ratio (OR:1.09) were found to be independent predictors of the indication for hospitalization in the intensive care unit.
Conclusion: As a result of our study, we think that especially low oxygen saturation and high neutrophil-lymphocyte ratio can be used in determining the indication for intensive care hospitalization in patients who apply to the emergency department due to COVID-19.

Key words: Emergency department, COVID-19, pandemic, NLR, intensive care

INTRODUCTION

Towards the end of 2019, cases of unexplained lung disease were reported in China (1). On January 7, 2020, a new beta-coronavirus was detected from patients' throat swab sample and was later named 2019-novel coronavirus disease (COVID-19) by the World Health Organization (WHO) (2,3). Upper respiratory tract disease findings such as cough, fever, shortness of breath, fatigue and sputum production are among the common symptoms of the disease. [4]. Approximately 81% of their patients had mild symptoms (low-grade fever, fatigue, dry cough, and abnormal chest findings, etc.), while signs of serious illness (severe acute respiratory distress syndrome, diffuse lung infiltration, renal failure or development of failure in many organs) are observed in 14% of cases. (4,5). Dyspnea and/or hypoxemia symptoms predominate in those with severe disease symptoms, and the majority of cases result in death. As we learn more about the spectrum of COVID-19 disease, it has been found that there is a complex interaction within the immune system initiated by viral infection, and the resulting uncontrolled and altered hyperinflammatory response contributes to high morbidity and mortality in addition to direct viral damage [5]. As there is no specific treatment and medication for this disease, it is necessary to identify the severity and diagnostic risk factors for COVID-19 infection. Biomarkers of circulating inflammation and immune status are prognostic predictors for patients with COVID-19. In this context, systemic inflammation markers such as peripheral white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR) have been shown to be important in predicting the prognosis of the disease in different studies (6-10).

It has been determined that COVID-19 cases need more follow-up in the intensive care unit and 40% to 96% of the patients hospitalized to the intensive care unit have acute respiratory distress syndrome. The need for invasive mechanical ventilation (IMV) has varied widely between different case series, but has always been associated with high mortality. When the mortality rates in the patients followed in the intensive care unit are examined, it has been shown that although it differs according to the anoher study, it varies between 16% and 78% (11).

In this study, we investigated whether biochemical parameters, vital signs and neutrophil lymphocyte ratio could be used to determine the indication for intensive care hospitalization in COVID-19 patients.

PATIENTS AND METHOD

With the approval of the ethics committee, patients who applied to our hospital between 1-31 July 2020 and whose diagnosis of COVID-19 were confirmed with a swab sample were retrospectively screened and included in the study. Under 18 years old, pregnant, missing data, voluntary discharged or referred another hospital were not included in the study. In the study, the medical records of 489 patients were searched through the hospital database. Laboratory results, demographic findings and clinical results of the patients were collected electronically. Complete blood count values, biochemical parameters, d-dimer and CRP values were checked for laboratory tests. The patients were divided into 3 groups as discharged, hospitalized to the service or intensive care unit. The incidence and severity of symptoms, comorbidities, laboratory values, and NLR values were compared between the groups. The local ethics committee approved the study protocol (decision no. 2021-31982).

The data obtained were evaluated using the Statistical Package for Social Sciences for Windows 21.0 (SPSS Inc., Chicago, Illinois, USA) statistical program. Descriptive statistics were determined for each variable. After analysis of normality of parameters, data were expressed as mean ± standard deviation or median and interquartile range (IQR). Mixed ANOVA models were used to assess differences between groups in terms of continuous variables. Bonferroni test was used for Post-Hoc analysis. A difference was considered statistically significant when p-value <0.05. We regrouped the patients as those admitted to the intensive care unit and not. And then binomial logistic regression analysis was performed to determine independent predictors for the intensive care hospitalization. Factors with a p value of <0.2 were included in the univariate analysis in the regression test, while those that were significant in the univariate analysis were included in the multivariable evaluation

RESULTS

This was a cross-sectional study evaluating 489 people (260 females, 229 males; mean age, 48.69 + 17.25 years) who applied to the emergency department due to COVID-19. Demographic, clinical characteristics and biochemical parameters of 489 patients with COVID-19 were depicted in Table 1.

When patients are grouped in terms of hospitalization indication after admission to the

Table 1. Demographic, Clinic, and Biochemical Features of The Patients.

Parameters	Patients with COVID-19 (n=489) (Mean±SD), Median (IQR) or Frequency (n-%)
Age (years)	48.69+17.25
Female/Male	260/229
History of Diabetes Mellitus	66 (%13.5)
History of Hypertension	96 (%19.6)
History of Coronary Artery Disease	62 (%12.7)
History of Chronic Obstructive Pulmonary Disease	50 (%10)
History of Malignancy	10 (%2)
Oxygen saturation (%)	93.72 + 5.84
Fever (C°)	36.86 + 0.66
Heart rate (bpm)	97.76 + 18.46
Systolic blood pressure (mmHg)	124.16 + 19.47
Diastolic blood pressure (mmHg)	78.99 + 13.16
Urea (mg/dl)	29 (13)
Creatinine (mg/dL)	1.05 + 0.46
Lymphocyte count (10^3/µL)	1.38 (1.16)
Neutrophil count (10^3/µL)	3.85 (2.55)
Neutrophil lymphocyte ratio	2.69 (3.62)
CRP (mg/L)	11.2 (30.4)
D-Dimer (µg/mL)	580.5 (631)
Troponin positivity	18 (%3.7)
Thorax tomography finding	339 (69.3%)
Outcome	
Discharged	248 (%50.9)
Follow-up in service	207 (%42.3)
Follow-up in intensive care	33 (%6.7)

hospital there were no significant diferences with respect to the following variables between groups; gender, and lymphocyte counts. The group that was given an indication for hospitalization in the intensive care unit had significantly lower oxygen saturation, while age, fever, heart rate, serum urea, creatinine, neutrophil count, neutrophil-lymphocyte ratio, CRP, and D-Dimer were significantly higher in this group (Table 2). When the patients were examined in terms of threshold chronic diseases, systemic diseases such as diabetes mellitus, primary hypertension, chronic obstructive pulmonary disease were more common in those hospitalized in the intensive care unit.

We also performed binomial logistic regression analysis to define variables that are independently associated with the indication of hospitalization in the intensive care unit (Table 3). Age, oxygen saturation, fever, heart rate, urea, creatinine, neutrophil-

Table 2. Treatment methods accoring to the closure patterns

Parameters	Discharged (n=249) (Mean±SD), Median (IQR) or Frequency (n-%)	Service (n=207) (Mean±SD), Median (IQR) or Frequency (n-%)	Intensive care (n=33) (Mean±SD), Median (IQR) or Frequency (n-%)	p
Age (years)	39.81 + 12.65	55.86 + 15.63	70.73 + 16.75	<0.001
Female/Male	134/115 (53.8/46.2)	107/100(51.6/48.4)	19/14(57.6/42.4)	0.719
Oxygen saturation (%)	95.9 + 1.9	93.21 + 3.98	79.8 + 12.69	<0.001
Fever (C°)	36.7 + 0.58	36.9 + 0.68	37 + 1.03	0.01
Heart rate (bpm)	94.58 + 15.1	99.49 + 16.31	111.28 + 38.27	<0.001
Urea (mg/dl)	28 (12)	32 (20)	96.5 (109)	<0.001
Creatinine (mg/dL)	0.93 + 0.19	1.04 + 0.35	2.01 + 1.07	<0.001
Lymphocyte count (10^3/µL)	1.25 (1.16)	1.05 (0.78)	0.6 (0.43)	0.138
Neutrophil count (10^3/µL)	3.59 (1.89)	4.23(3.62)	9.5 (4.67)	<0.001
Neutrophil lymphocyte ratio	2.96 (3.27)	3.32 (5.32)	16.72 (29.54)	<0.001
CRP (mg/L)	6 (16.8)	26.4 (41)	148 (176.3)	<0.001
D-Dimer (µg/mL)	254 (195)	615 (468)	2169 (2581)	<0.001

Table 3. Binomial Logistic Regression Analysis of Intensive Care Hospitalization and Other Parameters in Patients with COVID-19.

Parameters	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	1.09 (1.06-1.11)	<0.001	0.99 (0.95-1.03)	0.729
Oxygen saturation (%)	0.69 (0.63-0.76)	<0.001	0.803 (0.72-0.89)	<0.001
Fever (C°)	1.59 (1.01-2.52)	0.045	0.52 (0.24-1.11)	0.094
Heart rate (bpm)	1.03 (1.01-1.05)	<0.001	0.98 (0.96-1.01)	0.276
Urea (mg/dl)	1.04 (1.03-1.05)	<0.001	1.00 (0.97-1.04)	0.757
Creatinine (mg/dL)	13.13 (6.38-26.98)	<0.001	1.68 (0.61-4.62)	0.316
Neutrophil lymphocyte ratio	1.22 (1.15-1.29)	<0.001	1.09 (1.02-1.17)	0.01
CRP (mg/L)	1.02 (1.01-1.02)	<0.001	0.99 (0.98-1.01)	0.817
D-Dimer (µg/mL)	1.00 (1.00-1.002)	<0.001	1.00 (1.00-1.001)	0.098

lymphocyte ratio, CRP, and D-dimer were included in this model. As a result of our multivariable analysis, oxygen saturation and NLR values were found to be independent predictors of the indication for hospitalization in the intensive care unit (Table 3).

DISCUSSION

COVID-19 caused a rapid outbreak with human-to-human transmission, with a median incubation period of 3 days and a relatively low death rate (1). However, despite the low mortality rate, the disease progresses severely in elderly patients with concomitant chronic diseases such as diabetes or hypertension. It has been found that intensive care hospitalizations and mortality rates increase in direct proportion with age in studies examining COVID-19 cases worldwide (12-14). In another study conducted by Maddani et al. (15)., it was found that the risk of death in people over the age of 80 was 20 times higher than in those between 50 and 59 years of age, which supports the literature. In our study, we observed that the group with an indication for intensive care hospitalization was older and the presence of concomitant systemic disease caused an increase in the indication for intensive care admission.

Recent studies have shown that the virus binds to alveolar cells through receptor mediated and stimulates macrophages to release inflammatory markers (16). Accordingly, factors and chemokines that use other mononuclear cells are released. Mononuclear cells, mostly lymphocytes, were found to predominate in the interstitial space of the lung. The current situation partially explains the lymphopenia picture in peripheral blood. In another study, patients with severe disease had significantly lower lymphocyte levels, but no significant difference was found between neutrophil levels (16,17). At the same time, it has been stated that there is a direct proportional relationship between the degree of lymphopenia and the severity of the disease and intensive care admissions in different studies (4,15). In a meta-analysis evaluating patients with severe COVID-19, it was found that higher white blood cell counts and elevated leukocyte levels are hallmarks of patients in critical condition (18,19). In our findings, although it was not statistically significant, the lymphocyte count was found to be lower in patients with intensive care hospitalization, while the neutrophil count was significantly higher.

Although the lungs are the main target organ for the coronavirus, the end organ damage is not just the lungs. It is known that lymphocytes inhibit immune reactions caused by viral infection. Therefore, it has been shown that the lack of effective lymphocyte levels caused by SARSCoV-2 infection causes an increase in cytokines and exacerbation of inflammatory responses, leading to liver and kidney damage (20,21). In addition, coagulation abnormalities frequently occur in COVID-19 patients, which complicates patient management. This disorder is manifested by a marked increase in D-dimer levels (22,23). Laboratory

parameters such as increased CRP, D-dimer, and NLR were associated with the incidence of severe disease, and as a result, it was mentioned that these markers can help predict severity and prognosis (15). In our study, urea, creatinine and D-dimer levels were found to be increased in patients admitted to the intensive care unit, in line with the literature.

Shang et al. (9) showed in a study that values such as platelet count, CRP, and NLR were effective in determining the prognosis of the disease. In another study, the relationship between the hematological values of the patients and the length of stay in the hospital was examined, and a decrease in lymphocyte count and a significant increase in NLR were found in patients with severe disease symptoms. When they examined the length of hospital stay, they found a positive correlation with NLR and as a result they stated that NLR could be used to predict the prognosis of the disease (17). In a study conducted to determine the cut-off value of NLR, which can be used for prognosis prediction, it was found that mortality and intensive care hospitalizations increased significantly when the NLR was above 4,5. In the same study, it was reported that NLR can help clinicians detect potentially serious cases early, perform early triage, and initiate effective management in a timely manner (24). In our study, in support of the above findings, serum NLR and CRP values were statistically significantly higher in the patient group requiring intensive care admission. In addition, age, oxygen saturation, fever, heart rate, urea, creatinine, neutrophil-lymphocyte ratio, CRP and D-dimer were found to be statistically significant in the univariate regression analysis we performed to define the variables associated with the indication for hospitalization in the intensive care unit. In multivariable analysis, high NLR and low oxygen saturation were independent predictors of intensive care hospitalization indication.

There are some limitations in our study. First of all, our study was designed as a single center because it was the only hospital in the province that evaluated pandemic patients, and our sample was not large enough. Almost all of the patients included in the study were Turkish. It should be considered that our results cannot be applied to all patients due to the differences that may occur between nationalities.

CONCLUSION
As a result, we found that oxygen saturation and neutrophil-lymphocyte ratio were independent predictors of the indication for hospitalization in the intensive care unit. Therefore, we think that these parameters can be used in determining the indication for intensive care hospitalization in patients who apply to the emergency department due to COVID-19.

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