The European Research Journal 2023;9(5):1074-1082 Original Article

DOI: 10.18621/eurj.1169438 *Hematology*

Anemia and COVID-19

Vildan Gürsoy[1], Suna Avcı[2], Selime Ermurat[3], Ali Erol[4], Melike Yazıcı[4]

[1]Department of Hematology, University of Health Sciences, Bursa City Hospital, Bursa, Turkey; [2]Department of Geriatrics, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey; [3]Department of Rheumatology, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey; [4]Department of Internal Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Objectives: Coronavirus disease-19 (COVID-19) is an infective-inflammatory disease that mainly affects the lungs. Hematological symptoms such as thrombocytopenia, decreased eosinophil and lymphocyte counts are quite common and are of prognostic importance. Although it is known that the presence of anemia generally increases the severity of respiratory diseases, there is little data on the prevalence and importance of anemia in COVID-19. In this study, our aim is to evaluate the clinical features of patients with anemia in COVID-19 infection and to investigate the relationship between the presence of anemia and the prognosis of the disease.

Methods: This retrospective, observational study included 353 patients who presented to our pandemic reference hospital between 15.04.2020 and 15.05.2020 and were diagnosed with SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction (PCR) test and typical clinical symptoms.

Results: Our study included 167 female and 186 male patients. The mean age was 54.54 ± 18.28 years (range 19-99). One hundred forty-eight (41.93%) patients had anemia. In patients with anemia, age was higher than others ($p < 0.001$). The percentage of women was significantly higher in the anemia group ($p < 0.001$). Comorbidities were observed more in the anemia group. The percentages of intensive care stay ($p = 0.003$) and mortality ($p = 0.001$) were significantly higher in the anemia group compared to the group without anemia. Logistic regression analysis was performed to determine the important risk factors of death. We found patients with high age ($p = 0.001$), high red cell distribution width-coefficient of variation (RDW-CV) levels ($p = 0.009$), high D-dimer levels ($p = 0.012$) and high ferritin levels ($p < 0.001$) have higher risk of death. Anemia was found to be non-significant.

Conclusions: Anemia is frequently observed in patients with severe COVID-19 disease and low hemoglobin values at presentation are thought to be associated with a worse prognosis. Being more sensitive to the hemoglobin levels of COVID-19 patients is important for early recognition of the high-risk patient group and for successful patient management. However, in our study, the presence of anemia was found to be effective in mortality in univariate analysis, but not in multivariate analysis. According to the multivariate analysis of this study, advanced age, high D-dimer, high ferritin and RDW-CV determine death.

Keywords: COVID-19, anemia, iron metabolism, mortality

Received: ***December 5, 2022;*** *Accepted:* ***March 8, 2023;*** *Published Online:* ***April 3, 2023***

How to cite this article: *Gürsoy V, Avcı S, Ermurat S, Erol A, Yazıcı M. Anemia and COVID-19. Eur Res J 2023;9(5):1074-1082. DOI: 10.18621/eurj.1169438*

e-ISSN: 2149-3189

Address for correspondence: *Vildan Gürsoy, MD., Bursa City Hospital, Department of Hematology, Bursa, Turkey. E-mail: vildanterzioglu@hotmail.com, Phone: +90 224 975 00 00*

Coronavirus Disease (COVID-19) is a new viral disease with high mortality and infectivity, which has spread to many countries around the world since the end of 2019 and seriously affects the elderly, people with chronic diseases such as diabetes, cardiovascular disease and hypertension [1, 2]. Although most patients infected with COVID-19 have a mild clinical course, up to 20% of patients are hospitalized mainly for pneumonia. Some of these patients who require hospitalization are followed in the intensive care unit and may need mechanical ventilation support [3, 4]. In such severe COVID-19 infections, a hyperinflammatory state characterized by an increase in inflammation markers such as interleukin-6 (IL-6), C-reactive protein (CRP) and ferritin is observed [5, 6]. Age is an important risk factor in mortality. It is known that mortality rates due to COVID-19 infection are higher in the geriatric population [7, 8]. It was observed that high ferritin levels were associated with disease severity, development of acute respiratory distress syndrome (ARDS) and death [9, 10].

Iron metabolism and the presence of anemia are thought to play an important role in coronavirus disease, the course of the disease, and the progression to multiple organ dysfunction syndrome [11]. Hemoglobin is involved in oxygen transport, and the decrease in hemoglobin concentration leads to a decrease in oxygen carrying capacity and arterial oxygen content. As a result, anemia facilitates hypoxia and can lead to end-organ ischemia [12, 13]. The presence of anemia has been associated with the adverse clinical course of many diseases [14, 15]. Previous studies have reported that anemia often increases the severity of respiratory tract diseases and is associated with poor outcomes and increased mortality in patients with community-acquired pneumococcal pneumonia [16-199. Therefore, it is very important to understand the relationship between anemia, iron metabolism and the prognosis of COVID-19. Studies have reported that the more severe course of COVID-19 disease is associated with low hemoglobin levels and anemia is a risk factor for serious disease [20].

In our study, we aimed to evaluate the prevalence of anemia in hospitalized COVID-19 patients and the effect of the presence of anemia on the clinical course of COVID-19 patients. In particular, we evaluated on the differences between anemic and non-anemic patients, the severity and type of anemia. We hypothesized that low Hgb levels were associated with a worse course of COVID-19 disease. In order to contribute to the early recognition of disease severity, we tried to reveal the dynamic relationship between anemia and COVID-19 severity, need for intensive care and mortality. However, the presence of anemia was not found to be associated with mortality in multivariate analysis. Along with anemia, we also evaluated other prognostic laboratory measurements that may be effective in the course of the disease.

METHODS

Patients and Laboratory

This retrospective study included 353 patients who presented to our pandemic reference hospital between 15.04.2020 and 15.05.2020. Patients were diagnosed with SARS-CoV-2 infection confirmed by typical clinical symptoms and real-time reverse transcription polymerase chain reaction (PCR) test and received inpatient treatment. These patients were diagnosed with COVID-19 in accordance with the ‘interim‘ guide issued by the Ministry of Health of the Republic of Turkey. The demographic characteristics of the patients, biochemical, hematological and inflammatory parameters, length of hospital stay, mortality and intensive care status were obtained by scanning their electronic medical records. People who were PCR negative, younger than 18 years old, outpatients and whose data could not be reached were not included in the study. The study protocol was approved by the Bursa Yüksek İhtisas Clinical Research Ethics Committee (Date:10.06.2020, Decision no: 2020/06-07]. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was also approved by the Turkish Ministry of Health.

PCR samples were taken from the patients. The samples were evaluated by an experienced team in the microbiology laboratory. Only patients with positive PCR tests were included in the study. Blood samples taken from the patients at the time of admission were analyzed in the laboratories of our hospital with fully automatic tests. Laboratory evaluations including routine blood tests, coagulation profiles, inflammation profiles, liver function, cardiac function and kidney function were performed. Laboratory findings were then extracted from the clinical information system.

Definition of Anemia and Iron Status

Based on the laboratory data obtained, we evaluated the prevalence and pathogenesis of anemia in patients infected with COVID-19. We determined the relationship between the presence of anemia and other clinical and laboratory findings in patients. In our study, anemia was defined according to the World Health Organization (WHO). Hemoglobin < 13 g/dL in males and < 12 g/dL in females was accepted as anemia. Anemia was classified as severe anemia (hemoglobin < 8 g/dL), moderate anemia (hemoglobin 8-10.9 g/dL), and mild anemia (hemoglobin 11-12.9 g/L in men and 11−11.9 g/dL in women) [21]. In addition, anemic patients were classified according to the mean corpuscular volume value (MCV). These were morphologically classified as microcytic (MCV < 80), normocytic (MCV: 80-100), and macrocytic (MCV > 100) anemias. Iron deficiency (ID) was defined as transferrin saturation (TSAT) < 20% in combination either with serum ferritin < 100 µg/L (absolute ID) or serum ferritin > 100 µg/L (functional ID) [16, 22].

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Histogram and Q-Q plots were used to determine whether variables are normally distributed. Data are provided as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t test. Non-normally distributed variables were analyzed with the Mann Whitney U test. Categorical variables were analyzed with the chi-square tests or Fisher's exact tests. Logistic regression analysis (forward conditional method) was performed to determine significant risk factors of death. $p < 0.05$ values accepted as statistically significant results.

RESULTS

Three hundred and fifty-three patients (167 women and 186 men) were included in this study. The mean age was 54.54 ± 18.28 years (range 19 to 99). One hundred and forty-eight (41.93%) patients had anemia. Age was significantly higher in patients with anemia compared to the others ($p < 0.001$). The percentage of women in the anemia group was significantly higher than in the non-anemia group ($p < 0.001$). The percentages of diabetes mellitus, hypertension, heart disease, atrial fibrillation, dementia, and kidney disease were significantly higher in the anemia group than in the non-anemia group ($p < 0.005$). Lymphocyte count, GFR, serum iron levels and transferrin saturation were significantly higher in the no anemia group than in the anemia group ($p < 0.001$). Red cell distribution width-coefficient of variation (RDW-CV), sedimentation, CRP, D-dimer and troponin levels were significantly higher in the anemia group than in the no anemia group ($p < 0.001$). In the anemia group, the rates of staying in the intensive care unit and death were found to be significantly higher than in the non-anemia group (Table 1).

Sixty-eight (45.95%) patients had mild anemia, 59 (39.86%) patients had moderate anemia and 21 (14.19%) patients had severe anemia. The percentage of women in the moderate and severe anemia group ($p = 0.034$) was significantly higher than in the mild anemia group. Renal diseases percentage ($p = 0.016$) was significantly higher in the moderate and severe anemia group than in the mild anemia group. RDW-CV, sedimentation, D-dimer and troponin levels were significantly higher in the moderate and severe anemia group than in the mild anemia group ($p < 0.005$). GFR, serum iron level and transferrin saturation were significantly higher in the mild anemia group than in the moderate and severe anemia group ($p < 0.005$). According to the severity of anemia, there was no significant difference between the percentages of intensive care stay and death.

Forty-seven (31.76%) patients had microcytic anemia and 101 (68.24%) patients had normocytic and macrocytic anemia. Age was significantly higher in normocytic and macrocytic groups compared to microcytic group ($p < 0.001$). The percentage of women in the microcytic group was higher than in the normocytic and macrocytic groups ($p = 0.002$). Heart disease and renal disease percentages were significantly higher in the normocytic & macrocytic group than in the microcytic group ($p < 0.005$). Glomerular filtration rate (GFR), RDW-CV and iron binding capacity were significantly higher in the microcytic group than in the normocytic and macrocytic group ($p < 0.001$). Lymphocyte count, sedimentation, C-reactive protein

Table 1. Summary of patients' characteristics and laboratory measurements with regard to presence of anemia

	Anemia			
	Absent (n = 205)	**Present (n = 148)**	**Total (n = 353)**	***p* value**
Age (years)	50.20 ± 16.32	60.54 ± 19.18	54.54 ± 18.28	**< 0.001**
Sex				
Female	72 (35.12%)	95 (64.19%)	167 (47.31%)	**< 0.001**
Male	133 (64.88%)	53 (35.81%)	186 (52.69%)	
Comorbidity	53 (25.85%)	70 (47.30%)	123 (34.84%)	**< 0.001**
Hemoglobin (g/dL)	13.88 ± 1.11	10.27 ± 1.89	12.36 ± 2.32	**< 0.001**
D-Dimer (µ/mL)	0.54 (0.30-1.00)	1.04 (0.51 - 2.24)	0.67 (0.35-1.45)	**< 0.001**
Fibrinogen (mg/dL)	446.38 ± 163.44	484.39 ± 174.92	463.17 ± 169.33	**0.073**
Ferritin (ng/mL)	151.90 (86.81-286.40)	151.30 (49.30- 471.20)	151.30 (72.89-365.80)	0.947
Transferrin saturation (%)	18.33 (13.52-26.02)	13.54 (8.97-20.03)	16.22 (11.31-24.34)	**< 0.001**
Ferritin / Transferrin saturation ratio	8.93 (4.53-20.29)	9.40 (4.01-28.42)	9.22 (4.20-21.62)	0.583
Stay in ICU (days)	4 (1.95%)	14 (9.66%)	18 (5.14%)	**0.003**
Length of stay in hospital (days)	7 (5-11)	7.5 (5-13)	7 (5-12)	0.242
Mortality	6 (2.93%)	18 (12.16%)	24 (6.80%)	**0.001**

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

(CRP), D-dimer, troponin, blood urea nitrogen (BUN), creatinine, serum iron, ferritin levels, transferrin saturation, ferritin / transferrin saturation ratio and length of stay in hospital were significantly higher in the normocytic and macrocytic group than in the microcytic group ($p < 0.005$). According to the MCV groups, there was no significant difference between the percentages of intensive care stay and death (Table 2).

Two hundred and twenty-seven (64.31%) patients had iron deficiency. The percentage of women in the iron deficiency group was significantly higher than the non-iron deficiency group ($p = 0.005$). RDW-CV was significantly higher in the iron deficiency group than in the no iron deficiency group ($p < 0.001$). Lymphocyte ($p = 0.004$) counts was significantly higher in the non-iron deficiency group than in the iron deficiency group. In terms of iron deficiency, there was no significant difference between the percentages of stay in the intensive care unit and death.

Logistic regression analysis was performed to determine the important risk factors of death. Significant factors of the univariate analysis were included in the multivariate analysis with forward conditional method. We found patients with high age ($p = 0.001$), high RDW-CV levels ($p = 0.009$), high D-dimer levels ($p = 0.012$) and high ferritin levels ($p < 0.001$) have higher risk of death (Table 3). Other variables included in the multivariate model, comorbidity ($p = 0.266$), eGFR ($p = 0.672$), anemia ($p = 0.304$), moderate and severe anemia ($p = 0.475$), WBC ($p = 0.074$), CRP ($p = 0.073$), serum iron ($p = 0.170$), iron binding capacity ($p = 0.346$), transferrin saturation (p = 0.114) and ferritin / transferrin ratio ($p = 0.413$) were found to be non-significant.

Patients with ≥ 75 age have 5.208-fold higher risk of death than the other patients (odds ratio [OR]: 5.208, 95% confidence interval [CI]: 2.220 - 12.213, $p < 0.001$). Patients with ≥ 15 RDW-CV level have 3.872-fold higher risk of death than the other patients (OR: 3.872, 95% CI: 1.654 - 9.068, $p = 0.002$). Pa-

Table 2. Summary of characteristics and laboratory measurements of the patients with regard to anemia types

	Anemia		
	Normocytic and Macrocytic (n = 101)	**Microcytic (n = 47)**	***p* value**
Age (years)	64.54 ± 18.09	51.94 ± 18.79	**< 0.001**
Sex			
Female	56 (55.45%)	39 (82.98%)	**0.002**
Male	45 (44.55%)	8 (17.02%)	
Comorbidity	52 (51.49%)	18 (38.30%)	0.187
Hemoglobin (g/dL)	10.39 ± 1.98	10.01 ± 1.67	0.226
D-Dimer (µ/mL)	1.35 (0.64-2.37)	0.61 (0.36-1.05)	**< 0.001**
Fibrinogen (mg/dL)	494,63 ±.169,81	461,26 ± 186,38	0.350
Ferritin (ng/mL)	263.90 (86.57-554.00)	59.72 (21.00-139.10)	**0.001**
Transferrin saturation (%)	16.33 (10.36-24.44)	10.00 (7.04-13.57)	**< 0.001**
Ferritin / Transferrin saturation ratio	15.36 (4.51-31.64)	6.13 (2.12-10.83)	**0.010**
Stay in ICU (days)	11 (11.22%)	3 (6.38%)	0.549
Length of stay in hospital (days)	9 (5-13)	6 (5-9)	**0.026**
Mortality	15 (14.85%)	3 (6.38%)	0.231

Data are provided as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Table 3. Significant risk factors of death, logistic regression analysis

	Univariate		**Multivariate**	
	OR (95% CI)	***p* value**		***p* value**
Age, years	1.067 (1.036-1.099)	**< 0.001**	1.119 (1.049-1.194)	**0.001**
Sex, male	2.299 (0.929-5.691)	0.072		
Comorbidity	6.400 (2.469-16.591)	**< 0.001**		
eGFR	0.959 (0.946-0.973)	**< 0.001**		
Anemia	4.592 (1.776-11.874)	**0.002**		
Anemia				
Mild anemia	2.073 (0.567-7.577)	0.270		
Moderate and severe anemia	7.035 (2.598-19.049)	**< 0.001**		
Anemia				
Normocytic& macrocytic anemia	5.785 (2.171-15.413)	**< 0.001**		
Microcytic anemia	2.261 (0.545-9.392)	0.261		
Ferritin	1.002 (1.001-1.003)	**< 0.001**	1.004 (1.002-1.006)	**< 0.001**
Transferrin saturation	1.028 (1.000-1.056)	**0.048**		
Ferritin / Transferrin saturation ratio	1.027 (1.010-1.044)	**0.002**		
Iron deficiency	1.118 (0.465-2.691)	0.803		

OR = Odds ratio, CI = Confidence interval

tients with ≥ 500 ferritin level have 15.896-fold higher risk of death than the other patients (OR: 15.896, 95% CI: 5.543 - 45.586, $p < 0.001$).

DISCUSSION

In this study, the data of 353 patients who received inpatient treatment in our hospital due to COVID-19 infection were evaluated retrospectively. Our results report that anemia is common in patients with COVID-19 infection. The presence of anemia causes poor clinical conditions and the need for intensive care. Comorbidities were observed more frequently in patients with anemia. However, anemia was not found to be effective in predicting mortality in multivariate analysis. In the study, it was observed that anemic patients were at high risk for severe inflammatory responses and were older. While there is a positive relationship between the severity of anemia and female gender, presence of renal disease and elevation in coagulation parameters, there is no significant difference between the intensive care unit needs and death rates. In the multivariate analysis, it was found that elderly patients with high RDW-CV, D-dimer and ferritin levels had a higher risk of death.

One of the most important determinants of the oxygen carrying capacity of the blood is the hemoglobin concentration. Low hemoglobin levels result in an inability to support increased peripheral tissue oxygen needs due to hypermetabolic conditions during infection, especially in populations at high risk of complications and death. A meta-analysis showed that regardless of age, gender and cardiovascular disease, anemia caused an increased risk of all-cause death and cardiovascular death by 41% and 33%, respectively [23]. It has been reported that the presence of anemia is associated with poor outcomes and increased mortality in respiratory tract diseases, as it increases the severity of the disease [18, 19]. It was found that the presence of anemia in chronic obstructive pulmonary diseases was associated with a 2.6-fold increased risk of mortality [24, 25]. In a study involving 191 patients with COVID-19, the frequency of anemia, Zhou *et al*. [5] reported as 15%. In our study, this rate was higher as 41.9%. The reason for this may be the inclusion of more severe patients who require hospitalization in our study. The correct prevalence of anemia remains uncertain in this patient group.

Few studies have so far examined the direct relationship between clinical and laboratory features, anemia and disease severity in patients with COVID-19. In patients with anemia, it is important to pay attention to the clinical features as well as the severity of the anemia. Taneri *et al*. [11] reported that hemoglobin levels were significantly lower in patients with severe COVID-19 infection in a meta-analysis and that the prognosis and severity of COVID-19 patients may be associated with low hemoglobin levels. In the studies, a significant trend towards lower hemoglobin values was observed with the worsening severity of COVID-19 [10, 26]. We could not find a significant relationship between the severity of anemia and the need for intensive care and mortality.

Changes in anemia and iron homeostasis are quite common in hospitalized patients. Tao *et al*. found that anemia, which was diagnosed based on hemoglobin measured within the first 24 hours after admission was strongly associated with progression (27). Since iron metabolism is associated with biomarkers and increased mortality at baseline, it is thought to contribute to the risk classification of patients. Zhou *et al*. [5] reported in a study that COVID-19 patients with anemia were more susceptible to death (26% vs 11%, p = 0.009).

There is a decrease in hemoglobin level in acute inflammation due to many complex mechanisms. Inflammation observed in COVID-19 infections can lead to iron homeostasis changes by keeping iron in macrophages and reducing its absorption from the intestine [28]. As a result, circulating iron levels decrease and hemoglobin production decreases. The cytokine-mediated inhibition of erythropoiesis decreases the biological activity of erythropoietin and shortens its erythrocyte half-life. And this leads to the development of inflammation anemia (AI) [22]. In our study, we observed that inflammation-related indicators (e.g., D-dimer, CRP, sedimentation) were higher in the anemia patients group. In addition, we found a significant increase in coagulation markers and inflammatory markers in patients with moderate to severe anemia.

One of the most common causes of anemia during infections is iron deficiency anemia. Iron requirements are essential for maintaining hemoglobin synthesis. In our study, iron deficiency was not found to be associ-

ated with the need for intensive care and mortality on its own. However, iron homeostasis disorders and the presence of anemia are important clinical determinants for risk stratification of patients infected with COVID-19 and it can guide the clinical management of those at highest risk, especially [29]. Accurate criteria must be established to define iron deficiency and iron-restricted erythropoiesis in COVID-19, particularly in the "hyper-inflammatory" stage of the disease. Changes in iron homeostasis may contribute to the pathogenesis of severe COVID-19 infection, with mechanisms that need to be resolved by future research.

There is a close relationship between the levels of ferritin and inflammation markers of macrophage activation and lung damage [30]. Studies have shown that increased risk of death in COVID-19 is associated with high ferritin levels [6, 9, 109. Hyperferritinemia has been suggested to be associated with iron toxicity and end organ damage in COVID-19 [31, 32]. Chronic disease anemia due to underlying comorbidities may also occur in patients. Also, the prevalence of comorbidities such as cardiovascular disease, hypertension or chronic kidney disease is higher in anemic patients [5]. In our study, it was found similar to the literature. In addition, patients with more than one comorbidity are expected to be more likely to be anemic and to be transferred to the intensive care unit when their physical condition worsens. Advanced age is an important risk factor for anemia. The prevalence of anemia rises to 12% in people aged 65 and over, and up to 47% in nursing home residents [15, 33, 34]. In our study, it was found that being older than 75 years increases the risk of death approximately 5 times.

Similar to the literature, only the prognostic significance of RDW was observed among the hematological parameters in our study. Increased RDW is an important risk factor for mortality. Previous studies have also shown that high RDW are associated with heart disease, sepsis, and more severe COVID-19 infection and increased mortality rates [35, 36]. Although the underlying mechanisms of the association between increased RDW and critical disease and mortality are unclear [37].

Limitations

This study includes a retrospective analysis of COVID-19 patients. Since there was no prospective study, iron metabolism variables could not be fully evaluated. In addition, cases with laboratory parameters were included in the study, which may lead to a possible selection bias for patients. Laboratory parameters of the patients were taken at the first admission and were determined according to the diagnosis of anemia, hemoglobin levels at the time of admission and iron parameters. Pre-application values, how long the anemia has existed, its follow-up values and the course of the anemia have not been mentioned. However, the exact cause and duration of anemia remains uncertain. It is difficult to confirm whether patients have chronic disease anemia.

CONCLUSION

Our results provides evidence that anemia is common in patients with COVID-19 requiring hospitalization. Low hemoglobin at admission is associated with a worse prognosis. Given the impact of anemia on quality of life and disease prognosis, the problem cannot be ruled out. Early recognition of those at risk and allergy to earlier and more aggressive medical intervention are important. Given the high costs, the risk of side effects and the shortage of blood supply, which have become a more serious problem during the COVID-19 pandemic, studies should be directed towards efforts to reduce the prevalence and severity of anemia. Our systematic review highlights important gaps in the presence of iron biomarkers and anemia other than ferritin in the prognosis of COVID-19. It shows that hemoglobin and ferritin levels vary according to the severity of COVID-19, as well as the presence of age, gender and comorbidity among COVID-19 patients. We hope that accurate diagnosis and effective treatment of the causes of anemia together with newly emerging treatment strategies will reduce the clinical burden of anemia in COVID-19. However, future prospective studies are still needed to confirm the effect of anemia on COVID-19 outcomes, management of patients and whether low hemoglobin levels predict mortality in these patients.

Authors' Contribution

Study Conception: VG; Study Design: VG, SA; Supervision: VG, SA; Funding: N/A; Materials: VG; Data Collection and/or Processing: AE, MY; Statistical

Analysis and/or Data Interpretation: SE; Literature Review: VG; Manuscript Preparation: VG, SA and Critical Review: SE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Wang L, Duan Y, Zhang W, Liang J, Xu J, Zhang Y, et al. Epidemiologic and clinical characteristics of 26 cases of COVID-19 arising from patient-to-patient transmission in Liaocheng, China. Clin Epidemiol 2020;12:387-91.
2. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.
3. Wu Y, Feng Z, Li P, Yu Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clin Chim Acta 2020;509:220-3.
4. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020;20:911-9.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
6. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020;146:128-36.
7. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2019;323:2052-9.
8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775-6.
9. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
10. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58:1021-8.
11. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol 2020;35:763-73.
12. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Diederichsen ACP, Hallas J, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. Am J Med 2013;126:789-97.
13. DeFilippis AP, Chapman AR, Mills NL, De Lemos JA, Arbab-Zadeh A, Newby LK, et al. Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. Circ J 2019;140:1661-78.
14. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol 2017;92:1068-78.
15. Wouters HJ, van der Klauw MM, de Witte T, Stauder R, Swinkels DW, Wolffenbuttel BH, et al. Association of anemia with health-related quality of life and survival: a large population-based cohort study. Haematologica 2019;104:468-76.
16. Camaschella C. Iron deficiency. Blood 2019;133:30-9.
17. Weiss G, Schett G. Anaemia in inflammatory rheumatic diseases. Nat Rev Rheumatol 2013;9:205-15.
18. Doshi S, Rueda A, Corrales-Medina V, Musher D. Anemia and community-acquired pneumococcal pneumonia. Infection 2011;39:379-83.
19. Reade MC, Weissfeld L, Angus DC, Kellum JA, Milbrandt EB. The prevalence of anemia and its association with 90-day mortality in hospitalized community-acquired pneumonia. BMC Pulm Med 2010;10:15.
20. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
21. Geneva S, Organization WH. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Vitamin and Mineral Nutrition Information System. Document Reference WHO. NMH/NHD/MNM/11.1. http://www. who. int/entity/vmnis/indicators/haemoglobin; 2011.
22. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019;133:40-50.
23. Liu Z, Sun R, Li J, Cheng W, Li L. Relations of anemia with the all-cause mortality and cardiovascular mortality in general population: a meta-analysis. Am J Med Sci 2019;358:191-9.
24. Lomholt FK, Laulund AS, Bjarnason NH, Jørgensen HL, Godtfredsen NS. Meta-analysis of routine blood tests as predictors of mortality in COPD. Eur Clin Respir J 2014;1:24110.
25. Rasmussen L, Christensen S, Lenler-Petersen P, Johnsen SP. Anemia and 90-day mortality in COPD patients requiring invasive mechanical ventilation. Clin Epidemiol 2011;3:1-5.
26. Henry BM, Benoit JL, Benoit S, Pulvino C, Berger BA, Olivera MHSd, et al. Red blood cell distribution width (RDW) Predicts COVID-19 severity: a prospective, observational study from the cincinnati SARS-CoV-2 emergency department cohort. Diagnostics (Basel) 2020;10:618.
27. Tao Z, Xu J, Chen W, Yang Z, Xu X, Liu L, et al. Anemia is associated with severe illness in COVID-19: a retrospective cohort study. J Med Virol 2021;93:1478-88.

28. Theurl I, Aigner E, Theurl M, Nairz M, Seifert M, Schroll A, et al. Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. Blood 2009;113:5277-86.
29. Wolf MS, Serper M, Opsasnick L, O'Conor RM, Curtis L, Benavente JY, et al. Awareness, attitudes, and actions related to COVID-19 among adults with chronic conditions at the onset of the US outbreak: a cross-sectional survey. Ann Intern Med 2020;173:100-9.
30. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020;19:102537.
31. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
32. Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020;8:506-17.
33. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. Clin Interv Aging 2014;9:1187-96.
34. Artz AS, Xue Q-L, Wickrema A, Hesdorffer C, Ferrucci L, Langdon JM, et al. Unexplained anaemia in the elderly is characterised by features of low grade inflammation. Br J Haematol 2014;167:286-9.
35. Wang C, Deng R, Gou L, Fu Z, Zhang X, Shao F, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 2020;8:593.
36. Foy BH, Carlson JC, Reinertsen E, Valls RPI, Lopez RP, Palanques-Tost E, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. JAMA Netw Open 2020;3:e2022058.
37. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care 2013;17:R282.