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The Relationship Between Anemia and Mortality in Elderly COVID 19 Patients

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ABSTRACT

Background: COVID 19 continues to affect the whole world with its different presentations and unenlightened aspects.Older patients are the group most at risk. Low hemoglobin levels contribute to hypoxia during COVID 19 infection and increase the risk of complications, especially in risky groups. In this study, we aimed to investigate the prevalence of anemia and its effect on mortality in geriatric COVID 19 patients.

Materials and Methods: Data of 251 patients over the age of 65 who were followed up in the Internal Medicine services allocated for COVID 19 of our hospital between August and October 2020, were included in the study. Anemia was defined as a hemoglobin level of 13 mg/dl in men and below 12 mg/dl in women at the time of admission. Demographic and laboratory data of the patients and hemoglobin levels were compared.

Results: The mean age of 251 COVID-19 patients included in the study was 75.6±7.6 years. 45.8% (n:115) of the patients were female and 54.2% (n:136). While 51.8% of the patients had anemia, the presence of anemia was found to be 67.9% in patients who died due to COVID 19. According to multivariate logistic regression analysis, advanced age (OR=1.082; 95% CI=1.03-1.137; p=0.002), presence of anemia (OR=1.969; 95% CI=1.113-4.246; p=0.034),hypertension (OR =5.763; 95% CI=1.713-19.389; p=0.005), dementia (OR=3.614; 95% CI=1.128-11.578; p=0.031) were determined as independent risk factors predicting mortality in patients with COVID-19.

Conclusion: Advance age, presence of anemia, hypertension and dementia has been found as İndependant risk factors for mortality in COVID 19 infection in our study. In elderly Covid 19 patients hemoglobin levels at admission may be helpful in predicting mortality.

Keywords: COVID 19, Geriatric population, Anemia, Mortality

Yaşlı COVID 19 Hastalarında Anemi ve Mortalite Arasındaki İlişki

Süreç

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ÖZ

Amaç: COVID 19, farklı prezentasyon ve aydınlanmamış yönleriyle tüm dünyayı etkilemeye devam etmektedir. Yaşlı hastalar, en fazla risk altındaki gruptur. Düşük hemoglobin seviyeleri, COVID 19 enfeksiyonu sırasında hipoksiye katkıda bulunur ve özellikle riskli gruplarda komplikasyon riskini artırır. Bu çalışmada geriatrik COVID 19 hastalarında anemi prevalansını ve mortaliteye etkisini araştırmayı amaçladık.

Metod: Ağustos-Ekim 2020 tarihleri arasında hastanemizin COVID 19 için ayrılan Dahiliye servislerinde takip edilen 65 yaş üstü 251 hastanın verileri çalışmaya dahil edildi. Anemi, başvuru anında hemoglobin düzeyinin erkeklerde 13 mg/dl, kadınlarda 12 mg/dl'nin altında olması olarak tanımlandı. Hastaların demografik ve laboratuvar verileri ile hemoglobin düzeyleri karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 251 COVID-19 hastasının ortalama yaşı 75,6±7,6 yıldı. Hastaların %45.8'i (n:115) kadın, %54.2'si (n:136) idi. Hastaların %51.8'inde anemi varken, COVID 19 nedeniyle ölen hastalarda anemi varlığı %67.9 olarak bulundu. Çok değişkenli lojistik regresyon analizine göre ileri yaş (OR=1.082; %95 CI=1.03-1.137; p=0,002), anemi varlığı (OR=1.969; %95 CI=1.113-4.246; p=0.034), hipertansiyon (OR=5.763; %95 GA=1.713-19.389; p=0.005), demans (OR=3.614 ; %95 CI=1.128-11.578; p=0.031) COVID-19 hastalarında mortaliteyi öngören bağımsız risk faktörleri olarak belirlendi.

Sonuç: Çalışmamızda COVID-19 enfeksiyonunda ileri yaş, anemi, hipertansiyon ve demans varlığı mortalite için bağımsız risk faktörleri olarak bulundu. Yaşlı COVID-19 hastalarında başvuru sırasındaki hemoglobin seviyeleri, mortaliteyi tahmin etmede yardımcı olabilir.

Anahtar sözcükler: COVID 19, Geriatrik popülasyon, Anemi, Mortalite

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in China at the end of 2019; It was first named 2019 novel coronavirus (2019-nCoV), and the disease it caused was later named COVID19. The disease has become a global health problem causing an epidemic all over the world. In March 2020, it was declared as pandemic by the World Health Organization (WHO) [1].

According to the latest data in February 2022, the total number of cases was over 400 million, and global deaths approached 6 million [2].

The most common symptoms reported in patients with COVID-19 are malaise, fever, and nonproductive cough. Less common symptoms are headache, nausea, anosmia, cough with phlegm, joint aches and chills. In contrast, older adults may present with atypical symptoms such as delirium, unexplained hypoxia, tachypnea, and tachycardia. COVID-19 can appear in a wide spectrum, from a mild picture to life-threatening serious pictures [3].

The elderly population has a risk of severe disease and high mortality due to weak immunity, cardiovascular diseases, diabetes and hypertension [4].

Biomarkers that predict morbidity and mortality have been identified to better classify and manage patients after admission to the hospital. This provides convenience to better manage treatment. Advanced age, male gender, comorbid conditions were associated with high morbidity and mortality. In addition, lymphopenia, high C-reactive protein (CRP), interleukin 6 (IL-6), ferritin levels and low transferrin levels, and anemia are biomarkers associated with the morbidity and mortality. Erythropoiesis and iron metabolism are significantly affected by the inflammatory state [5].

In COVID-19, anemia may occur due to the acute effects of the disease. In addition, existing anemia may worsen. One of the binding targets of SARS-CoV-2 is the receptor on the erythrocyte (ACE2, CD147 and CD26). The increased inflammation triggered by COVID-19 and the cytokine storm we see in severe cases are associated with increased ferritin and IL-6 levels. These biomarkers will increase hepcidin secretion, and hemoglobin (Hb) levels will decrease by preventing the use of iron by cells. As a result, anemia may appear in COVID-19 [6].

Due to increased metabolism during COVID-19 infection, the oxygen demand has increased. In addition, due to lung involvement, oxygenation is impaired and blood oxygen levels decrease. Hb plays a very important role in maintaining the PaO2 level and blood oxygen balance. If the Hb level is low, the oxygen balance will be affected, contributing to hypoxemia [7,8].

Hb values gradually decrease as age progresses, and anemia becomes an important health problem for elderly. Management of anemia in the elderly is critical and appropriate assessment is essential [9].

There is no standard definition of anemia. According to WHO criteria, a hemoglobin value of <12g/dL in women and <13g/dL in men is defined as anemia in the elderly [10].

The prevalence of anemia reaches 17% over the age of 65 [11]. The prevalence is 40% in hospitalized elderly and 47% in nursing home residents[12]. The prevalence reaches 50% in the population over 80 years of age. In the USA NHANES III (National Health and Nutrition Examination Survey) study, it was determined that 11% of men over the age of 65 and 10.2% of women in the society were anemic [13].

The most common causes of anemia in the elderly population include chronic infectious diseases, chronic inflammatory diseases such as chronic kidney disease (CKD), collagen tissue diseases and malignancies, nutritional deficiencies such as folate, B12 and iron deficiencies [14].

As age progresses, the number of bone marrow progenitor cells decreases, the production of growth factors decreases, IL-6 levels increase, and changes in the microenvironment occur. The self-renewal capacity of hematopoietic cells also decreases with age [15]. As a result, there is a decrease in the function of the hematopoietic system.

Chronic inflammation, changes due to immune aging, and oxidative stress also cause anemia in the elderly. IL-6 and CRP, which increase with aging, are indicators of increased inflammation and contribute to anemia [16].

In elderly patients, anemia is associated with many adverse outcomes, including falls, frailty, loss of physical function, dementia, deterioration in quality of life, and mortality [17].

Given the increase in anemia-related mortality and hospitalization rates, anemia management in the elderly is critical. However, there are opinions that argue that the etiology of anemia should not be actively investigated due to the limited life expectancy and social approaches in the elderly [18].

Even in cases of mild anemia, hospitalization and mortality rates are increasing in the elderly population. Accurate evaluation and treatment of anemia will reduce the symptoms of this population, reduce hospital admissions and hospitalizations, and thus the cost of care [9].

The unknowns of COVID-19 continue to affect the world as an ongoing disease. Despite all kinds of limitations, a holistic approach to the patient should be continued. The goal should not be just to treat the infection.

In this study, we aimed to evaluate the relationship between COVID-19 and anemia in the elderly population who is already at risk for anemia and has a high prevalence. We wanted to emphasize that anemia is not the result of old age and that due importance should be given to it.

Methods

Our study is a retrospective cohort study.

Study population: Data of 251 patients over the age of 65 who were followed up in the Internal Medicine clinics allocated for COVID-19 of our hospital between August and October 2020, were included in the study. Patients under 65 years of age and whose data could not be reached were excluded from the study.

Demographic characteristics, comorbidities and laboratory data of the patients were recorded. Length of hospital stay, intensive care needs and deaths were determined.

The diagnosis of COVID-19 was made with the COVID PCR test.

Among the laboratory parameters, *erythrocyte sedimentation rate (ESR)* (mm/h), CRP (gr/L), D-dimer (mg/L), procalcitonin (µg/L), ferritin (µg/L), maximum ferritin level (µg/L), Interleukin- 6 (pg/mL), max IL-6 level (pg/mL), folate (ng/mL), vitamin B12 (ng/L), Hb (g/dl), mean corpuscular volume (MCV) (fL), red cell distribution width (RDW) (%), Iron (ug/dL), iron binding capacity (ug/dL), transferrin saturation (%) were recorded.

Anemia was defined as a hemoglobin level of 13 mg/dl in men and below 12 mg/dl in women at the time of admission [19].

The diagnosis of anemia was made according to the hemoglobin value at the first hospitalization. Patients who developed anemia during follow-up were not included in the study.

Demographic and laboratory data of the patients and hemoglobin levels were compared.

Statistical Analysis

Data coding and statistical analyzes were performed on the computer using the SPSS 22 software package program (IBM SPSS Statistics, IBM Corporation, Chicago, IL). The conformity of the variables to the normal distribution was examined using the Shapiro-Wilk tests. Normally distributed variables were expressed as mean ± standard deviation, non-normally distributed variables were expressed as median (minimum-maximum) values. Mann-Whitney U test was used to compare parameters between groups. Chi-square or Fisher's exact tests were used for categorical variables. Risk factors for mortality in COVID-19 patients were determined by univariate logistic regression analysis. Whether the possible factors identified in this analysis were independent risk factors were evaluated using the Backward LR method with multivariate analysis. Cases with a p value below 0.05 were considered statistically significant.

Results

The mean age of 251 COVID-19 patients included in the study was 75.6±7.6 years, while 115 (45.8%) were female. While 195 (77.7%) patients were in the convalescent group, 56 (22.3%) patients were in the deceased group. Age, hospitalization time, oxygen need and intensive care requirement were higher in the group of the deceased.

The patients in this group had higher D-dimer, procalcitonin, maximum ferritin, IL-6, maximum IL-6, MCV and RDW levels, while Hb levels were lower. In addition, it was noted that the presence of anemia was higher in this group. Demographic and clinical features, additional diseases and laboratory data about the patients are shown in Table 1.

In our study, univariate and multivariate logistic regression analysis was performed to determine risk factors for mortality in COVID-19 patients. According to multivariate logistic regression analysis, advanced age (OR=1.082; 95% CI=1.03-1.137; p=0.002), presence of anemia (OR=1.969; 95% CI=1.113-4.246; p=0.034), presence of HT (OR =5.763; 95% CI=1.713-19.389; p=0.005) presence of dementia (OR=3.614; 95% CI=1.128-11.578; p=0.031), high maximum ferritin level (OR=1.001; 95% Cl=1- 1.001; p=0.001) and high maximum IL-6 level (OR=1.003; 95% CI=1.002-1.005; p=0.004) were determined as independent risk factors predicting mortality in COVID-19 patients (Table 2).

Table 1. Demographic, clinical and laboratory characteristics of patients who were treated for COVID-19 and recovered and died

	Total (n=251)	Recovering (n=195, % 77.7)	Died (n=56, % 22.3)	p
Demographic data				
Age (years) (Mean ± SD)	75.6±7.6	74.6±7.1	79.2±8.1	**<0.001[m]**
Female gender, n (%)	115 (45.8)	89 (45.6)	26 (46.4)	0.917[x]
Clinical data				
Hospitalization time (days) (median)(min-max)	10 (1-49)	10 (2-49)	14 (1-31)	**0.013[m]**
Presence of oxygen demand, n (%)	152 (60.6)	101 (51.8)	51 (91.1)	**<0.001[x]**
Intensive care requirement, n (%)	65 (25.9)	24 (12.3)	41 (73.2)	**<0.001[x]**
Presence of anemia, n(%)	130 (51.8)	92 (47.2)	38 (67.9)	**0.006[x]**
Additional diseases				
Hypertension, n (%)	186 (74.1)	137 (70.3)	49 (87.5)	**0.009[x]**
Diabetes Mellitus, n (%)	103 (41)	83 (42.6)	20 (35.7)	0.358[x]
COPD, n (%)	56 (22.3)	40 (20.5)	16 (28.6)	0.202[x]
CAD, n (%)	86 (34.3)	62 (31.8)	24 (42.9)	0.124[x]
Dementia, n (%)	20 (8)	10 (5.1)	10 (17.9)	**0.004[f]**
Hypothyroidism, n (%)	19 (7.6)	13 (6.7)	6 (10.7)	0.388[f]
Chronic renal failure, n (%)	25 (10)	15 (7.7)	10 (17.9)	**0.025[x]**
Laboratory data				
Sedimentation (mm/h) (median)(min-max)	40 (3-137)	40 (3-137)	40 (3-123)	0.989[m]
CRP (gr/L) (median)(min-maks)	81 (0.5-264)	73 (0.5-264)	92 (3-230)	0.093[m]
D-dimer (mg/L) (median)(min-max)	1.2 (0.2-43)	1.1 (0.2-43)	1.4 (0.3-21)	**0.027[m]**
Procalcitonin (µg/L) (median)(min-max)	0.1 (0.02-34)	0.1 (0.02-32)	0.2 (0.03-34)	**<0.001[m]**
Ferritin (µg/L) (median)(min-max)	345 (13-12391)	346 (13-12391)	335 (23-6022)	0.806[m]
Maximum ferritin level(µg/L) (median)(min-max)	528 (24-65356)	412 (24-12391)	1283.5 (59-65356)	**<0.001[m]**
Interleukin-6 **(pg/mL)** (median)(min-max)	35.6 (1.7-1515)	31 (1.7-1515)	53 (9-956)	**<0.001[m]**
Max interleukin-6 level (pg/mL) (median)(min-max)	42 (3-16003)	32 (3-1515)	77.8 (9-16003)	**<0.001[m]**
Folate (ng/mL) (median)(min-max)	10 (2-72)	10 (2-47)	9 (2-72)	0.151[m]
Vitamin B12 (ng/L) (median)(min-max)	382 (37-4876)	384 (37-4066)	382 (140-4876)	0.639[m]
Hemoglobin (g/dl) (median)(min-max)	12.4 (7.6-17.7)	12.6 (8-17.3)	11.7 (7.6-17.7)	**0.005[m]**
MCV (fL) (median)(min-max)	88.2 (8.5-119)	87.6 (26-119)	90.5 (8.5-118)	**0.012[m]**
RDW (%) (median)(min-max)	14.5 (1.4-88.5)	14.4 (1.4-88.5)	14.9 (13.1-26)	**0.001[m]**
Iron (ug/dL) (median)(min-max)	20 (1-173)	19 (1-123)	23 (2-173)	0.517[m]
Iron binding capacity (ug/dL) (median)(min-max)	239 (13-442)	240 (13-442)	228 (75-370)	0.064[m]
Transferrin saturation (%)(min-max)	8 (0-100)	8 (0-54)	8.8 (1-100)	0.665[m]

COVID-19: Choronavirüs Disease 19 **COPD :** Chronic Obstructive Pulmonary Disease **CAD:**coronary artery disease **CRP:** C reaktive protein, **İL-6:** Interleukin 6,**MCV:** Mean Corpuscular Volume, **RDW:** Red Cell Distribution Width, **[m]**: Mann Whitney U Test, x: Chi-square Test, f: Fisher's Exact Test

Table 2. Determination of risk factors for death in patients with COVID-19 using univariate and multivariate logistic regression analysis

	Univariate			Multivariate	
	OR (% 95 GA)	p		OR (% 95 GA)	p
Age (years)	1.084 (1.041-1.129)	**<0.001**	**Age (years)**	1.082 (1.03-1.137)	**0.002**
Anemia	2.364 (1.262-4.426)	**0.007**	**Anemia**	1.969 (1.113-4.246)	**0.034**
Hypertension	2.964 (1.267-6.929)	**0.012**	**Hypertension**	5.763 (1.713-19.389)	**0.005**
Dementia	4.022 (1.58-10.235)	**0.003**	**Dementia**	3.614 (1.128-11.578)	**0.031**
Chronic renal failure	2.609 (1.1-6.184)	**0.029**	**Chronic renal failure**	1.512 (0.491-4.652)	0.471
D-dimer (mg/L)	1.018 (0.952-1.088)	0.605			
Procalcitonin (µg/L)	1.075 (0.989-1.169)	0.091			
Maximum ferritin level (µg/L)	1 (1-1.001)	**<0.001**	**Maximum ferritin level (µg/L)**	1.001 (1-1.001)	**0.001**
Maximum IL-6 level (pg/mL)	1.003 (1.002-1.005)	**<0.001**	**Maximum IL-6 level (pg/mL)**	1.003 (1.002-1.005)	**0.004**

COVID-19: Choronavirüs Disease 19**, İL-6:** İnterleukin 6

Discussion

Although there are many studies investigating the relationship between COVID-19 and anemia in the literature, there is no study addressing this relationship only in the elderly patient population.

Age and additional diseases are causes of mortality and morbidity in COVID-19, as in every disease. In our study, we aimed to evaluate the status of anemia, which is a prognostic factor for COVID-19, in the elderly.

In the elderly, anemia is often perceived only as a result of aging or as a symptom of a disease. For these reasons, it may appear as an under-diagnosed condition that is usually not reported to the patient. Recent studies have also revealed the negative consequences of anemia in the elderly [20].

This can have an impact on health care needs and become a significant health care burden.

Available data suggest that anemia is associated with an increased risk of serious COVID-19. The possible pathophysiological link between anemia and severe COVID-19 can be explained as follows. In the circulatory system, Hb is responsible for oxygen transport to target organs. When the circulating Hb concentration is low, the transport of oxygen to the organs will be impaired, and multiple organ dysfunctions due to hypoxia will develop. Pulmonary dysfunction will also contribute to hypoxia [21]. Multiple organ dysfunction is associated with serious consequences in COVID-19. Elderly patients are already at risk for anemia. The current COVID-19 status will worsen this situation. The relationship between anemia and COVID-19 has been demonstrated in many studies. Tao et al. found that anemia diagnosed based on hemoglobin measured within the first 24 hours after hospitalization is independently associated with progression to severe coronavirus disease 2019 (COVID-19) [22].

In a meta-analysis by Hariyante et al., 7 studies with a total of 9,912 COVID-19 patients were evaluated. Anemia has been shown to be associated with the risk of serious COVID-19 [23].

In the study by Bellmann-Weiler et al., anemia was detected in 24.7% of COVID-19 patients at the time of admission to the hospital. Similar rates were observed in the study by Tao et al [19]. In these studies, the patient population was not divided into elderly. In our study, the rate of patients with anemia at admission was 51.8%. This situation was thought to be dependent on the age group of the population.

In studies, only the prognostic significance of RDW was determined among the hematological parameters included in complete blood counts. Increased RDW was found to be an independent risk factor for mortality [24] . Foy et al. found that higher RDW values in heart disease, sepsis, and critically ill patients were associated with more severe COVID-19 and increased mortality rates [25] .

In our study, we found RDW to be higher in the group of patients who died. No significant correlation was found between other anemia parameters such as MCW, iron, iron binding capacity, and transferrin saturations.

In the light of all this information, physicians should closely monitor anemic patients with suspected COVID-19 in terms of the prognosis of the disease. Further guidelines should be established for elderly patients at highest risk. The presence of anemia should be considered as an important factor in future risk stratification models for COVID-19 [23].

The point we wanted to emphasize here was to evaluate the elderly group with a high incidence of anemia within itself.

We wanted to draw attention to the fact that anemia should not be accepted as an expected situation in the elderly population and it should be ensured that necessary precautions are taken.

Limitations

Our study was planned as a retrospective study. The most important limitation was that we did not separate the patients according to the etiology of anemia. Patients were compared only according to whether they had anemia or not. Knowing the cause of anemia would contribute to illuminating the mortality process. Another limitation was that only hospitalization Hb values were taken into account. The contribution of Hb reduction to mortality could not be evaluated in the follow-up of the patients.

Conclusion

There are many studies showing that anemia is associated with COVID-19 mortality. However, there is no study on anemia and its effects in geriatric patients, who are more susceptible to anemia and are more sensitive to COVID-19. Advance age, presence of anemia, hypertension and dementia has been found as independant risk factors for mortality in COVID-19 in our study. In elderly COVID-19 patients Hb levels at admission may be helpful in predicting mortality.

Learning points:

- COVID-19 is more mortal for elderly patients.
- Hb values gradually decrease as age progresses, and anemia becomes an important health problem for elderly.
- Anemia has prognostic importance in the course of COVID-19.
- Management of anemia in the elderly is critical and appropriate assessment is essential.

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