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The Relationship Between Hemoglobin Levels and Intensive Care Mortality in COVID-19 Patients

COVID-19 Hastalarında Hemoglobin Seviyeleri ve Yoğun Bakım Mortalitesi Arasındaki İlişki

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Abstract

Objective: We aimed to investigate whether hemoglobin levels in COVID-19 patients can serve as a valuable predictor of mortality.

Material and Method: This retrospective study included 156 COVID-19 cases who were admitted to the intensive care unit (ICU), demographic characteristics, clinical data, and laboratory findings were recorded.

Results: There are no significant differences in mean age, gender ratio, comorbidities, symptoms, mean APACHE-2, and SOFA values upon admission observed between the anemic and normal groups. The normal hemoglobin (Hgb) group's mean lymphocyte and lactate values were statistically high($p<0.05$), and mean procalcitonin and D-dimer values were high in the anemic group ($p<0.05$). The severity of COVID-19 in patients was evaluated by the requirement of mechanical ventilation, inotropic agents, and renal replacement treatments as well as the development of acute respiratory distress syndrome (ARDS), acute renal failure (ARF), and multiple organ failure (MOF). Patient outcomes were lengths of ICU stays and ICU mortality. No significant difference was observed in any of the severity parameters or outcomes between the anemic and normal groups. Hemoglobin levels upon admission and final ICU days for the non-survivors group were significantly low than for the survivors group ($p<0.05$).

Conclusions: We found decreased hemoglobin levels in non-surviving COVID-19 patients. However, we could not find a relationship between anemia and mortality. Further trials are needed to evaluate the impact of hemoglobin levels on mortality in COVID-19 patients.

Keywords: Hemoglobin, Intensive Care, Mortality, COVID-19

Öz

Amaç: Bu çalışmanın amacı, hemoglobin seviyelerinin, COVID-19 hastalarında mortaliteyi ön görmede etkili olup olmadığının araştırılmasıdır.

Gereç ve Yöntem: Bu retrospektif çalışmaya yoğun bakımda takip edilen 156 COVID-19 hastası dahil edildi. Demografik özellikleri, klinik verileri ve laboratuar bulguları kaydedildi.

Bulgular: Anemi grubu ve normal hemoglobin değerleri olan grubun başvuru esnasındaki ortalama yaş, cinsiyet oranları, komorbiditeleri, semptomları, ortalama APACHE-2 ve SOFA değerleri arasında anlamlı fark yoktu. Normal hemoglobin değerleri olan grubun ortalama lenfosit ve laktat değerleri istatiksel olarak anlamlı düzeyde yüksek bulundu ($p<0,05$). Anemi grubunda ise ortalama prokalsitonin ve D-dimer değerleri anlamlı düzeyde yüksek bulundu ($p<0,05$). COVID-19 hastalığının ağırlığı mekanik ventilasyon ihtiyacı, inotropik ajan ve renal replasman tedavisi ihtiyacı yanı sıra Akut Respiratuar Distres Sendrom (ARDS), akut böbrek yetmezliği (ABY) ve çoklu organ yetmezliği gelişimi ile değerlendirildi. Hasta sonuçları yoğun bakımda kalış süresi ve yoğun bakım mortalitesi olarak belirlendi. COVID-19 hastalığının ağırlığını belirleyen parametreler ve hasta sonuçları açısından anemi grubu ve normal grup arasında anlamlı fark bulunmadı. Ancak başvuru esnasındaki ve yoğun bakımın son günündeki hemoglobin seviyeleri ölen grupta sağkalanlara göre anlamlı olarak düşük tespit edildi ($p<0,05$).

Sonuç: Bu çalışmada, ölen COVID-19 hastalarında hemoglobin seviyeleri daha düşük bulundu. Bununla birlikte anemi ve mortalite arasında anlamlı bir ilişki saptanmadı. COVID-19 hastalarında hemoglobin seviyelerinin mortaliteye etkisinin değerlendirilmesi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Hemoglobin, yoğun bakım, mortalite, COVID-19

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), which causes serious respiratory illness, was first reported in Wuhan. The etiological agent of the disease has been confirmed as a novel coronavirus, now known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is most likely originated from zoonotic coronaviruses.[1]

The most common COVID-19 symptoms were cough, fever, dyspnea, muscle aches/fatigue, sore throat, gastrointestinal symptoms, and headache. It may have a more severe course, especially in older patients, and additional disease. Patients with severe COVID-19 may develop hypoxemia and dyspnea after one week, which may progress to acute respiratory distress syndrome (ARDS) or end-organ failure.[3]

The pathogenesis of COVID-19 is different from other viral types of pneumonia. A series of autopsies in COVID-19 patients showed that thrombotic microangiopathy that was restricted to the lungs.[4]

Therefore, these patients develop maladaptive immune responses not only to the virus itself but also to thrombotic and microangiopathic events. Severe COVID-19 patients develop an atypical form of ARDS with preserved lung gas volume, that suggests hypoxia due to physiological processes may play a role in the prognosis of the disease.[5,6]

In COVID-19 patients reported that the virus damage to the ACE2-receptor-rich kidney tissue and increases of inflammatory factors, which can cause increased destruction of red blood cells (RBC), reduced erythrogenesis, and lead to anemia.[7] Recently studies found mild anemia in COVID-19 patients admitted to ICU.[8] And patients with COVID-19 have significantly lower hemoglobin levels, compared to patients not admitted to ICU.[9] A meta-analysis showed that disease severity and prognosis are due to low hemoglobin levels, as hemoglobin levels are lower in severe COVID-19 cases than in moderately severe cases.[10]

In this study, we investigate the relationship between hemoglobin levels and mortality of COVID-19 patients in intensive care units.

MATERIAL-METHOD

Study Design and Participants

The study was carried out with the permission of Sakarya University Ethics Committee (Date: 15.05.2020, Decision No: 71522473/050.01.04/325). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

All COVID-19 cases were confirmed by using a real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) assay to test nasal and pharyngeal swab specimens according to the WHO guidance and admitted to the ICU of a tertiary hospital between March 17 and May 15, 2020. 156 patients were included in to study.

All patients received antiviral therapy as our country's scientific committee guidelines recommended. The demographic characteristics, clinical data, and laboratory findings were recorded. The blood test parameters on the first day of admission to the ICU and the hemoglobin value on the last ICU day were analyzed. The COVID-19 patients were divided into two groups according to Hgb values on admission. We described anemia as Hgb <12.5 g/dl in females and Hgb <13 g/dl in males. Patients were divided into two groups for hemoglobin levels as anemia and normal.

Demographic, clinical features, and laboratory findings of all patients and two groups were compared.

All patients were evaluated according to survivors and non-survivors and compared hemoglobin levels on admission and last day. Blood transfusion, ICU stay day, and outcome of ICU were also recorded. We excluded the patients under 18 years of age.

Statistical Analysis

Descriptive analysis of the variables were expressed as mean±SD in the normal distribution, and parameters with abnormal distribution were expressed as the median of the 25th–75th percentile. Categorical data are expressed as proportions. The chi-square and the Student's t-test were used for categorical and continuous variables, respectively. Fisher's exact test was applied in analyzing small samples. For continuous variables, differences between the two groups were evaluated using the Student's t-test when data were normally distributed and the Mann–Whitney U test when the assumption of normality was not met. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using statistical software (SPSS 20.0, Chicago, IL, USA).

RESULTS

Demographics and Clinical Features

A total of 156 patients who tested positive for COVID-19 by undergoing the SARS-CoV-2 RNA test were included in our study. The mean age of the patients was 69.62±12.9 years. 60 of the patients were female (38.5%). The most common symptoms were shortness of breath (138 [88.5%]), fatigue (131 [84%]), cough (123 [78.8%]), fever (75 [48.1%]), anosmia (20 [12.8%]), sore throat (20 [12.8%]) and diarrhea (6 [3.8%]). 91 of the patients (58.3%) had a history of hypertension, 67 (42.9%) had diabetes mellitus, 45 (28.8%) had coronary artery disease, 29 (18.6%) had chronic obstructive pulmonary disease, 19 (12.2%) had cerebrovascular disease, 14 (9%) had chronic renal disease, 16 (10.3%) had congestive heart failure, and 15 (9.6%) had malignities (**Table 1**). On admission, the median (IQR) APACHE-2 value of the patients was 21 (16-28), and the median SOFA value was 4 (3-6) (**Table 1**).

Table 1: Demographic and clinical features

	All (n=156)	Anemic (n=100)	Normal (n=56)	p
Age (year)	69.62±12.9	70.70±12.6	67.9±13.25	0.164
Sex				
Male	96 (61.5)	45(47.9%)	51 (82.3%)	< 0.01
Female	60 (38.5%)	49 (52.1%)	11 (17.7%)	
Comorbidity				
HT	91 (58.3%)	58 (58.0%)	33 (58.9%)	0.910
DM	67 (42.9%)	45 (45.0%)	22 (39.3%)	0.489
CAH	45 (28.8%)	29 (29.0%)	16 (28.6%)	0.955
CVD	19 (12.2%)	15 (15.0%)	4 (7.1%)	0.150
CHF	16 (10.3%)	10 (10.0%)	6 (37.5%)	0.888
CRF	14 (9.0%)	11 (11.0%)	3 (5.4%)	0.237
COPD	29 (18.6%)	17 (17.0%)	12 (21.4%)	0.495
Malignity	15 (9.6%)	10 (10.0%)	5 (8.9%)	0.828
Fever	75 (48.1%)	50 (50.0%)	26 (46.4%)	0.705
Cough	123 (78.8%)	75 (75.0%)	48 (85.7%)	0.116
Shortness of breath	138 (88.5%)	91 (91.0%)	47 (83.9%)	0.185
Fatigue	131 (84.0%)	80 (80.0%)	51 (91.1%)	0.071
Diarrhea	6 (3.8%)	3 (3.0%)	3 (5.4%)	0.370
Sore throat	20 (12.8%)	16 (16.0%)	4 (7.1%)	0.087
Anosmia	20 (12.8%)	12 (12.0%)	8 (14.3)	0.682
APACHE-2	21 (16–28)	21 (16–28)	21 (15–28)	0.725
SOFA	4 (3–6)	4 (4–8)	4 (3–6)	0.177

HT: Hypertension, DM: Diabetes mellitus, CAH: Coronary artery disease, CVD:Cerebrovascular disease, CHF: Congestive heart failure, CRF: Chronic renal disease, COPD: Chronic obstructive pulmonary disease

Laboratory Findings

Table 2 presents the parameters of blood routine in patients with COVID-19 in ICU. The median (IQR) leucocyte levels is 8.3 (6.2-10.8) (×10^9 perL), neutrophil levels is 6.8 (4.6-9.5)(×10^9 perL), lymphocyte levels is 0.8 (0.5-1.2) (×10^9 perL), platelet 198 (151-294) (×10^9/mL). All cases have lymphopenia. The median (IQR) Na valeu is 135 (132-139), K valeu is 4.1 (3.6-4.5), AST valeu is 42 (66-281) , ALT valeu is 26 (17-41) . The median (IQR) CRP and procalcitonin levels were (112 [62-180], 0.3 [0.1-1.1]) respectively. The median (IQR) D-dimer and ferritin levels were high in all patients (1465 [732-3402], 663 [275-1629]).

In our study 100 of the patients were anemia (64.1%). There were no significant differences in mean age, gender ratio, comorbidities, symptoms, mean APACHE-2, and SOFA values on the admission between the two groups. The normal Hgb group's mean lymphocyte and lactate values were statistically high (p:0.010, 0.011). And mean procalcitonin and d-dimer values were high in the anemia group (p:0.033, 0.002).

The severity of COVID-19 patients was evaluated with requirement of mechanical ventilation, inotropic agent, renal replasman treatment and developing ARDS, acute renal failure (ARF), and multiple organ failure (MOF). The outcomes of patients were length of stay in ICU and mortality of ICU. There is no significantly different all of severity parameters and outcomes between anemia and normal groups (**Table 3**).

We analyzed all patients according to survivors and the non-survivors. There was a statistically significant difference between groups in hemoglobin levels on admission and the last day. Hemoglobin levels on admission and the last day in the non-survivors group were significantly low than in the survivors group (p<0.05). The blood transfusion ratio was similar between the two groups (**Table 3**).

Table 2: Blood routine parameters of patients with COVID-19 upon admission

	All (n=156)	Anemia (n=100)	Normal (n =56)	p
Leucocytes (×10 per L)	8.3 (6.2–10.8)	8.5 (5.7-10.9)	8.3 (6.3–10.3)	0.746
Lymphocyte (×10 per L)	0.8 (0.5–1.2)	0.7 (0.4–1.1)	1.0 (0.6–1.3)	0.010*
Neutrophils (×10 per L)	6.8 (4.6–9.5)	7.0 (4.6–9.8)	6.4 (4.9–8.7)	0.549
Platelet (×10 per L)	198 (151–254)	195 (139–263)	200 (163–251)	0.948
CRP(mg/L)	112 (62–180)	113 (53–180)	120 (62–189)	0.561
Procalcitonin (ng/ml)	0.3 (0.1–1.1)	0.4 (0.1–2.8)	0.2 (0.1–0.5)	0.033*
D-Dimer (ugFEU/L)	1465 (732–3,402)	1740 (970–4,090)	1085 (527–1,870)	0.002*
Troponin(ng/L)	23 (9.1–96)	30 (9.5–109)	18 (8.9–44)	0.098
Ferritin(µg/L)	633 (275–1,629)	498 (225–1,254)	865 (420–2,013)	0.004
Creatine (mg/dL)	0.9 (0.7–1.4)	0.9 (0.6–1.5)	0.9 (0.7–1.3)	0.760
Urea(mg/dl)	56 (34–91)	59 (38–91)	44 (32–76)	0.072
ALT(U/L)	26 (17–41)	24 (15–35)	28 (20–43)	0.130
AST(U/L)	42 (66–281)	38 (10–24)	44 (32–61)	0.337
Na(mmol/L)	135 (132–139)	135 (132–138)	134 (131–138)	0.195
K(mmol/L)	4.1 (3.6–4.5)	4.1 (3.5–4.4)	4.1 (3.7–4.5)	0.773
CK(U/L)	121 (66–281)	125 (56–292)	126 (76–240)	0.561
CK–MB(U/L)	18 (13–25)	17 (12–25)	18 (15–25)	0.186
Ph	7.3 (7.3–7.4)	7.3 (7.3–7.4)	7.4 (7.3–7.4)	0.457
Lactate(mmol/L)	2.0 (1.5–2.5)	1.9 (1.4–2.4)	2.3 (1.7–2.7)	0.011*
PO_2(mmHg)	57 (41–80)	55 (41–73)	62 (43–89)	0.175
PCO_2(mmHg)	39 (35–45)	40 (35–44)	38 (34–49)	0.594
HCO_3(mmol/L)	23 (21–26)	23 (21–26)	24 (21–27)	0.612
PaO_2/v	110 (70–167)	105 (68–173)	110 (76–162)	0.655

CRP: C- reactive protein, ALT: Alanine aminotransferase,AST: Aspartate aminotransferase, K: Potassium, CK : Creatine Kinase , CK–MB: Creatine kinase myocardial band

Table 3: Severity parameters and outcome of COVID-19 patients

	All (n=156)	Anemic (n=100)	Normal (n=56)	p
Inotropic agent	76 (48.7%)	53 (53.0%)	23 (41.1%)	0.183
MV-need	99 (63.5%)	63 (63.0%)	36 (64.3%)	0.873
RRT-need	32 (20.5%)	24 (24.0%)	8 (14.3%)	0.133
ARDS	93 (59.6%)	59 (59.0%)	34 (60.7%)	0.834
ARF	41 (26.3%)	29 (29.0%)	12 (21.4%)	0.303
MOF	76 (48.7%)	50 (50.0%)	26 (46.4%)	0.669
Length of stay in ICU(day)	7 (4–11)	6.5 (3.2–11)	7 (4–12)	0.256
Exitus	86 (55.1%)	59 (59.0%)	27 (48.2%)	0.194

MV: Mechanical ventilation, RRT: Renal replacement therapy, ARF: Acute renal failure, MOF: Multiple organ failure, ICU: Intensive care unit

Table 4 :Comparison of patients according to ICU outcomes

	Survivors	Non-Survivors	p
Blood transfusion	8 (14.5%)	24 (28.2%)	0.060
Hemoglobin upon admission(g/dL)(mean±SD)	11.9±1.9	11.3±1.7	0.044*
Hemoglobin on final day in ICU(g/dL)(mean±SD)	10.9±1.8	10.3±1.6	0.032*

ICU: Intensive care unit

DISCUSSION

COVID-19 is a systemic disease that damages many organs such as lungs, heart, kidneys. It can cause severe damage to the lungs and ARDS, which can cause death.[8] The pathophysiology of COVID-19 has not been fully elucidated. There are many theories on this subject. Autopsy results of COVID-19 fatality showed that deaths were due to bilateral diffuse alveolar damage associated with pulmonary edema, proinflammatory concentrates, and signs of early phase acute respiratory distress syndrome.[11] Another autopsy series of COVID-19 showed that thrombotic microangiopathy that was restricted to the lung can also have contributed to the death. Some patients with COVID-19 have abnormal blood coagulation function, such as prolongation of prothrombin time, increase in d-dimer, and decrease in platelets.[12]

The atypical form of ARDS in COVID-19 patients leads to low blood oxygenation levels and can be life-threatening. Hemoglobin concentration in the blood is one of the most important determinants of the oxygen-carrying capacity of the blood. So in this respect hemoglobin levels in COVID-19 patients were important. In this study, we aimed to investigate the relationship between anemia and mortality in COVID-19 patients.

Recently, the relationship between COVID-19 and anemia was investigated and different results were obtained. In a study, reduction in hemoglobin levels in 38.2% of hospitalized COVID-19 patients, but did not specify the definition of decreased hemoglobin.[13] While Wang et al. reported reduced hemoglobin levels (<110 g/L) in 19.23% of the study population admitted to the hospital.[14] In contrast, in another study, asymptomatic COVID-19 patients reported none of the cases had decreased hemoglobin levels, not defining the cut-off of decreased levels.[15] In our study, we reported anemia in 64.1% of the study population.

In this study, we found similar results for PO_2/ FiO_2, the requirement of mechanical ventilation, inotropic agent, renal replasman treatment, and development of ARDS, ARF, and MOF in anemia and normal Hgb groups. Previous studies showed that in anemic hypoxia, when tissue oxygenation is affected, transfusion is required and anemia affects mortality.[16,17]

In our study similar results of these parameters which occur as a result of impaired tissue oxygenation, support literature information.

Length of stay in ICU and mortality in ICU were similar in anemia and normal hemoglobin groups. In a retrospective study, Liu et al. found similar results that there was the non-significant relationship between baseline hemoglobin levels and all-cause mortality during hospitalization.[18] However, Cai et al. studied factors associated with ICU admission in COVID-19 patients and could not find a relationship between hemoglobin levels and admission rates to the ICU.[19]

In our study, we could not find an association between anemia and mortality. Also, we found no relationship between anemia and the severity of the disease. But when we elevated the data for survivors and non-survivors, we found that mean hemoglobin levels on admission and on the last day were significantly low in the non-survivors group. Giacomelli et al. found similar results as our study, they reported anemia (defined as hemoglobin levels below 12.5 g/dl) was more common in non-survivors (66.7%) compared to survivors (42.7%).[20] In another study hemoglobin levels below 11 g/dl were linked with disease progression in patients with COVID-19.[21]

This retrospective study showed that there is no relationship between anemia and mortality and also severity of disease in COVID-19 patients. But hemoglobin levels were significantly low in non-survivors compared to survivors in COVID-19 patients.

Limitations

This was a small sample size retrospective study, so some important laboratory results were incomplete. And also, our study includes the other limitations of retrospective studies.

CONCLUSION

In conclusion, we found decreased hemoglobin levels in non-survivors for COVID-19 patients. But we could not find the relationship between anemia and mortality. Further trials are needed to evaluate the impact of hemoglobin levels on mortality in COVID-19 patients

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sakarya University Ethics Committee (Date: 15.05.2020, Decision No: 71522473/050.01.04/325).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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