

## DIFFERENCES IN INFLAMMATORY MARKERS IN COVID-19 MORTALITY IN PATIENTS AGED 18-65, 65-80 AND 80 YEARS AND OLDER

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**Abstract: Background:** Since its emergence, coronavirus disease 2019 (COVID-19) has been a challenge to manage and has resulted in high mortality rates.

**Aim:** This study aimed to reveal the differences in the parameters at the time during the first admission, according to age groups in patients who applied due to Covid-19 and died in the hospital.

**Methods:** This was a retrospective, cross-sectional, and descriptive study covering the period from March 16 to May 9, 2021. The study population (1169 patients) included patients with COVID-19 who presented to the emergency department and died in the hospital. The data required for this study were obtained from the electronic medical records of the patients in the information system of our hospital. The patients were divided into three groups and analyzed.

**Results:** It was determined that the highest mortality rate was 547 (46.8%) in the 65-80 age group. In terms of comorbidities, there was a statistically significant difference between the three groups only in the incidence of asthma ( $p = 0.037$ ). When the laboratory parameters and patient age groups were compared; a statistically significant difference was found in D-dimer, ferritin, WBC, platelet, and neutrophil values (respectively:  $p = 0.001$ ,  $p = 0.020$ ,  $p = 0.005$ ,  $p = 0.029$ ,  $p = 0.037$ ).

**Conclusion:** The highest death rate in Covid 19 patients is seen in the 65-80 age group. In patients over 80 years of age, the presence of asthma and the increase in D-dimer and ferritin levels among laboratory parameters can be used to predict mortality.

**Keywords:** Age group, COVID-19, D-dimer, emergency room, ferritin, mortality.

### INTRODUCTION

Since its emergence, coronavirus disease 2019 (COVID-19) has been a challenge to manage and has

resulted in high mortality rates. According to data from the World Health Organization (WHO), 5,331,019 people have died globally, and 79,813 people died in Turkey as of May 4, 2021 (1). There have been publications stating that COVID-19-related mortality is higher in older age groups. Mortality was reported to be significantly higher, particularly in patients aged > 65 years (2, 3). The guidelines published by the WHO state that the mortality rate increases by 20% in individuals aged > 80 years (3).

Many studies have been conducted on the factors that cause mortality in COVID-19 cases. While studies initially focused on viral load, inflammatory markers seem to have come to the forefront recently. As a result of these studies, the most important cause of severity and mortality in patients with COVID-19 is considered an excessive inflammatory response. Higher blood levels of inflammatory markers; including white blood cell (WBC), C-reactive protein (CRP), ferritin, and D-dimer, increased neutrophil-to-lymphocyte ratio (NLR), increased platelet-to-lymphocyte ratio (PLR), and increased serum levels of various inflammatory cytokines and chemokines have been associated with disease severity and mortality. It has also been suggested that these inflammatory cytokines, the levels of which are high in circulation, cause severe lymphopenia (2, 4). In addition, low platelet (PLT) counts, increased fibrin degradation products (D-dimer), and coagulation abnormalities are also reported to indicate poor prognosis. Organ failure of vital organs, such as the lungs, brain, heart, liver, and kidneys, due to microthrombi resulting from coagulation abnormalities is argued to be among the main causes of mortality in patients with COVID-19 (5).

This study aimed to reveal the relationship between age, inflammatory parameters, and mortality in patients who were admitted to the emergency department due to COVID-19 and died in the hospital.

## MATERIALS AND METHODS

### Study Group

The study protocol was approved by the Sakarya University Faculty of Medicine Local Ethics Committee, Turkey [IRB No.: 71522473 / 050.01.04 -39903-360]. This was a retrospective, cross-sectional, and descriptive study covering the period from March 16 to May 9, 2021. The study population included patients with COVID-19 who presented to the emergency department of Sakarya Training and Research Hospital and died in the hospital.

In this study, COVID-19 was diagnosed in the emergency department based on a positive Real-time Polymerase Chain Reaction (RT-PCR) test result in patients who conformed to the definition of a probable case of COVID-19 according to the diagnosis and treatment guidelines of the WHO and the Ministry of Health of the Republic of Turkey (6). Patients with indications were admitted to the COVID-19 services or intensive care units outside the emergency department based again on these guidelines. Patients < 18 years, negative RT-PCR test results, patients not first examined in the emergency department, and patients with no available data were excluded from the study. The patients were classified into three groups in this study: Group 1 (231 patients), Patients aged 18–65 years; Group 2 (567 patients), Patients aged 65–80 years; Group 3 (371 patients), Patients aged  $\geq$  80 years.

### Data Collection

The data required for this study were obtained from the electronic medical records of the patients in

the information system of our hospital. Information on demographic characteristics, comorbid diseases, laboratory parameters (WBC count, neutrophil count, PLT, NLR, PLR, CRP levels, D-dimer levels, and ferritin levels), RT-PCR test results, and mortality was recorded as part of the study.

NLR and PLR were calculated as follows:

- NLR = ratio of neutrophil count to lymphocyte count
- PLR = ratio of platelet count to lymphocyte count

### Statistics

SPSS software version 21.0 was used for statistical analysis. Median values were specified for continuous variables because they did not fit the normal distribution. Mann Whitney U and Kruskal Wallis tests were used for statistical analysis of continuous variables. Percentage values were given for the sharing of nominal categorical data, and statistical analyzes were made with the X2 test. All tests were performed with 5% two-tailed significance. Absolute and relative effects and corresponding 95% CIs for each endpoint were calculated as recommended by Altman et al. (7).

## RESULTS

Our study included 1169 patients who applied to the SEAH emergency department, were diagnosed with COVID-19 by PCR, and subsequently died. The median age of the patients was 74 (66–82) years. Evaluation of the deceased patients in terms of sex revealed that male patients died more frequently, with males accounting for 62.9% (n = 735) of the mortality. The

**Table 1.** Patients' demographic data, comorbidities, and laboratory parameters

		<b>n = 1169</b>
<b>Age (median; IQR)</b>		74 (66–82)
<b>Sex</b>	Female (n; %)	434 (37.1)
	Male (n; %)	<b>735 (62.9)</b>
<b>Comorbidity</b>	Hypertension (n; %)	<b>376 (32.2)</b>
	Chronic Kidney Failure (n; %)	81 (6.9)
	Chronic Obstructive Pulmonary Disease (n; %)	110 (9.4)
	Asthma (n; %)	49 (4.2)
	Diabetes (n; %)	20 (1.2)
<b>D-dimer (mg/L) (median; IQR)</b>	Normal: 0–500 mg/L	<b>907.0 (493.5–2250.0)</b>
<b>Ferritin (<math>\mu</math>g/L) (median; IQR)</b>	Normal: 0–500 $\mu$ g/L	<b>524.68 (246.05–1124.49)</b>
<b>CRP (mg/L) (median; IQR)</b>	Normal: 0–5 mg/L	<b>125.54 (66.51–198.33)</b>
<b>WBC (K/uL) (median; IQR)</b>	Normal: 4.6–10.2 K/uL	8.39 (5.86–11.65)
<b>Platelet (<math>10^9/L</math>) (median; IQR)</b>	Normal: 142.0–424.0 $10^9/L$	177.00 (132.85–227.00)
<b>Neutrophil (K/uL) (median; IQR)</b>	Normal: 2.0–6.9 K/uL	6.67 (4.46–9.72)
<b>Lymphocyte (K/uL) (median; IQR)</b>	Normal: 0.8–3.4 K/uL	<b>0.93 (0.61–1.40)</b>
<b>NLR (median; IQR)</b>		6.89 (3.92–12.85)
<b>PLR (median; IQR)</b>		188.50 (118.45–291.29)
<b>Number of hospitalization (days) (median; IQR)</b>		7 (2–13)

**Table 2.** Intra- and inter group statistical analysis of the age groups

		18-65 years n = 231	65-80 years n = 567	≥ 80 years n = 371	P	
Sex	Female (n; %)	74 (32)	192 (33.9)	168 (45.3)	<b>0.000</b>	
	Male (n; %)	157 (68)	375 (66.1)	203 (54.7)		
Comorbidity	Hypertension (n; %)	59 (25.5)	<b>204 (36.0)</b>	113 (30.5)	0.428	
	CRF (n; %)	19 (8.2)	35 (6.2)	27 (7.3)	0.782	
	COPD (n; %)	19 (8.2)	58 (10.2)	33 (8.9)	0.907	
	Asthma (n; %)	8 (3.5)	17 (3.0)	24 (6.5)	<b>0.037</b>	
	Diabetes (n; %)	1 (0.4)	14 (2.5)	5 (1.3)	0.609	
Inflammatory parameters	D-dimer (mg/L) (median; IQR)	Normal 0-500 mg/L	790.00 (439.00-1980.00) <sup>a</sup>	889.00 (460.00-2015.00) <sup>b</sup>	1050.00 (612.50-3305.00) <sup>a,b</sup>	<b>0.000</b>
	Ferritin (µg/L) (median; IQR)	Normal 0-500 µg/L	542.15 (283.99-1789.67) <sup>a</sup>	535.53 (246.43-1187.62)	491.70 (228.06-950.25) <sup>a</sup>	<b>0.020</b>
	CRP (mg/L) (median; IQR)	Normal 0-5 mg/L	124.00 (65.42-182.78)	126.14 (66.32-203.02)	127.03 (67.10-201.16)	0.738
	WBC (K/uL) (median; IQR)	Normal 4.6-10.2 K/uL	7.58 (4.95-11.50) <sup>a,b</sup>	8.42 (6.11-11.60) <sup>a</sup>	8.69 (6.30-11.70) <sup>b</sup>	0.005
	Platelet (K/uL) (median; IQR)	Normal 142-424 K/uL	172.50 (126.00-223.00) <sup>a</sup>	174.10 (135.55-226.50)	182.00 (130.00-234.15) <sup>a</sup>	<b>0.029</b>
	Neutrophil (K/uL) (median; IQR)	Normal 2.0-6.9 K/uL	6.19 (3.77-9.46) <sup>a</sup>	6.66 (4.58-9.62)	5 (4.84-9.89) <sup>a</sup>	<b>0.037</b>
	Lymphocyte (K/uL) (median; IQR)	Normal 0.8-3.4 K/uL	0.94 (0.61-1.37)	0.92 (0.61-1.42)	0.93 (0.61-1.37)	0.806
	NLR (median; IQR)		6.54 (3.66-11.56)	6.79 (3.86-12.98)	7.30 (4.21-13.85)	0.130
	PLR (median; IQR)		169.05 (118.86-293.47)	188.37 (116.40-291.82)	194.51 (126.27-290.23)	0.303
Mortality days (median; IQR)		8.00 (4.00-15.00)	8 (2.00-4.00)	6 (1.50-11.00)	0.059	

deceased patients' number of hospitalization days was 7 (2-13) days. Evaluation in terms of comorbidities revealed that hypertension (32.2%), COPD (9.4%), and CRF (6.9%) were the most commonly found comorbidities in deceased patients. As for the laboratory parameters, detailed data is provided in Table 1.

Results of intra- and intergroup statistical analysis of the age groups are provided in Table 2. Accordingly, the difference in the sex distribution between the age groups was determined to be statistically significant ( $p = 0.000$ ). In terms of comorbidities, there was a statistically significant difference between the three groups only in the incidence of asthma ( $p = 0.037$ ). Asthma prevalence, in particular, was found to increase in patients aged  $\geq 80$  years. In terms of laboratory parameters, a statistically significant difference was found between the three groups in terms of D-dimer, ferritin, WBC, platelet, neutrophil, and lymphocyte percentages. (respectively;  $p = 0.000$ ,  $0.020$ ,  $0.005$ ,  $0.029$ ,  $0.037$ , and  $0.806$ ).

In the subgroup analysis of the laboratory values in terms of age groups, a statistically significant difference was found between Group 1 and Group 3, Group 2 and Group 3 in D-dimer values (respectively;  $p = 0.001$  and  $0.004$ ). When the subgroup analysis was conducted in terms of WBC values, a statistically significant difference was observed between Group 1 and Group 2, Group 1, and Group 3 (respectively;  $p = 0.013$  and  $0.006$ ). Furthermore, a statistically significant difference was found between Group 1 and Group 3 in the subgroup analysis of ferritin, platelet, and neutrophil levels (respectively;  $p = 0.025$ ,  $0.024$ , and  $0.036$ ).

## DISCUSSION

COVID-19 is still among the most important causes of morbidity and mortality in most countries around the world despite ongoing vaccination efforts. In particular, advanced age and male sex have been revealed to be associated with mortality. A study conducted on

this subject reported that the highest mortality rate in the group of patients aged > 60 years was among those aged  $\geq 80$  years (8, 9). Our study results corroborate the findings of the existing literature. Mortality was observed to be more common in the advanced age groups, particularly in those aged 65–80 years.

Considering the studies on COVID-19 in the literature, it has been previously reported that disease severity and mortality are higher in males (4, 9). This may be attributed to the higher risk of cardiovascular diseases, increased smoking, alcohol consumption, dietary differences, and decreased physical activity, in addition to the less use of healthcare services among men compared with women. Further, genetic factors may also be implicated (10, 11). Our study also showed that mortality was higher among men than women in all age groups, but this difference in mortality decreased in patients aged > 65 years. A similar study conducted on this subject found that the difference in mortality between the sexes decreased in advanced age groups, which was attributed to the decrease in the protective effect of estrogen (12). However, in our study, the difference between males and females was less in patients aged  $\geq 80$  years, suggesting that factors other than estrogen may be implicated.

In addition to epidemiological factors, comorbid diseases, such as hypertension, obesity, diabetes, cardiovascular diseases, chronic lung disease, CRF, and malignancy, have been reported to be associated with disease severity and poor prognosis in patients with COVID-19 (13, 14). The most common comorbid disease in patients with COVID-19 is hypertension, which has also been reported to be associated with the development of ARDS (15, 16). Although hypertension was the most common comorbidity in our study, which is consistent with the literature, the fact that asthma was also a prominent comorbid disease in our patients aged  $\geq 80$  years makes our study results noteworthy.

Patients with COVID-19 are known to be prone to thrombosis due to increased inflammatory response, hypoxia, immobilization, and widespread intravascular coagulation, which can be evaluated based on laboratory parameters such as D-dimer levels (17). Hence, it is stated that the age-adjusted D-dimer level threshold in patients with pulmonary embolism can be used for both diagnosis and prognosis (18). Similar COVID-19 studies have reported that different D-dimer level cutoff values, such as 1000 mg/L and 2000 mg/L, can be used to predict prognosis (19,20). Our study found D-dimer levels to be high in patients with COVID-19, as expected. However, the greatest increase was observed in patients aged  $\geq 80$  years. Based on this result, we believe that it would be appropriate to calculate and use age-adjusted D-dimer level thresholds to predict mortality.

Ferritin is a marker that plays a role in the inflammatory response and contributes to the cytokine storm observed in patients with COVID-19 (21). Ferritin levels are expected to increase in patients with COVID-19, and this is why it is used both as a diagnostic as well as a prognostic parameter (6, 21). Many studies have been conducted to demonstrate the success of ferritin in predicting disease severity and mortality. It has been reported that ferritin levels can indeed predict prognosis at the cutoff values of 451 ng/mL and 574.5 ng/MI (22, 23). Our study results corroborate the existing literature, and it was observed that ferritin levels were increased in patients with COVID-19. This increase was more pronounced in those aged 18-65 years and was within the reference range mentioned in the literature for those aged  $\geq 80$  years. These results suggest that the threshold value should be determined according to age groups for ferritin levels as well, similar to D-dimer levels, to predict mortality.

A complete blood count is an easily accessible, relatively fast, and inexpensive diagnostic tool that can also be used in the management of patients with COVID-19 (24). The most studied parameters include WBC count, platelet count, neutrophil count, lymphocyte count, NLR, and PLR. A review of the literature suggests that an increase is expected in the WBC count, neutrophil count, NLR, and PLR, whereas a decrease is expected in lymphocyte and platelet counts (4, 25). It is noteworthy that PLR and NLR have been the most studied parameters in terms of predicting disease severity and mortality in patients with COVID-19. In fact, in a previous study on the subject, we reported that mortality could be successfully predicted using neutrophil count, NLR, and PLR at the cutoff values of 5.12 K/ul, 2.55, and 148.85 respectively (4). Other studies on the subject have also reported similar results (25, 26). The results of this study support both our previous study and the literature. Nevertheless, the fact that the most significant increases were observed in those aged  $\geq 80$  years makes this study a noteworthy contribution to the literature.

### Limitations

Our study is retrospective and is not multicentered. In addition, the IL-6 level, which is an important parameter in COVID-19 mortality, could not be included due to the retrospective nature of the study. Besides, the lack of information about the patient's vaccination status against COVID-19 is one of the study's limitations.

### CONCLUSION

The highest death rate in COVID 19 patients is seen in the 65-80 age group. In patients over 80 years



of age, the presence of asthma and increases in D-dimer and ferritin levels among laboratory parameters can be used to predict mortality.

### AUTHOR CONTRIBUTION STATEMENT

1-Study concept and design: N.A. and F.G. 2-Acquisition of data: N.A., F.G., Y.Y., E.D., and N.G.G. 3-Analysis and interpretation of data: N.A., N.G.G., and E.D. 4-Drafting of the manuscript: Y.Y. and N.A. 5-Critical revision of the manuscript for important intellectual content: F.G., E.D., Y.Y., N.G.G. and E.D. 6-Statistical analysis: N.G.G., N.A. and F.G. 7 Administrative, technical, and material support: E.D., Y.Y., and F.G. 8 Study supervision: N.A., F.G., N.G.G., and E.D.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Sakarya University Faculty of Medicine Local Ethics Committee, Turkey [IRB No.: 71522473 / 050.01.04 -39903-360].

### HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. This research was conducted

on humans in accordance with the Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

### CONSENT FOR PUBLICATION

Not applicable.

### THE STANDARD FOR REPORTING:

STROBE guidelines and methodology were followed.

### AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available within the article.

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### Sažetak

## RAZLIKE U INFLAMATORNIM MARKERIMA U SMRTNOSTI OD COVID-19 KOD PACIJENATA UZRASTA 18-65, 65-80 i 80 GODINA I STARIJIH

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**Uvod:** Od svog nastanka, bolest korona virusa 2019 (COVID-19) predstavljala je izazov i rezultirala je visokim stopama smrtnosti.

**Cilj:** Ova studija je imala za cilj da otkrije razlike u parametrima u vreme prvog prijema, prema starosnim grupama pacijenata koji su se primljeni zbog Kovid-19 i umrli u bolnici.

**Metode:** Ovo je bila retrospektivna, studija preseka i deskriptivna studija koja je pokrivala period od 16. marta do 9. maja 2021. Ispitivana populacija (1169 pacijenata) uključivala je pacijente sa COVID-19 koji su se javili u Službu za hitnu pomoć i umrli u bolnici. Podaci potrebni za ovu studiju dobijeni su iz elektronske medicinske dokumentacije pacijenata u informacionom sistemu naše bolnice. Pacijenti su podeljeni u tri grupe i analizirani.

**Rezultati:** Utvrđeno je da je najveća stopa mortaliteta 547 (46,8%) u starosnoj grupi 65-80 godina. U pogledu komorbiditeta, statistički značajna razlika između tri grupe postojala je samo u incidenci astme ( $p = 0,037$ ). Kada su laboratorijski parametri i starosne grupe pacijenata upoređeni; utvrđena je statistički značajna razlika u vrednostima D-dimera, feritina, leukocita, trombocita i neutrofila (respektivno:  $p = 0,001$ ,  $p = 0,020$ ,  $p = 0,005$ ,  $p = 0,029$ ,  $p = 0,037$ ).

**Zaključak:** Najveća stopa smrtnosti kod pacijenata sa COVID-19 zabeležena je u starosnoj grupi od 65 do 80 godina. Kod pacijenata starijih od 80 godina, prisustvo astme i porast nivoa D-dimera i feritina među laboratorijskim parametrima može se koristiti za predviđanje mortaliteta.

**Ključne reči:** starosna grupa, COVID-19, D-dimer, hitna pomoć, feritin, mortalitet.

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