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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

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Effects of Anemia on Clinical Outcomes in Hospitalized Patients with COVID-19 Pneumonia

Hilal Kurtoğlu Gümüşel[1], Selçuk Görmez[1], Ömer Özçağlayan[2], Burak Pamukçu[1]

[1]Acıbadem Healthcare Group, Acibadem Kadikoy Hospital, Department of Cardiology, Istanbul, Turkey

[2]Istanbul Oncology Hospital Department of Radiology, Istanbul, Turkey

Hilal KURTOĞLU GÜMÜŞEL
Selçuk GÖRMEZ
Ömer ÖZÇAĞLAYAN
Burak PAMUKÇU

Correspondence: Burak Pamukçu
Acıbadem Healthcare Group, Acibadem Kozyatağı Hospital, Department of Cardiology, Istanbul, Turkey
Phone: +902165714449
E-mail: burak.pamukcu@acibadem.edu.tr

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ABSTRACT

Objective: We aimed to examine the role of anemia on clinical outcomes including intensive care unit (ICU) admission and mechanical ventilation (MV) in coronavirus disease 2019 (COVID-19) patients.

Materials and methods: Totally 175 hospitalized COVID-19 patients were retrospectively included. Patients with a hemoglobin level of <12 g/dL in women and <13 g/dL in men constituted the anemic group, while COVID-19 patients with normal hemoglobin levels constituted the non-anemic group. A logistic regression analysis was performed to investigate the role of anemia and serum ferritin value for prediction of ICU and MV requirement.

Results: Of patients, 46 (45.7%, 21 men) had anemia and 129 (68.2%, 88 men) had normal hemoglobin levels. The ICU requirement and MV rates were significantly higher in anemic group compared to non-anemic group (30.4% vs. 15.5%, respectively; p=0.028 and 23.9% vs. 10.9%, respectively; p=0.030). Median length of hospital and ICU stay was longer in patients with anemia (10.5 days vs. 8 days, respectively; p=0.047 and 0 days vs. 0 days, respectively; p=0.027). Anemia and ferritin were significant risk factors for ICU admission in univariate model and multivariate model [OR: 2.384 (95% CI: 1.084-5.246), p=0.031] vs. [OR: 2.738 (95% CI: 1.130-6.635), p=0.026] and [OR: 5.058 (95% CI: 1.968-12.998), p=0.001] vs. [OR: 4.218 (95% CI: 1.521-11.697), p=0.006]. Anemia was also a risk factor for MV [OR: 2.582 (95% CI: 1.075-6.197), p=0.034].

Conclusion: Requirement for therapy in ICU and MV were high among anemic COVID-19 patients. Anemia is also associated with prolonged length of stay in hospital and ICU.

Keywords: Coronavirus disease 2019 (COVID-19); anemia; ferritin; intensive care unit; mechanical ventilation

COVID-19 Pnömonisi Nedeni ile Yatarak Tedavi Gören Hastalarda Aneminin Klinik Sonuçlara Etkisi

ÖZET

Amaç: COVID-19 hastalarında aneminin yoğun bakım ünitesine yatış ve mekanik ventilasyon gibi klnik sonuçlara etkilerini incelemeyi amaçladık.

Materyal ve metodlar: Toplam 175 yatarak tedavi gören COVID-19 hastası retrospektif olarak çalışmaya alındı. Kadınlarda hemoglobin düzeyi <12 g/dL ve erkeklerde <13 g/dL olan hastalar anemi grubunu oluştururken, normal hemoglobin düzeyi olan hastalar anemik olmayan grubu oluşturdu. Anemi ve ferritin seviyesinin yoğun bakım ve mekanik ventilasyon ihtiyacını öngörmede rolü lojistik regresyon analizi ile incelendi.

Bulgular: Hastalardan 46'sı (%45.7, 21 erkek) anemik ve 129'u (%68.2, 88 erkek) normal hemoglobin düzeylerine sahipti. Yoğun bakım ihtiyacı ve mekanik ventilasyon hızı anemik hastalarda anemik olmayanlara göre anlamlı oranda yüksekti (%30.4% vs. %15.5, sırasıyla; p=0.028 ve %23.9 vs. %10.9, sırasıyla; p=0.030). Medyan hastanede ve yoğun bakımda kalış süreleri anemik hastalarda daha uzundu (10.5 gün vs. 8 gün; p=0.047). Anemi ve ferritin düzeyi tek değişkenli ve çok değişkenli analizlerde yoğun bakıma yatış için belirgin risk faktörü olarak saptandı [OR: 2.384 (%95 CI: 1.084-5.246), p=0.031] vs. [OR: 2.738 (%95 CI: 1.130-6.635), p=0.026] ve[OR: 5.058 (%95 CI: 1.968-12.998), p=0.001] vs. [OR: 4.218 (95% CI: 1.521-11.697), p=0.006]. Anemi mekanik ventilasyon için de risk faktörü olarak saptandı [OR: 2.582 (%95 CI: 1.075-6.197), p=0.034].

Sonuçlar: Anemik Covid-19 hastalarında yoğun bakım ve mekanik ventilasyon ihtiyacı yüksekti Anemi aynı zamanda hastane ve yoğun bakımda uzamış kalış süreleri ile ilişkili bulundu.

Anahtar sözcükler: COVID-19 (koronavirüs hastalığı 2019); anemi; ferritin; yoğun bakım ünitesi; mekanik ventilasyon

Novel coronavirus 2019 (COVID-19) outbreak, which first emerged in Wuhan, Hubei province of China in December 2019, continues as a serious pandemic affecting millions of individuals around the world. The disease severity varies among individuals from mild asymptomatic disease to severe pneumonia. COVID-19 pneumonia, which can involve multiple lung segments, may cause mild, moderate or severe disease (1). Although most infections have a mild clinical course, up to 20% of infected patients need to be hospitalized mainly for pneumonia, and some of these patients may need therapy in an intensive care unit (ICU) and may require mechanical ventilation (MV) (2,3). It has been reported that, in severe cases, dyspnea and hypoxemia are often observed, and a group of patients develop septic shock and acute respiratory distress syndrome (ARDS) (4). Approximately 5 to 8% of the total infected population and 25% of all hospitalized patients need hospitalization in the ICU setting (5). COVID-19 infection may also lead to multiple organ dysfunction syndrome, resulting in increased inflammation, cytokine storm, hypoxia, and thrombosis (6). However, the underlying pathophysiology affecting clinical endpoints has not been completely elucidated, yet. Theoretically, anemia may play an important role in the development of multiple organ failure by reducing oxygen transport to tissues (7).

Anemia is a common health problem affecting approximately 2 billion individuals worldwide (8). It has been associated with many critical illnesses (9). It increases mortality and morbidity in many diseases such as heart failure, chronic obstructive pulmonary disease, and myocardial infarction (10-12). A higher rate of mortality has been observed in anemic patients with community-acquired pneumonia (13).

Serum ferritin is one of the biomarkers of iron deficiency anemia. Ferritin level reflects iron or iron accumulation stored in liver tissue. Therefore, the level of ferritin is low in iron deficiency anemia (14). On the other hand, a high ferritin level may indicate a chronic inflammatory process or the presence of infection (15). Ferritin is an acute phase protein which can be also assessed in various inflammatory diseases. Ferritin levels of up to 10,000 ng/mL can be seen in macrophage activation syndrome (16). In COVID-19, low hemoglobin levels may be one of the reasons of failed supply of the increased oxygen demand at peripheral tissues due to hypermetabolic conditions that develop during infection.

In the present study, we aimed to examine the relationship between the initial hemoglobin level during hospitalization and duration of hospital stay, ICU and MV requirement and duration of ICU in patients with COVID-19 pneumonia. In addition, we investigated the role of the serum ferritin in the clinical course of COVID-19 disease and to identify whether anemia was a possible predictor of ICU and MV for COVID-19 disease.

MATERIALS AND METHODS

This multi-center, retrospective study was conducted between march 2020 and may 2020. The study protocol was approved by the institutional Ethics Committee (No: 2021-05/26, Date: 03/10/2021). The study was also approved by the central government health authority with the approval number of 2021-03-03T00_03_17. The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from all patients included in the study.

A total of 175 adult (≥18 years) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) cases with a confirmed diagnosis by real-time polymerase chain reaction (RT-PCR) who had ground glass appearance and/or consolidation compatible with COVID-19 pneumonia on thoracic computed tomography (CT) were included in the study. Patients with missing medical data, having pregnancy, and age under 18 years were excluded. Clinical characteristics, symptoms and laboratory parameters of patients were recorded on the electronic patient data sheet. Clinical outcomes were retrieved from the hospital database and recorded. The length of hospitalization, therapy interval at ICU, requirement for MV, and clinical events were noted.

Blood samples were collected within 4 h after admission to perform routine laboratory tests including complete blood count, coagulation tests, and biochemical assays. Blood counts were performed using the Sysmex™ Xn 1800i (Sysmex Co., Kobe, Japan) system. Inter- and intra-day variability coefficients were calculated as 3.5% and 4.1%, respectively. All measurements were carried out within 2 h after blood sampling.

Patients with a hemoglobin level of <12 g/dL in women and <13 g/dL in men were considered as anemic and consisted the anemic group. The COVID-19 patients with normal hemoglobin levels consisted the non-anemic group. Normal ferritin values were accepted between 22 ng/dL

and 322 ng/dL and normal D-dimer values were accepted below 0.5 ug/mL in our laboratory.

In our study, the presence of tachypnea (respiratory rate >30/min), progressive dyspnea and increased work of breathing, peripheral oxygen saturation (SpO_2) <90% without response to oxygen up to 12 L/min with reservoir, lactate levels of >2 mmol/L, and systolic blood pressure below 80 mmHg were the indications for ICU admission. Despite high-flow oxygen therapy and non-invasive MV therapy, blood gas analysis oxygen saturation (SaO_2) <90%, pH <7.3, and carbon dioxide (CO_2) >50 mmHg, increased respiratory work, worsening mental state, hemodynamic instability, or multiple organ failure were the indications for MV.

Both study groups were compared in terms of demographic features, ICU and MV requirements, and duration of hospitalization.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 statistical software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the distributions of continuous variables were normal or not. Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) and interquartile range (IQR) or number and frequency, where applicable. The Student t-test and Mann-Whitney U tests were used to compare the normally and non-normally distributed numerical variables between the study groups. Categorical variables were compared using the chi-square (χ^2) test. Since the ferritin value was non-normally distributed, log-transformation was performed. Normally distributed log-transformed ferritin values were included in the logistic regression analysis. Univariate and multivariate binary logistic regression analysis with the enter mode were carried out to investigate the predictive value of anemia and serum ferritin value (log-transformed) for ICU and MV requirements. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of the patients 46 had anemia and 129 had normal hemoglobin levels. The COVID-19 patients in the anemic group were older than the patients in non-anemic group (55.0±13.5 years vs. 49.0±13.45 years, respectively; p=0.011). There was also a statistically significant difference regarding male sex between the anemic and non-anemic patient groups [(45.7% (n=21) vs. 68.2% (n=88), respectively; p= 0.007].

In our study, ferritin values were pathologically high in both groups of patients hospitalized due to COVID-19. However, the median ferritin values in both groups were measured as 324 ng/dL (range, 6 to 3700, IQR=464) in the anemic group and 318 ng/dL (range, 0 to 2727, IQR=366) in the non-anemic group, respectively, indicating no statistically significant difference between the groups (p=0.941).

The median D-dimer values were measured as 0.65 ug/mL (range, 0.14 to 8300, IQR=0.9) in the anemic group and 0.58 ug/dL (range, 0.12 to 4.91, IQR=0.44) in the non-anemic group and D-dimer values were also pathologically high in both study groups. There was no statistically significant difference in the D-dimer values between the groups (p=0.231).

The prevalence of hypertension, diabetes mellitus, heart failure, smoking status were similar between the groups. However, coronary artery disease was more common in the anemic group (p=0.036). Baseline demographic and clinical characteristics and laboratory parameters are shown in Table 1.

The median total length of hospitalization was longer in the anemic group, compared to the non-anemic group, indicating a statistically significant difference (10.5 days (range, 4 to 32) vs. 8 days (range, 3 to 73), respectively; p=0.047). Also, the rate of the patients requiring hospitalization in the ICU was significantly higher in the anemic group (30.4% vs. 15.5%, respectively; p=0.028) (Figure 1). The median length of stay in the ICU was also longer in the anemic group, indicating a statistically significant difference (0 days (range, 0 to 22), IQR=6.5 vs. 0 days (range, 0 to 69), IQR=0, respectively; p=0.027).

In our study, two patients in the anemic COVID-19 group and one patient in the non-anemic COVID-19 group died in the ICU setting due to respiratory distress syndrome and multiple organ failure. Comparison of clinical outcomes among COVID-19 patients with and without anemia, including the need for ICU admission and the need for MV, as well as length of stay in the hospital and ICU, are presented in Table 2.

Table 1. Baseline demographics, clinical characteristics and laboratory parameters of patients

	Anemic group (n=46)	Non-anemic group (n=129)	P value
Age (years)	55.0 ± 13.5	49.0 ± 13.5	**0,011†**
Sex (male)	21 (45.7%)	88 (68.2%)	**0,007#**
Diabetes mellitus	4 (8.7%)	14 (10.9%)	0,679#
Hypertension	14 (30.4%)	39 (30.2%)	0,980#
Coronary artery disease	7 (15.2%)	7 (5.4%)	**0.036#**
Heart failure	1 (2.2%)	0 (0 %)	0.263*
Cigarette smoking	11 (23.9%)	33 (25.6%)	0,823#
Hemoglobin (g/dL)	11.7±0.9	14.2±1.1	**<0.001†**
Ferritin (ng/dl)	324 (6-3700) IQR = 464	318 (0-2727) IQR = 366	0.941§
D-dimer (ug/ml)	0.65 (0.14-8300) IQR = 0.90	0.58 (0.12-4.91) IQR = 0.44	0.231§
MCV	83±4	86±4	0.653
MCHC	33.5±1.2	34.6±1.3	0.467
Creatinine	1.05±0.05	1.03±0.04	0.726

Data are shown as mean ± standard deviation (SD), median (min-max, IQR) and n (%), unless otherwise stated. †Student *t*-test, §Mann-Whitney U test, #chi-square test, *Fisher exact test. IQR: interquartile range, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration.

Table 2. Comparison of clinical outcomes

	Anemic group (n=46)	Non-anemic group (n=129)	P value
Hospitalization (days)	10.5 (4-32) IQR=9	8 (3-73) IQR=8	**0,047§**
ICU admission	14 (30.4%)	20 (15.5%)	**0.028#**
MV	11 (23.9%)	14 (10.9%)	**0.030#**
ICU duration (days)	0 (0 – 22) IQR=6.5	0 (0 – 69) IQR=0	**0.027§**

Data are shown as median (min-max, IQR) and n (%), unless otherwise stated. §Mann -Whitney U test, #chi-square test, IQR: interquartile range, ICU: Intensive Care Unit, MV: Mechanical Ventilation.

In the logistic regression analysis, anemia was found to be a statistically significant risk factor in the univariate model [OR: 2.384 (95% CI: 1.084-5.246), p=0.031] and multivariate model (age- and sex-adjusted) [OR: 2.738 (95% CI: 1.130-6.635), p=0.026] for ICU admission. Log-transformed ferritin value in both univariate [OR: 5.058 (95% CI: 1.968-12.998), p=0.001] and multivariate models [OR: 4.218 (95% CI: 1.521-11.697), p=0.006] was also found to be a statistically significant risk factor for ICU (Table 3).

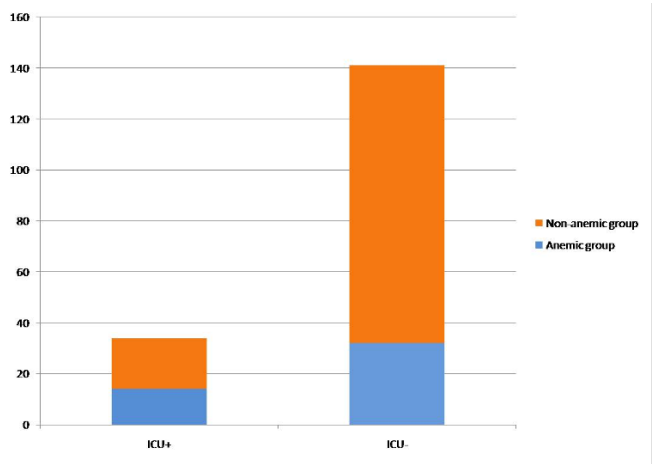

Figure 1. Distribution of study groups according to ICU admission

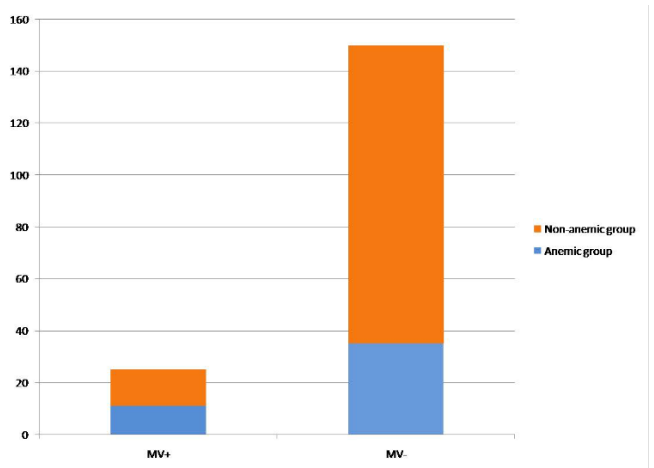

Figure 2. Distribution of study groups according to MV requirement

The patients with anemia did not respond well to high-flow oxygen therapy and non-invasive MV support with bilevel positive airway pressure (BiPAP). COVID-19 patients with anemia needed more frequently endotracheal intubation and MV therapy (23.9% vs. 10.9%, respectively; p=0.030) (Figure 2). Using the logistic regression analysis in the univariate model, anemia was found to be a statistically significant risk factor for MV requirement [OR: 2.582 (95% CI: 1.075-6.197), p=0.034]. However, in the multivariate model, anemia was not found to be a statistically significant risk factor MV requirement [OR: 2.322 (95% CI: 0.886-6.086), p=0.087]. Additionally, for the MV requirement, log-ferritin value was found to be a statistically significant risk factor in the univariate model [OR: 5.500 (95% CI: 1.871-16.165), p=0.002] and multivariate model [OR: 5.596 (95% CI: 1.738-18.011), p=0.004], respectively (Table 4).

Table 3. Possible predictors for ICU admission								
	Univariate model				**Multivariate model**			
	OR	95% CI		P value	OR	95% CI		P value
Age	1.025	0.997	1.054	0.079	1.014	0.982	1.048	0.381
Male sex	2.271	0.961	5.370	0.062	1.657	0.612	4.485	0.320
Anemia	2.384	1.084	5.246	**0.031**	2.738	1.130	6.635	**0.026**
Log ferritin	5.058	1.968	12.998	**0.001**	4.218	1.521	11.697	**0.006**
CI; Confidence Interval, OR; Odds Ratio, ferritin values are shown as log-transformed.								

Table 4. Possible predictors for mechanical ventilation								
	Univariate model				**Multivariate model**			
	OR	95% CI		P value	OR	95% CI		P value
Age	1.052	1.019	1.087	**0.002**	1.048	1.010	1.087	**0.013**
Male sex	1.340	0.543	3.303	0.525	0.892	0.308	2.586	0.834
Anemia	2.582	1.075	6.197	**0.034**	2.322	0.886	6.086	0.087
Log ferritin	5.500	1.871	16.165	**0.002**	5.596	1.738	18.011	**0.004**
CI; Confidence Interval, OR; Odds Ratio, ferritin values are shown as log-transformed.								

DISCUSSION

The present study clearly showed that COVID-19 disease was clinically progressed more severely in patients with low hemoglobin levels during hospital admission. These results also indicated that almost one-fourth of the COVID-19 patients with anemia experienced more severe hypoxia requiring therapy in the ICU setting which did not respond adequately to high-flow oxygen therapy and non-invasive MV support through BiPAP systems, thereby, leading to endotracheal intubation and MV.

Although lower hemoglobin levels have been reported in critical COVID-19 patients, the exact relationship between these two conditions has not been fully understood, yet (17). Until now, there are few studies examining the effect of anemia on the progression and outcomes of COVID-19. In a recent study including 67 COVID-19 patients in Singapore, patients followed in the ICU had lower hemoglobin levels, compared to those followed in the ward (18). Another study reported that anemia was associated with a severe inflammatory response and could be an independent risk factor for COVID-19 (19). However, there are no conclusive data yet indicating the impact of anemia on disease prognosis in COVID-19. To the best of our knowledge, there is a limited number of studies examining the relationship between pre-existing anemia and COVID-19 disease in the literature, as in our study (20).

Anemia potentially worsens the clinical situation in COVID-19 patients. It has been proposed that SARS-CoV-2 can interact with hemoglobin molecules on the erythrocyte via angiotensin-converting enzyme 2 (ACE2), cluster of differentiation 147 (CD147), and cluster of differentiation 26 (CD26) receptors. This virus-hemoglobin interaction has been shown to result in a viral attack to the heme circle in the beta-1 chain of hemoglobin that can cause hemolysis (21). Furthermore, SARS-CoV-2 can mimic the effect of hepcidin, which increases circulating and tissue ferritin while causing serum iron deficiency, and decreases hemoglobin levels (22). Hepcidin is a hormone which regulates the iron metabolism, modifying iron balance by reducing iron in the organism and preventing duodenal iron absorption and macrophage iron release (23). Also, hepcidin is an acute phase reactant and its synthesis from the liver increases in the presence of inflammation. Hemoglobin concentration is one of the main determinants of the oxygen carrying capacity of the blood. We believe that, as a result of the increased metabolic activities that develop in the course of infectious diseases, the increased oxygen demand of peripheral tissues cannot be supplied sufficiently in patients with low hemoglobin levels. Therefore, low hemoglobin concentration in anemic patients may cause inadequate delivery of oxygen to organs, resulting in various organ dysfunctions. The damage in respiratory system contributes to the development of hypoxia at tissue level (24). As a result of the increased inflammatory and thrombotic mechanisms, multiple organ dysfunction and failure cause worse clinical outcomes in COVID-19.

In addition to showing iron stores in iron deficiency anemia, ferritin also plays a role as an acute phase reactant in infectious diseases. Ferritin has been shown in previous studies as a pro-inflammatory factor in cytokine storm and a predictor of poor outcomes in COVID-19 patients (25). The increased oxidative stress and lipo-peroxidation may also accelerate inflammatory response, leading to the increased responsiveness of the immune system resulting in the "cytokine storm" phenomenon (26). The increased ferritin levels may lead to a phenomenon so called "ferroptosis", which can be defined as an iron-dependent cell death form.

Similar to our study results, in a systematic review and meta-analysis by Cheng et al. (25), high ferritin levels in COVID-19 were associated with the ICU transfer under intensive supportive care, including MV. Furthermore, in our study, ferritin value increased the need for ICU and MV, regardless of age and sex in the multivariate analysis.

In recent studies evaluating COVID-19 pneumonia risk factors, advanced age and male sex were associated with higher in-hospital mortality rates and usually worse in-hospital outcomes in hospitalized COVID-19 patients (27-30). In addition, male sex was independently associated with the need for ICU (31). In our study, the mean age of anemic patients was higher and the number of male patients was lower in the anemic group. However, in the multivariate analysis, we observed that anemia increased the need for intensive care regardless of age, sex, and ferritin value. While anemia significantly increased the need for MV in the univariate analysis, multivariate analysis revealed no significant correlation of the age, sex, and ferritin values with the need for MV. This can be attributed to the low sample size and the effect of confounding risk factors. Correlations between other independent factors and anemia may have affected the results.

Recently, the number of COVID-19 patients has been increasing worldwide. As a result, the number of critically ill patients requiring intensive care has dramatically increased. Early recognition of severe forms and timely triage of patients is of utmost importance. While the clinical condition of the patients, SpO_2 levels and comorbidities are the main determinants of the need for ICU admission, some laboratory parameters may also facilitate the assessment of the severity of the disease. We believe that anemic patients should be recommended to take additional precautions to minimize their risk of exposure to the virus. In addition, anemic patients with suspected COVID-19 should be followed more closely to detect signs of disease progression. In our opinion, anemia diagnosed at the first admission to the hospital in COVID-19 patients may be an important factor in future risk classification models to predict the progression of the disease.

The main limitations of our study include that the mortality status in the study population was unable to be evaluated. In future large-scale studies, the relationship of anemia not only with ICU and MV, but also with mortality should be examined. In addition, different models can be created for male and female patient groups.

In conclusion, anemic COVID-19 patients need more frequent ICU hospitalization and MV therapy. In addition, these patients have prolonged hospital and ICU stay. Anemic patients should be followed more closely in terms of disease progression. Consideration of anemia at the time of admission may be helpful in COVID-19 patient management and risk stratification.

DECLARATIONS

Conflict of Interests

The authors declare they have no conflict of interest.

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