To cite this article: Tezcan B, Ciftci HE. Which anemia is associated with mortality in COVID-19? Mild, moderate or severe ?. Turk J Clin Lab 2021; 2: 166-170.

Original Article

Which anemia is associated with mortality in COVID-19? Mild, moderate or severe ?

COVID-19'da hangi anemi mortaliteyle ilişkili? Hafif, orta, ciddi?

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ABSTRACT

Aim: We aimed to investigate the prevalence of anemia at admission to intensive care unit (ICU), association between anemia and mortality, lengths of stay in hospital and ICU (LOS-H and LOS-ICU) in COVID-19 patients.

Material and Methods: We retrospectively analyzed the data of 288 COVID-19 patients who needed ICU admission. Patients were divided into two groups: anemic and nonanemic. Demographic data, labaratory findings at ICU admission, LOS-H and LOS-ICU, mortality were compared between groups. A further classification was made based on hemoglobin levels; severe, moderate and mild anemic patients were analyzed. LOS-H, LOS-ICU and mortality were compared between patients with hemoglobin > 109 g/L and ≤ 109 g/L. Thus; moderate and severe anemic patients were compared to mild anemic and nonanemic patients.

Results: Anemia was detected in 137 (47.6%) patients upon admission to the ICU. Of those; 54 patients (39.4%) had mild, 76 patients (55.5%) had moderate, 7 patients (5.1%) had severe anemia. Anemic patients were older, had multiple comorbidities, lower hemoglobin and albumin, higher red cell distribution width (RDW), creatinine and procalcitonin levels. While LOS-H, LOS-ICU and mortality rates did not significantly differ between anemic and nonanemic patients; mortality rate was significantly high in patients with hemoglobin levels ≤ 109 g/L (moderate anemic) compared to patients with a hemoglobin level > 109 g/L (mild anemic and nonanemic). LOS-H and LOS-ICU were not significantly different between these patient groups. Only seven patients had severe anemia and all of these died.

Conclusion: The results of this retrospective study showed that the anemia prevalence in ICU patients with COVID-19 was high, and mild anemia was not associated with higher mortality rates, while moderate and severe anemia were. Hemoglobin levels of anemic patients with COVID-19 should be closely monitored for timely detecting signs of disease progression.

Keywords: Mild anemia; mortality; intensive care; SARS-CoV-2

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Recevied: 20.03.2021 accepted: 02.06.2021
Doi: 10.18663/tjcl.922747

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ÖZ

Amaç: COVID-19 hastalarında yoğun bakım (ICU) kabulü sırasında anemi prevalansını, anemi ile mortalite, hastanede ve yoğun bakımda kalış sürelerinin((LOS-H ve LOC-ICU) ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Yoğun bakım ihtiyacı olan 288 COVID-19 hastasını retrospektif olarak analiz ettik. Hastalar iki gruba ayrıldı: anemikler ve anemik olmayanlar. Grupların demografik verileri, ICU kabulleri sırasındaki labaratuar bulguları, LOS-H ve LOS-ICU ve mortaliteleri kıyaslandı. Hemoglobin düzeyleri temel alınarak ileri bir sınıflama yapıldı; ciddi, orta ve hafif anemik hastalar analiz edildi. LOS-H, LOS-ICU ve mortalite hemoglobin düzeyi 109 g/L altındaki ve üstündeki hastalar arasında kıyaslandı. Böylece orta ve ciddi anemik hastalarla hafif anemikler ve anemik olmayanlar karşılaştırıldı.

Bulgular: Yoğun bakım kabulü sırasında 137 hastada (%47,6) anemi saptandı. Bunların 54'ünün (%39,4) hafif, 76'sının (%55,5) orta, 7'sinin (%5,1) ağır anemisi vardı. Anemik hastalar daha yaşlı, çoklu komorbiditeye sahip, daha düşük hemoglobin ve albümin, daha yüksek kırmızı küre dağılım genişliği (RDW), kreatinin ve prokalsitonin düzeylerine sahipti. LOS-H , LOS-ICU ve mortalite oranları anemik olan ve olmayan hastalar arasında anlamlı olarak fark göstermezken, hemoglobin düzeyleri ≤ 109 g/L hastalarda (orta ve ağır anemikler) mortalite oranları hemoglobin düzeyleri > 109 g/L (hafif anemikler ve anemik olmayanlar) göre anlamlı olarak yüksekti. LOS-H ve LOS-ICU bu hasta gruplarında anlamlı fark göstermedi. Sadece yedi hastanın ağır anemisi vardı ve bunların tamamı öldü

Sonuç: Bu çalışmanın sonuçları; yoğun bakımdaki COVID-19 hastalarında anemi prevalansının yüksek ve hafif anemi artmış mortalite ile ilişkili değilken orta ve ağır aneminin artmış mortalite ile ilişkili olduğunu göstermiştir.COVID-19 hastalarında anemik hastaların hemoglobin düzeyleri hastalığın ilerleyişinin erken tespiti için sık monitorize edilmelidir.

Anahtar kelimeler: Hafif anemi,; mortalite; yoğun bakım; SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) and has been pandemic across the whole world since December 2019. It has, unfortunately, caused a significant burden on social life and all healthcare systems. This pandemic disease is mainly characterized by respiratory symptoms and has different levels of severity frommild upper respiratory disease to severe pneumonia requiring mechanical ventilation and multiorgan failure leading to death [1]. Identification of risk factors that contribute to the development of the severe disease and death is essential to enable risk stratification and optimize hospital resources reallocation. In this regard some researchers studied the assocation between anemia and the severity or mortality of COVID-19 but had controversial results [2-5].

In this study we aimed to investigate the prevalence of anemia at admission to intensive care unit (ICU), association between anemia and mortality, lengths of stay in hospital and ICU (LOS-H and LOS-ICU).

Material and Methods

Study Population

We retrospectively analyzed the data of 288 patients with PCR and/or computed tomography (CT) confirmed COVID-19 diseases who needed ICU admission at the Ankara City Hospital between 1 September,2020 and 31 January,2021. The study was approved by the ethics committee of the Ankara City Hospital. This study was conducted in compliance with the principles of the Declaration of Helsinki. Informed constents were taken from all participants.

Classifications of Anemia

Anemia was defined according to the World Health Organization (WHO) as hemoglobin < 130 g/L in men and hemoglobin < 120 g/L in women. A further classification was made according to the hemoglobin levels; severe anemia, definedas hemoglobin < 80 g/L, moderate anemia, defined as hemoglobin 80–109 g/L, and mild anemia,defined as hemoglobin 110–129 g/L in men and 110–119 g/L in women [6].

Outcome Analysis and Measurements

Data were extracted from the computerized clinical information system of the hospital. Blood samples which were taken from patients at baseline (first hour) were used to analyze.

Patients were divided into two groups; anemic and nonanemic. Demographic data, labaratory findings (hemoglobin, red cell distribution width, platelet, d-dimer, urea, creatinine, albumin, sodium, potassium, ferritin, neutrophil, lymphocyte, neutrophil lymphocyte ratio, C-reactive protein, procalcitonin, interleukin-6), LOS-H, LOS-ICU, deaths were compared between groups. After further classification of anemia, patients

were divided into two new groups with a hemoglobin cut-off point 109 g/L. LOS-H, LOS-ICU and mortality were compared between patients with hemoglobin > 109 g/L and ≤ 109 g/L.

Statistical Analysis

All statistical analyses were carried out using SPSS 20 for Windows (IBM, 2011). Number, percentages, means, standard deviations, medians, and minimum and maximum values were used for descriptive statistics of the study. Demographic comparisons of the two groups were conducted using a chi-square analysis for categorical variables and independent t-tests for continuous variables. The distribution of the data was tested with the Kolmogorov–Smirnoff test. Moreover, skewness and kurtosis were calculated and both should be < 1 to use parametric tests. Normally distributed data were tested using the parametric Student's t-test and data not normally distributed by the nonparametric Mann–Whitney U test. Two tailed tests were used and $p < 0.05$ was regarded as being statistically significant.

Results

We retrospectively analyzed 288 patients with COVID-19 with a median age of 71 years (27–96 years): 183 men and 105 women. Anemia was detected in 137 (47.6%) patients upon admission to the ICU. Of those; 54 patients (39.4%) had mild, 76 patients (55.5%) had moderate, 7 patients (5.1%) has severe anemia.

Anemic patients were older, had multiple comorbidities, lower hemoglobin and albumin, higher red cell distribution width (RDW), creatinine and procalcitonin levels (Table 1). While LOS-H, LOS-ICU and mortality rates did not significantly differ between anemic and nonanemic patients; mortality rate was significantly high in patients with hemoglobin levels ≤ 109 g/L (moderate anemic) compared to patients with a hemoglobin level > 109 g/L (mild anemic and nonanemic). LOS-H and LOS-ICU were not significantly different between these patient groups (Tablo 2). Only seven patients had severe anemia and all of these died. Because of inadequate sample size (7 to 281), we did not compare LOS-H, LOS-ICU of severe anemic patients and others.

Discussion

In this study we mainly found that; 1) the prevalence of anemia was high (47.6%) in COVID-19 patients at ICU admission suggesting that anemic patients are more likely to have severe disease , 2) anemia with hemoglobin levels < 130 g/L in men and < 120 g/L in women is not associated with higher mortality rates, longer LOS-H and LOS-ICU, 3) anemia with a hemoglobin level < 80 g/L (moderate and severe anemia) is associated with higher mortality rates in ICU patients.

The WHO has estimated that global prevalence of anemia to be ~24.8% [7]. This prevalence is variable depending on the population and country studied.Benoit JL et al. reported 34.7% of COVID-19 patients were diagnosed as having anemia at emergency department presentation in USA [8]. However, Dinevari MF et al. evaluated 1274 COVID-19 patients who were hospitalized in İran and out of whom 615 (48.27%) were anemic and concluded that this higher prevalence may be related to higher prevalence of pre-existing anemia in İran and higher percentage of the female patients in their study [9]. Bellmann-Weiller et al. reported that 24.7% of patients with COVID-19 on admission were anemic in Austria [10]. Saydam BK et al. showed an anemia prevalance of 27.8% in Turkish women in their study [11]. With the facts that males have a higher percentage (63.5%) in our study population and anemia diagnoses were based on the ICU admission blood samples; the higher anemia prevalence (47.6%) in our study may be related to the suggestion that anemic patients are more likely to have severe disease [3,4,10].One of the possible explanations for this observation is the negative effects of anemia on immunity, while the other is it increases heart rate, blood pressure and pulmonary capillary leakage by activating sympathetic nervous system and furthermore enables development of acute respiratory distress syndrome (ARDS) [12, 13].

While most of the studies focused on the association between anemia and the severity of COVID-19, some also report the association between anemia and mortality of COVID-19 [3,10,14]. Bellmann-Weiller et al. reported that anemia, specifically anemia of inflammation is not only associated with longer hospital stays and poor clinical conditions, but also poor survival [10]. Our data also indicate thathemoglobin levels ≤ 109 g/L (moderate and severe anemia) in COVID-19 patients is associated with higher mortality rates, while mild anemia is not. This may be attributed to impaired tissue oxygenation with this cut-off point of hemoglobin in COVID-19 patients, along with anemia being a reflection of co-morbidities such as impaired renal function or older age or advanced inflammation [15, 16]. Our results support this with significantly older age, higher creatinine, procalcitonin and lower albumin levels of anemic patients. It is also possible that patients who have multiple comorbidities were more likely to be anemic.

RDW is a quantitative measurement of variation in red cell size which increased values indicate anisocytosis. It ranges from approximately 11% to 15% in normal subjects. Although it has been widely used as a guide for the differential diagnosis of

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Table 1: Comparison between anemic and nonanemic COVID-19 patients.

	Total (n=288)	Patients without anemia (n=137)	Patients with anemia (n=151)	p
Sex(Male)	183 (63.5)	91 (66.4)	92 (60.9)	0.333
Age	71±14 (72;27-96)	69±13 (71; 27-95)	72±14 (73; 50-96)	0.048
Comorbidities No One Multiple	 34 (11.8) 62 (21.5) 192 (66.7)	 25 (18.2) 36 (26.3) 76 (55.5)	 9 (6.0) 26 (17.2) 116 (76.8)	 0.001 0.062 0.000
Hemoglobin	12.3±2.3 (12.4; 6.9-18.0)	14.3 ± 1.2 (14.2; 12.0 -18.0)	10.6 ±1.6 (10.9; 6.9 - 12.9)	0.000
RDW	14.8 ± 1.9 (14.5; 5.0 – 25.0)	14.1 ± 1.21 (15.1; 11.9 – 18.9)	15.4 ± 2.1 (15.1; 5.0-25.0)	0.000
Platelet	244± 111 (224; 7 – 600)	251± 104 (228; 72 – 586)	238± 118 (221; 7 – 600)	0.259
d-dimer	4.2± 7.7 (1.6; 0.2 – 41.0)	3.9± 8.0 (1.4; 0.2 – 41)	4.4± 7.4 (1.7; 0.2 – 41)	0.137
Urea	69± 46 (60; 11 – 347)	61± 34 (60; 12 – 240)	74± 53 (60; 11 – 347)	0.057
Creatinine	1.31 ± 1.30 (0.91; 0.27 – 9.93)	1.05 ± 0.64 (0.89; 0.36 – 4.65)	1.53 ± 1.66 (1.05; 0.27 – 9.93)	0.002
Albumin	33.6± 5.9 (34.0; 3 – 52)	35.5 ± 5.4 (35.0; 3 – 52)	31.8 ± 5.7 (32.0; 17 – 46)	0.000
Sodium	139± 7 (138; 119 – 185)	139 ± 8 (138; 121 – 185)	139± 7 (138; 119 – 168)	0.578
Potassium	4.3 ±0.7 (4.2; 2.6 – 6.7)	4.7± 0.62 (4.2; 3.0 – 6.4)	4.2± 0.7 (4.2; 2.6 – 6.7)	0.688
Ferritin	940± 1626 (596; 12 – 21726)	858± 865 (643; 14 – 7583)	1015± 2090 (514; 12 – 21726)	0.416
Neutrophil	8.6± 6.1 (7.9; 0.1 – 72.6)	9.4± 4.7 (8.6; 1.4 – 24.5)	8.4± 7.2 (7.4; 0.1 – 72.6)	0.177
Lymphocyte	0.82± 0.82 (0.60; 0.05 – 7.00)	0.79± 0.65 (0.60; 0.15 – 5.50)	0.85± 0.95 0.60; 0.05 – 7.00)	0.357
NLR	16.3± 14.2 (12.9; 0.4 – 106.9)	17.0± 13.5 (13.6; 1.1 – 83.6)	15.6± 14.8 (12.2; 0.4 – 106.9)	0.456
CRP	9.9±38.4 (0.1; 0.0 – 232)	6.9±28.2 (0.2; 0.1 – 144.0)	12.1± 44.6 (0.1; 0.0 – 232)	0.375
Procalcitonin	2.1± 8.8 (0.2; 0.0 – 93.0)	1.4 ± 5.6 0.2; 0.0 – 45.6)	2.8 ± 10.9 (0.4; 0.0 – 93.0)	0.000
Interleukin-6	206.3± 851.4 (46.1; 1.0 – 10489)	170.7± 546.9 (46.6; 1 – 5047)	236.1± 1041.8 (44.7; 1.0 – 10489)	0.608
Length of stay (ICU)	11± 10 (8; 1 – 93)	10± 8 (8; 1 – 40)	11± 12 (8; 1 – 93)	0.719
Length of stay (Hospital)	14± 12 (11; 1 – 100)	14± 11 (12; 1 – 100)	14± 13 (10; 1 – 93)	0.660
Mortality	186 (64.6)	87 (63.5)	99 (65.6)	0.715

Values are shown as number (percentage) or mean±standard deviation (median; minimum-maximum). Significant values marked in bold
Abbreviations:RDW;red cell distribution width, NLR; neutrophil lymphocyte ratio, CRP; C-reactive protein, ICU; intensive care unit

Table 2: Comparison of mortality, length of ICU and hospital stays between patients with hemoglobin values of >109 g/L and ≤ 109 g/L.

	Patients with hemoglobin > 109 g/L (n=212)	Patients with hemoglobin ≤ 109 g/L (n=76)	p
Length of stay (ICU)	10 ± 8 (9; 1 – 40)	12 ± 16 (8; 1 – 93)	0.281
Length of stay (Hospital)	14 ± 11 (12; 1 – 100)	14 ± 15 (8; 1 – 93)	0.089
Mortality	129 (60.8)	57 (75.0)	0.027

Values are shown as number (percentage) or mean ± standard deviation (median; minimum-maximum). Significant values marked in bold
Abbreviations: ICU; intensive care unit

anemia, with high values found in iron deficiency;an increased RDWmainly reflects a profound deregulation of erythrocyte homeostasisinvolving both impaired erythropoiesis and abnormal erythrocyte metabolism and survival. These may be caused by avariety of abnormalities, like dyslipidemia, aging, oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, shortening of telomeresandabnormality of erythropoietin function [17,18]. The significantly higher values of RDW in anemic COVID-19 patients compared to nonanemic COVID-19 patients can be a result of older age, multiple comorbidities or any other factors above which needs further evaluation.

Study Limitations

This was a retrospective observational analysis of COVID-19 patients with the need for ICU admission in the region of Ankaraas a regionalreferral center for COVID-19, which might limit thegeneralizability of results. As it is in the nature of a retrospective analysis, these results donot prove any causality.Second, we definedanemia based on the levels of hemoglobin on ICU admission, and we hadno information on the hemoglobin levels before infection and dynamic Hb levels during ICU stay. Third, we did notmeasure other biomarkers of anemia, including serum iron and transferrin levels.

Conclusion

The results of this retrospective study showed that the anemia prevalence in ICU patients with COVID-19 was high and anemia was not associated with higher mortality rates if dignosed with a hemoglobin cut-off point < 130 g/L in men and hemoglobin < 120 g/L in women. Furthermore it was associated with higher mortality if mild anemics were considered as nonanemic, based on a cut-off point of 109 g/L for hemoglobin. Hemoglobin levels of anemic patients with COVID-19 should be closely monitored for timely detecting signs of disease progression.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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