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Research Article

The importance of anemia in predicting the prognosis of hospitalized COVID-19 patients: A retrospective and single-center study

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Abstract

Objectives: In our study, we aimed to evaluate the importance of anemia in predicting prognosis in hospitalized COVID-19 patients.

Methods: A total of 340 patients, 110 with anemia and 230 without anemia, were included in the study. Biochemical parameters were compared between groups with and without anemia, and between severe and non-severe COVID-19 patient groups. Binary logistic regression analysis was performed to evaluate the impact of anemia on the prognosis of COVID-19 patients.

Results: In patients with anemia, age, length of hospital stay, neutrophil count, serum glucose, urea, creatinine, C-reactive protein (CRP), ferritin, procalcitonin (PCT), high-sensitivity troponin I, activated partial thromboplastin time (aPTT), prothrombin time (PT), and D-dimer levels were significantly higher. Among the severe and non-severe COVID-19 patient groups, while hemoglobin (hb), hematocrit (ht) and serum calcium levels were significantly lower; PT, serum glucose, urea, creatinine, lactate dehydrogenase (LDH), ferritin, CRP, PCT, and D-dimer levels were significantly higher. In evaluating the prognosis of COVID-19 patients; anemia Odds Ratio (OR) 1.996 (95% confidence interval [CI]: 1.153–3.453, p<0.014), age (OR) 0.033 (95% CI: 1.016–1.058, p<0.001), and CRP level (OR) 1.009 (95%CI: 1.005–1.013, p<0.001) were found to be independent risk factors.

Conclusion: Advanced age and high serum CRP levels, as well as the presence of anemia, are important risk factors for hospitalized COVID-19 patients. Clinicians should consider that anemia may also be a risk factor in the prognosis of patients with COVID-19.

Keywords: Anemia, COVID-19, prognosis

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Since the pandemic was declared in February 2019, severe acute respiratory syndrome coronavirus-2, which caused the 2019 coronavirus disease (COVID-19) pandemic, has affected our country as well as the whole world. Advanced age, male gender, presence of comorbidity, and lymphopenia have been shown in many studies as poor prognostic factors in COVID-19 patients [1–4]. According to the recommendations published by the International Federation of Clinical Chemistry COVID-19 Working Group, biochemical and hematological tests will be useful in monitoring the severity of the disease and the course of the disease in COVID-19 infection [5]. Studies have shown that anemia is an independently important parameter in pre-

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dicting the severity of COVID-19 [6, 7]. Hemoglobin (Hb) concentration is one of the most important indicators of oxygen carrying capacity in blood circulation. In COVID-19 patients, the presence of anemia in addition to interstitial pneumonia may further reduce oxygen delivery to peripheral tissue [8]. As the pneumonia progresses, the oxygen level in the blood gradually decreases and the oxygenation of the tissues becomes insufficient that causes pulmonary dysfunction [7]. Thus, the presence of anemia in COVID-19 patients increases the severity of respiratory tract infections [6]. Anemia is the result of acute inflammation, in part resulting from impaired iron homeostasis and suppression of erythropoietin. Iatrogenic active bleeding in COVID-19 patients may also potentially contribute to anemia secondary to disseminated intravascular coagulation [9, 10]. In our study, we aimed to evaluate the importance of anemia in the prognosis of hospitalized COVID-19 patients.

Materials and Methods

This study was conducted in a single center in a tertiary hospital. Between April 1 and June 30, 2020, the medical records of 340 hospitalized patients with a definitive diagnosis of COVID-19 were reviewed retrospectively.

Demographic data such as age, gender, comorbidities, symptoms, and laboratory findings of the patients were obtained from the hospital information system. The patients were divided into two groups as anemic and non-anemic. According to the definition of the World Health Organization (WHO), anemia was defined as Hb levels <13 g/dL in men and <12 g/dL in women [11]. According to the WHO's guidelines applied at hospitalization, patients have been defined as having mild, moderate, severe, and critical COVID-19 infection. Mild and moderate groups have been defined as non-severe, while severe and critically ill groups have been defined as severe [12]. The non-severe group consisted of symptomatic patients without signs of hypoxia and pneumonia, and patients with moderate pneumonia had symptoms such as dyspnea, cough, fever, and blood oxygen saturation (SpO_2) ≥90% in room air. Severe group consisted of patients with respiratory rate >30/min, severe respiratory distress, SpO_2 <90% in room air plus arterial partial pressure of oxygen/fraction inspiratory O_2 ≤300 mmHg, symptoms of pneumonia such as dyspnea, cough, and fever, as well as those required mechanical ventilation due to respiratory failure. Patients under the age of 18 and pregnant women were excluded from the study.

Complete blood count analyzes were performed on the UniCel DxH 800 hematology analyzer (Beckman Coulter, Miami, FL, USA). Serum glucose, urea, creatinine, lactate dehydrogenase (LDH), calcium, C-reactive protein (CRP), and ferritin analyzes were performed on the AU 5800 autoanalyzer (Beckman Coulter, High Wycombe, UK). Serum high sensitivity troponin I (hs-TNI) and procalcitonin (PCT) levels analysis was performed on the ADVIA Centaur XP immunoassay analyzer (Siemens Healthineers, Erlangen, Germany). D-dimer, prothrombin time (PT), and activated PT were performed on the CS 2500 autoanalyzer (Sysmex Corporation, Kobe, Japan).

The diagnosis of COVID-19 was made by real-time polymerase chain reaction (RT-PCR) (Bio-Speedy COVID-19 RT-qPCR kit, Bioeksen R&D Technologies Ltd, Istanbul, Turkiye) of viral nucleic acids obtained from nasopharyngeal and oropharyngeal swab samples.

Statistical analysis

SPSS 25.0 (SPSS Inc., Chicago, USA) program was used. The normality of the distributions of the variables was evaluated with the Shapiro–Wilk test. Independent t-test was used for the comparison between groups for normally distributed data, and Mann–Whitney U test was used for non-normally distributed data. Chi-square test was used for comparison between groups for categorical variables. Results are given as mean±standard deviation or median (interquartile range). Binary logistic regression analysis was performed to predict the prognosis of COVID-19 patients.

Results

In our study, 110 (32%) of the 340 patients who were hospitalized with the diagnosis of COVID-19 constituted the anemic group, and 230 (68%) constituted the non-anemic group. There was a statistically significant difference between the mean age of the patient group with anemia (61±15) and the mean age of the patient group without anemia (51±14) ($p<0.001$). While 67 (29%) of the patients in the group without anemia had severe disease, 67 (69%) in the group with anemia had severe disease. During a median hospitalization time of 7 days (5–10 days), 15 patients died.

While the need for oxygen support was 26% in the group without anemia, it was 50% in the group with anemia, and there was a significant difference between them ($p<0.001$). About 10% of the anemic group needed intensive care unit and the difference was significant compared to the non-anemic group. Overall, 201 (59%) patients had one or more comorbidities, of which hypertension 135 (40%) was the most common one, followed by diabetes 78 (23%), cardiovascular disease (CVD) 47 (14%), and chronic obstructive pulmonary disease 40 (12%). The most common symptoms in the patients were cough (48%), dyspnea (33%), fever (34%), fatigue (19%), and sore throat (11%). When the patient groups with and without anemia were compared, it was observed that patients with anemia had more comorbidities and the difference between them was significant ($p<0.001$).

In patients with anemia, compared to the group without anemia, hospitalization time ($p<0.001$), neutrophil count ($p=0.002$), serum glucose ($p=0.014$), urea ($p<0.001$), creatinine ($p<0.001$), CRP ($p<0.001$), PCT ($p<0.001$), ferritin ($p=0.012$), aPTT ($p=0.017$), PT ($p<0.001$), and D-dimer ($p<0.001$) levels were observed to be higher. Hb ($p<0.001$), hematocrit (Htc) ($p<0.001$), mean corpuscular volume (MCV) ($p=0.100$), lymphocyte count ($p=0.043$), and serum calcium ($p<0.001$) levels were lower. Statistically significant differences between both

Table 1. Demographic hematological and biochemical values of anemic and non-anemic COVID-19 patient groups

Parameter	Non-anemic n=230	Anemic n=110	p
Age (year) (mean±SD)	51±14	61±15	<0.001
Female, n (%)	99 (43)	55 (50)	0.228
Hemoglobin (g/dl)	14.0 (13.3–15.0)	11.1 (10.2–11.9)	<0.001
Hematocrit (%)	41.35 (39.2–44.0)	33.45 (30.5–35.1)	<0.001
MCV (fl)	85.6 (83.1–88.3)	85.2 (79.5–88.1)	0.100
WBC ($\times10^9$/L)	6.6 (5.0–8.7)	7.4 (4.9–9.9)	0.184
NEU ($\times10^9$/L)	4.2 (2.9–5.7)	5.2 (3.6–7.1)	0.002
LYM ($\times10^9$/L)	1.6 (1.1-2.4)	1.3 (0.8–2.1)	0.043
PLT ($\times10^9$/L)	211 (169–269)	202 (151–307)	0.823
Glucose (mg/dl)	113 (102–136)	123 (103–179)	0.014
Urea (mg/dl)	29 (23–37)	40 (26–69)	<0.001
Creatinine (mg/dl)	0.9 (0.8–1.0)	1.1 (0.8–1.5)	<0.001
LDH (U/L)	259 (204–351)	289 (220–373)	0.128
Ca (mg/dl)	9.2 (8.7–9.5)	8.70 (8.3–9.1)	<0.001
Ferritin (µg/dl)	111 (65–238)	223 (54–422)	0.012
CRP (mg/L)	5.1 (5.6–54.3)	75.6 (20.6–131.2)	<0.001
PCT (ng/mL)	0.04 (0.01–0.07)	0.09 (0.04–0.23)	<0.001
hs-TNI (ng/L)	2.50 (0.02–4.89)	4.22 (2.50–21.11)	<0.001
D-dimer (mg/L)	530 (310–1022)	950 (620–1650)	<0.001
PT (sec)	12.3 (11.8–12.9)	13.0 (12.1–14.4)	<0.001
aPTT (sec)	24.4 (23.1–26.3)	25.8 (23.0–28.8)	0.017
Length of stay in hospital (day)	7 (5–10)	9 (6–13)	<0.001

Date were median (P25, P75) and mean±SD. SD: Standard deviation; MCV: Mean corpuscular volume; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocytes; PLT: thrombocytes; LDH: Lactate dehydrogenase; CRP: C-reactive protein; PCT: Procalcitonin; hs-TNI: High sensitivity troponin I; PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

groups were observed in terms of above-mentioned variables (Table 1). There was no significant difference between the groups regarding white blood cell (WBC) counts, platelet counts, and serum LDH levels.

Of the in COVID-19 patients included in the study, 134 were in the severe group and 206 were in the non-severe group. In COVID-19 patients, compared to the severe and non-severe groups, Hb (p<0.001), Htc (p<0.001), and serum calcium levels (p<0.001) were found to be significantly lower, and serum glucose (p<0.001), urea (p<0.001), creatinine (p=0.009), LDH (p<0.001), ferritin (p<0.001), CRP (p<0.001), PCT (p<0.001), D-dimer (p<0.001), and PT (p=0.005) were significantly higher (Table 2).

In predicting the prognosis of COVID-19 patients; anemia Odds Radio (OR) 1.996 (95% confidence interval [CI]: 1.153–3.453, p<0.014), age (OR) 0.033 (95% CI: 1.016–1.058, p<0.001), and serum CRP level (OR) 1.009 (95% CI: 1.005–1.013, p<0.001) were found to be independent risk factors (Table 3).

Discussion

The presence of anemia has been associated with an adverse clinical course of many diseases, especially infections and inflammatory disorders [13]. The impact of anemia and iron metabolism disorders on the prognosis of COVID-19 is significant. In this study, anemia was present in 32% of hospitalized patients with a diagnosis of COVID-19, and 69% of the anemia group had severe COVID-19. Besides, patients with anemia had more comorbidities and 10% of them needed intensive care unit care.

In a prospective study of 1274 patients hospitalized for COVID-19 in Iran, 48% of patients were anemic, comparatively older and had more comorbidities. The presence of anemia was found to be an independent risk factor in predicting mortality, ventilator requirement, and risk of intensive care unit admission [14].

A meta-analysis evaluating anemia in the prognosis of COVID-19 patients has shown that approximately 25% of patients with COVID-19 infection had anemia and anemia is associated with an increased risk of short-term mortality [7].

Among the anemic and non-anemic COVID-19 patient groups; we found higher serum glucose, urea, creatinine, CRP, PCT, hs-TNI, aPTT, PT, D-dimer levels, and lower Hb, Hct, lymphocyte counts, MCV, calcium levels, and significant differences between them both groups regarding these variables. Similar results have been shown in other studies examining COVID-19 patients with and without anemia [6, 8, 10, 13, 14]. By estimating patients at high risk of serious illness, it may be possible to reduce the need for intensive care unit and the mortality rate with earlier intervention.

Table 2. Demographic, hematological and biochemical values of with severe and non-severe COVID-19 patient groups

Parameter	Non-severe n=206	Severe n=134	p
Age (year) (mean±SD)	51±15	60±15	<0.001
Female, n (%)	95 (46)	59 (44)	0.706
Hemoglobin (g/dl)	13.5 (12.7–14.5)	11.9 (10.3–13.6)	<0.001
HCT (%)	40.5 (37.4–42.0)	35.1 (31.2–41.10)	<0.001
MCV (f/L)	85.2 (82.3–88.3)	84.9 (79.9–87.1)	0.213
WBC ($\times10^9$/L)	7.4 (5.2–9.4)	7.5 (5.6–10.2)	0.205
NEU ($\times10^9$/L)	4.4 (2.7–6.1)	5.1 (4.0–8.1)	0.007
LYM ($\times10^9$/L)	1.7 (1.1–2.4)	1.2 (0.7–2.5)	0.119
PLT ($\times10^9$/L)	226 (185–288)	244 (179–352)	0.584
Glucose (mg/dl)	109 (93–141)	139 (112–198)	<0.001
Urea (mg/dl)	29 (23–39)	35 (26–55)	<0.001
Creatinine (mg/dl)	0.90 (0.80–1.08)	0.97 (0.80–1.17)	0.009
LDH (IU/L)	258 (205–302)	303 (244–456)	<0.001
Ca (mg/dl)	9.3 (8.9–9.6)	8.7 (8.4–9.2)	<0.001
Ferritin (µg/L)	107 (58–251)	210 (110–423)	<0.001
hs-TNI (ng/L)	2.5 (2.5–4.8)	4.6 (2.5–14.8)	0.391
CRP (mg/L)	12.8 (3.1–68.7)	58.2 (17.8–110.2)	<0.001
PCT (ng/ml)	0.03 (0.01–0.10)	0.08 (0.03–0.23)	<0.001
D-dimer (mg/L)	615 (317–1022)	1075 (605–2277)	<0.001
PT (sec)	12.3 (11.7–12.6)	13.1 (12.0–13.7)	0.005
aPTT (sec)	24.7 (23.2–26.9)	25.9 (23.5–28.2)	<0.001
Length of stay in hospital (day)	6 (4–8)	11 (8–15)	<0.001

Date were median (P25, P75) and mean±SD. SD: Standard deviation; HCT: Hematocrit; MCV: Mean corpuscular volume; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocytes; PLT: thrombocytes; LDH: Lactate dehydrogenase; hs-TNI: High sensitivity troponin I; CRP: C-reactive protein; PCT: Procalcitonin; PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

Table 3. Regression analysis between severe and non-severe COVID-19 patient groups

Parameter	B	SE	Wald	p	OR (95% CI)
ANEMIA	0.691	0.280	6.100	0.014	1.996 (1.153–3.453)
AGE	0.033	0.009	14.409	<0.001	1.033 (1.016–1.051)
CRP	0.009	0.002	18.264	<0.001	1.009 (1.005–1.013)

SE: Standard error; OR: Odds ratio; CI: Confidence interval; CRP: C-reactive protein.

Therefore, the assessment of these indicators conveys importance for the prediction of severity and prognosis of the disease [9]. In this study, in evaluating the prognosis of COVID-19 patients, anemia, age, and serum CRP levels were independent risk factors for COVID-19 disease. In COVID-19 patients, inflammation may be characterized by marked changes in iron homeostasis and erythropoiesis leading to the development of anemia. Decrease in Hb levels and the development of anemia during hospitalization may be associated with immune activation and cytokine-mediated changes in iron homeostasis, which are the characteristic features of anemia of inflammation [3]. A meta-analysis has shown that patients with severe COVID-19 have decreased Hb levels compared to the milder forms of the disease [15]. In a retrospective study which was conducted in our country, micronutrients, hemogram values, advanced age, male gender, and having comorbid diseases were correlated with the poor prognosis of COVID-19 [16].

In some studies, the relationship between the severity of COVID-19 disease and anemia was not observed. A study conducted in Italy showed no association between anemia and poor outcomes of COVID-19 [17]. In a study, Yang et al. [18] described the clinical features, and outcomes of critically ill patients with COVID-19 disease in China, and could not find any association between low Hb levels and risk of death. Their study included only critically ill patients, so they might obtain misleading results. One of the common features observed in COVID-19 patients is the presence of a complex pathophysiological mechanism involving the inflammatory process. Increased levels of wide variety of inflammatory mediators, including CRP and interleukins, pro-inflammatory cytokines such as tumor necrosis factor, and chemokines have been observed in this disease.

In our study, we have shown that levels of CRP and PCT were significantly higher in the COVID-19 patient group with severe disease and high CRP level was an independent risk factor in addition to anemia in predicting severe disease.

In a study conducted in Turkiye, advanced age, low albumin and lymphocyte levels, and high CRP levels have been associated with intensive care unit admission, intubation requirement, and mortality [19]. Studies have shown that red blood cell distribution width (RDW), as well as Hb, which is one of the parameters of complete blood count, is an important prognostic marker in patients with COVID-19 [10, 20]. Failure to measure RDW is an important deficiency of our study. As we were evaluating hospitalized COVID-19 patients during the first wave of the pandemic, some parameters that were not recognized as important at that time, but were found to be important prognostic factors later on were not assessed in our study.

The limitations of our study may be enumerated as follows: Being a retrospective study performed in a single-center; failure to evaluate some biochemical parameters, especially other markers of anemia such as iron, iron binding capacity, transferrin; and lack of any evidence of anemia in our patients at the time of hospitalization.

We believe that our study will also contribute to the studies examining the relationship between anemia and COVID-19. It may be more meaningful to better assess the relationship between anemia and severe COVID-19, which is possible if and only if the presence of pre-existing anemia or iron deficiency anemia is known.

Conclusion

In our study, we found age, presence of anemia, and serum CRP are independent risk factors in predicting the prognosis of COVID-19 patients. The findings of our study have shown that approximately one-third of hospitalized COVID-19 patients have anemia at the time of admission and anemia indicates poor prognosis of COVID-19 patients. Clinicians should also consider the presence of anemia in the predictive assessment of the prognosis in patients with COVID-19.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The University of Health Sciences, Tepecik Training and Research Hospital Clinical Research Ethics Committee (No: 2021/05-21, Date: 17/05/2021).

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