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Factors associated with COVID-19 mortality in elderly patients in intensive care unit

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ABSTRACT

Objectives: Mortality rates in patients with COVID-19 infection admitted to the intensive care unit are influenced by various factors. In this study, we aimed to investigate the mortality rate and factors affecting mortality in patients admitted to the intensive care unit due to COVID-19 infection who had not been vaccinated.

Methods: Our study was conducted retrospectively by scanning patients admitted to the intensive care unit of Izmir Bozyaka Education and Research Hospital of Health Sciences University from the beginning of 2020 to the end of 2022. Patients who were admitted to the intensive care unit were 65 years of age and older with COVID-19 infection. The patients' presenting complaints, degree of lung involvement, laboratory findings, and comorbidities were compared between patients who survived and those who passed away.

Results: A total of 166 patients were evaluated in our study. Of these, 48 patients were discharged, while 118 patients experienced an excitus. The median age (IQR) for discharged patients was 71.5 (8), and for patients who experienced an excitus, it was 78 (15), which was found to be statistically significant ($p < 0.001$). The most common presenting complaint in all patients was high fever. Patients with two or more comorbidities were more common in the excitus group ($p <0.001$). Severe involvement on initial computed tomography was observed in 28 patients in the excitus group, while no severe involvement was seen in the discharged group ($p < 0.001$).

Conclusion: Our study found that advanced age, extensive lung involvement at admission, the presence of two or more comorbidities, and the presence of dyspnea at admission were associated with increased mortality in elderly patients.

Keywords: Covid-19, Elderly patients, Mortality

COVID-19 is a SARS-CoV-2 virus infection that rapidly spread across China and subsequently affected the entire world after emerging in Wuhan at the end of 2019.[1-3] The World Health Organization declared a pandemic worldwide in 2020.

Among the symptoms of the disease are non-specific flu-like symptoms such as fever, dry cough, fatigue, headache, and dyspnea. However, symptoms and disease course can vary significantly among individuals. Many infected individuals show no symptoms, while some patients present with severe symptoms and require hospitalization.

COVID-19 infection in susceptible individuals can lead to severe respiratory failure, sepsis, coagulation disorders, acidosis, and ultimately death. Mortality rates are higher in individuals with underlying con-

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ditions such as diabetes mellitus, hypertension, renal failure, and heart disease. The severity of the disease and mortality rate are higher in elderly patients. In older patients, the course of the disease worsens, and mortality significantly increases.[4-6] One study found that advanced age is the most critical risk factor for the prognosis of the disease.[7]

One of the leading causes of death in Covid-19 is respiratory failure. Elderly patients are more sensitive to this condition because the function of many organs decreases to varying degrees with age. Additionally, it is known that the virus is more easily transmitted in elderly patients, and the inflammatory response can be dysregulated. For all these reasons, Covid-19 infection has a more severe and fatal course in the elderly population.[8]

In this study, we aimed to investigate the factors affecting mortality in patients aged 65 and over admitted to the intensive care unit due to Covid-19 infection.

METHODS

Our study was conducted retrospectively by scanning the hospital information system program of the University of Health Sciences İzmir Bozyaka Training and Research Hospital from the beginning of 2020 to the end of 2022. Patients admitted to the intensive care unit and 65 years of age and older, with confirmed COVID-19 infection through real-time polymerase chain reaction (RT-PCR) from nasal swab samples, were included.

In our study, patients under the age of 65, those vaccinated against COVID-19, patients with any malignancy, those who underwent surgical procedures for any reason during hospitalization, those with acute cerebrovascular events, and patients diagnosed with bacterial infections during admission were excluded.

Demographic data of the patients, their comorbidities, medications they were taking, reasons for hospital admission, the onset time of symptoms, findings, and extent of lung involvement in tomography, as well as hemoglobin levels, white blood cell counts, neutrophil and lymphocyte counts, C-reactive protein, procalcitonin, albumin, alanine aminotransferase, aspartate aminotransferase, d-dimer, and fibrinogen levels during admission were recorded.

Computed tomography findings of the patients were obtained from the hospital record system, based on interpretations by expert radiologists. According to the radiologist's interpretation, they were classified as mild, moderate, or severe radiological involvement. Patients without a computed tomography interpretation were excluded from the study.

At the end of hospitalization, patients were divided into two groups based on their discharge status: those with excitus and those without. A statistical comparison was performed between the two groups to identify factors potentially affecting morbidity and mortality.

Treatment Goals and Monitoring

All patients received oxygen support to maintain oxygen saturation (SpO2) levels at 94% or above. In cases where the target could not be achieved with oxygen support, the high-flow nasal cannula was provided, followed by non-invasive ventilation if necessary. Patients who did not respond to all non-invasive respiratory support systems were intubated and placed on invasive mechanical ventilation support. For patients with a PaO2/FiO2 ratio below 150, if there were no contraindications, they were positioned in the prone position for a minimum of 16 hours daily.

All patients received low-molecular-weight heparin and 0.5 mg/kg methylprednisolone treatment. In intubated patients, propofol and opioid (fentanyl or remifentanil) infusions were administered for sedation purposes. Favipiravir was administered to all patients as an antiviral agent. Additionally, patients who developed macrophage activation syndrome received pulse steroids and/or tocilizumab therapy.

Ethical approval

The study was approved by our hospital's local Clinical Research Ethics Committee (2022/38). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 21 (IBM) was used for statistical analysis. The compliance of the data to normal distribution was determined by the Shapiro-Wilk test. Normally distributed quantitative data were given as mean and standard deviation. Non-normally distributed data were given as a median and interquartile range. Categorical data were given as numbers and/or percentages. Differences in mean or median values were calculated using the Student's t-test (for normally distributed data) or Mann-Whitney U-test (for non-normally distributed data). Categorical data were evaluated using the Chi-

Squaretest. The significance level was taken as $p < 0.05$.

RESULTS

A total of 198 patients were evaluated in our study. 32 patients were excluded from the study for various reasons (23 patients had been vaccinated, four patients underwent surgical operations during their hospitalization, and five patients had life-threatening malignancies), leaving 166 patients for evaluation. Out of these, 48 patients were discharged, while 118 patients experienced an excitus. The median age (IQR) for discharged patients was 71.5 (8), and for patients who experienced an excitus, it was 78 (15), which was found to be statistically significant ($p < 0.001$). Of the patients, 82 were female, and 84 were male (Table 1). The most common presenting complaint in all patients was high fever. The most common comorbidity in both groups was hypertension. Patients with two or more comorbidities were more common in the excitus group ($p < 0.001$). Severe involvement on initial computed tomography was observed in 28 patients in the excitus group, while no severe involvement was seen in the discharged group ($p < 0.001$). During hospitalization, dyspnea was observed in 7 patients in the discharged group and 50 patients in the excitus group, which was statistically significant ($p < 0.001$). The two groups had no significant differences in other findings during hospitalization. The highest ferritin level, lowest fibrinogen level, and highest d-dimer level detected during hospitalization were statistically significant between the two groups (Table 2).

Table 1. Demographic properties, symptoms and radiologic findings

	Survive (n = 48)	Excitus (n = 118)	*p* value
Age[1]	71,5 (8)	78 (15)	< 0,001
Gender, n (%)			
Male	28 (58,3%)	56 (47,5%)	
Female	20 (41,6%)	62 (52,5%)	
Concomitant disease, n (%)			0,989
Type-2 Diabetes	11 (22,9%)	24 (20,3%)	
Hypertension	14 (29,1%)	32 (27,1%)	
Chronic renal disease	1 (2,08%)	3 (2,5%)	
Coronary arter disease	6 (12,5%)	8 (6,7%)	
COPD/Asthma	4 (8,3%)	6 (5%)	
Neurolojik disease	2 (4,1%)	4 (3,3%)	
Symptoms at admission, n (%)			0,789
Fever	28 (58,3%)	67 (56,7%)	0,954
Caught	26 (54,1%)	56 (47,5%)	0,433
Nasal congesion	7 (14,5%)	17 (14,4%)	0,977
Dispnea	7 (14,5%)	50 (42,3%)	< 0,001
Fatigue	8 (16,6%)	73 (61,8%)	0,176
Diarrhea	4 (8,3%)	9 (7,6%)	0,878
Stomach ache	8 (16,6%)	13 (11%)	0,321
Sore throat	23 (47,9%)	41 (34,7%)	0,114
Radiological findings[2], n (%)			< 0,001
No finding	14 (20,1%)	14 (11,8%)	
Mild	32 (66,6%)	36 (30,5%)	
Moderate	2 (4,1%)	40 (33,8%)	
Severe	-	28 (23,7%)	
Concomitant disease, n (%)			< 0,001
1 Concomitant disease	34 (70,8%)	46 (38,9%)	
2 or more Concomitant disease	10 (20,8%)	66 (55,9%)	

[1]median (interquartile range)
[2]lung involvement in computerized tomography
COPD: Chronic obstructive pulmonary disease

Table 2. Laboratory findings

	Survive	Excitus	*p* value
Heamoglobin[1] (g/dL)	9,6 (2)	13,6 (4,4)	0,898
Neutrophil count[1] (x10^9/L)	7030 (5783)	8120 (6810)	0,061
Lymphosit count[1] (x10^9/L)	560 (673)	610 (520)	0,930
C-reaktive protein[1,2] (mg/L)	82 (114)	89 (145)	0,248
C-reaktive protein[1,4] (mg/L)	130 (147)	155 (137)	0,129
Procalsitonine[1,2] (ng/mL)	0,32 (1)	0,5 (0,98)	0,133
D-dimer[1,4] (ng/mL)	930 (1361)	1964 (2780)	< 0 ,001
Fibrinogen[1,3] (mg/dL)	330 (157)	250 (188)	< 0,001
AST[1,2] (U/L)	33 (17)	30 (40)	0,004
ALT[1,2] (U/L)	16 (4)	23 (35)	0,308
Creatinine[1,2] (mg/dL)	0,95 (0,7)	1,2 (0,93)	0,011
Urea[1,2] (mg/dL)	87 (57)	83 (73,9)	0,029
Ferritin[1,4] (ng/mL)	606 (993)	977 (954)	0,001

[1]median (interquartile range)
[2] irst day
[3]lowest value during follow-up
[4]highest value during follow-up
ALT: Alanin aminotransferaz, AST: Aspartat aminotransferaz

DISCUSSION

In our study, we found that advanced age, the presence of two or more comorbidities, extensive lung involvement on computerized tomography, and the presence of dyspnea during hospitalization were factors associated with increased mortality in elderly patients with COVID-19. Furthermore, in the follow-up of patients, we observed higher ferritin and D-dimer levels and lower fibrinogen levels in the group with excitus patients.

In our study, the mortality rate in patients aged 65 and older was found to be 71%. This rate was similar to the mortality rate reported in previous studies on elderly patients admitted to the intensive care unit due to COVID-19 infection. In a study conducted by Xu and colleagues on critically ill patients aged 65 and older, a mortality rate of 73.2% was reported.[9] In comparison, Alshukry and colleagues found a mortality rate of 68% in COVID-19 patients aged 60 and older in a study involving 86 patients admitted to the intensive care unit. 10 Several similar studies have consistently reported higher mortality rates in the elderly compared to the younger population.[7,11-13]

Dyspnea was one of the most common symptoms in patients who had excitus, and this finding is not surprising. Dyspnea is often considered a sign of a more severe illness. The presence of dyspnea can be seen as an indication that the already limited lung reserve in elderly patients has deteriorated further. In a study conducted by Wang and colleagues, it was found that dyspnea was more common in patients admitted to the intensive care unit in adults.[14] In a study by Leung and colleagues conducted in China, it was observed that the prevalence of dyspnea and hemoptysis was higher in excitus patients, interpreted as an indicator of severe pneumonia.[15]

In our study, we found a higher prevalence of high D-dimer and low fibrinogen levels in the group with excitus patients. Elevated D-dimer levels and low fibrinogen levels are considered well-known features of COVID-19 infection and indicators of hypercoagulability and microvascular/macrovascular thromboembolic events. Many microembolic events go undiagnosed, but they can dramatically alter the severity and course of the disease. Thromboembolic events have been shown in many clinical studies to be among the poor prognostic markers of the disease in COVID-19 patients admitted to the intensive care unit with severe illness. Thromboembolic events are associated with hypercoagulability, damage to the vascular endothelial wall, and increased proinflammatory cytokines. Additionally, the virus is reported to cause direct damage by binding to type 2 pneumocytes and ACE-2 receptors in pulmonary vascular endothelium.[16-20]

In our study, patients with two or more comorbidities had a higher mortality rate, which is not surprising and can even be seen as an expected result. Comorbidities in patients can make things more complex during COVID-19 infection. While COVID-19 can aggravate comorbidities, conversely, comorbidities

often influence the immune response to COVID-19. In a study conducted by Zhou and colleagues in 2020, mortality was significantly higher in patients with hypertension, diabetes mellitus, and heart disease compared to non-excitus patients.[21]

In a study related to cases of ARDS in patients admitted to the intensive care unit due to COVID-19, mortality rates as high as 77-84% have been reported. [22] Our study also found a similar mortality rate in elderly patients with COVID-19 infection and those admitted to the intensive care unit. Studies focusing on ARDS without COVID-19 have reported much lower mortality rates in similar age groups. However, we could not make such a direct comparison due to the absence of relevant data.

One of the observations in our study is the lower frequency of high fever compared to younger individuals. Approximately 50% of the patients included in our study did not exhibit high fever. This condition is already known and attributed to the lower baseline body temperature of elderly individuals.[23-25] Additionally, dysregulated inflammatory responses in the elderly, especially those with comorbidities, may contribute to this condition. Therefore, the absence of high fever may not be a reliable diagnostic criterion in elderly patients.

CONCLUSION

Our study found that advanced age, extensive lung involvement at admission, the presence of two or more comorbidities, and the presence of dyspnea at admission were associated with increased mortality in elderly patients. Given that mortality due to COVID-19 is higher in the elderly compared to other age groups, we emphasize the importance of initiating treatment as soon as possible and utilizing support systems in these patients. Furthermore, we believe routine vaccination programs are even more crucial for the elderly.

Conflict of Interest

In this article, all authors have stated that they have no conflict of interest.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Izmir Bozyaka Training and Research Hospital, İzmir, Turkey. (Decision number: 2022/38, date: 23.02.2022).

Authors' Contribution

Study Conception: HÖ, İD; Study Design: HÖ; Supervision: HÖ, İD; Materials: HÖ; Data Collection and/or Processing: İD; Statistical Analysis and/or Data Interpretation: HÖ, İD; Literature Review: HÖ; Manuscript Preparation: HÖ and Critical Review: İD.

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