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

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

Busra TEZCAN* 1, Halis Emre CIFTCI 2

1 Ministry of Health, Ankara City Hospital, Intensive Care Clinic, Ankara/TURKEY
2 Ministry of Health, Ankara City Hospital, Neurosurgery Clinic, Ankara/TURKEY

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, laboratory 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
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 from mild 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 association 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 consents 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, defined as 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, laboratory 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...
associated with higher mortality rates in ICU patients. Hemoglobin level < 80 g/L (moderate and severe anemia) is associated with higher mortality rates, longer LOS-H and LOS-ICU, 3) anemia with a hemoglobin level < 130 g/L (mild anemic and nonanemic). LOS-H and LOS-ICU were not significantly different between these patient groups (Table 1). Only seven patients had severe anemia and all of these died. 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].

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 Iran 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 Iran 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 prevalence 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 that hemoglobin 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
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                       | 34 (11.8)     | 25 (18.2)                       | 9 (6.0)                      | 0.001 |
| One                      | 62 (21.5)     | 36 (26.3)                       | 26 (17.2)                    | 0.062 |
| Multiple                  | 192 (66.7)    | 76 (55.5)                       | 116 (76.8)                   | 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                      | 15.4 ± 2.1 (15.1; 5.0-25.0) | 15.4 ± 2.1 (15.1; 5.0-25.0)     | 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) | 4.2±7.7 (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 (0.9; 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; 14 – 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; 11 – 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 – 144.0)       | 12.1±44.6 (0.1; 0.0 – 232)   | 0.375 |
| Procalcitonin            | 2.1±8.8 (0.2; 0 – 93.0) | 1.4±5.6 (0.2; 0 – 45.6)         | 2.8±10.9 (0.4; 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 – 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 RDW mainly reflects a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal erythrocyte metabolism and survival. These may be caused by a variety of abnormalities, like dyslipidemia, aging, oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, shortening of telomeres and abnormality 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 Ankara as a regional referral center for COVID-19, which might limit the generalizability of results. As it is in the nature of a retrospective analysis, these results donot prove any causality. Second, we defined anemia based on the levels of hemoglobin on ICU admission, and we had no information on the hemoglobin levels before infection and dynamic Hb levels during ICU stay. Third, we did not measure 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 diagnosed 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
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