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The mortality predictors in non-vaccinated COVID-19 patients

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ABSTRACT

Aim: The novel coronavirus (SARS-CoV-2) causes COVID-19 disease. From December 31, 2019, to the present (July 2022), 545 million new cases have been detected, while the number of deaths due to the disease has reached 6.3 million. This study aims to reveal mortality-related risk factors, including comorbid conditions, clinical course, imaging, and laboratory parameters in COVID-19 patients hospitalized in a tertiary hospital.

Material and Method: An observational, retrospective study was conducted among hospitalized COVID-19 patients at the tertiary health center in Turkey between November 2020 and April 2021. A total of 601 patients were treated in this period and vaccinated 85 patients were excluded. The remaining 516 patients' demographical data, clinical severity, laboratory parameters, thorax computed tomography (CT) involvement, and mortalities were recorded.

Results: In evaluating the factors affecting COVID-19 mortality, it was observed that male gender and advanced age were significantly associated with mortality, and the mortality rate was higher in patients with involvement in thorax CT and patients with a clinically severe course. In the evaluation of the patients in terms of comorbidities, DM, HT, and CAD were significantly higher in the patients who died. It was determined that patients who died during hospitalization needed respiratory support at a higher rate.

Conclusion: Identifying predicting factors is essential for the early recognition the vulnerable patients for hospitalization decisions and early aggressive treatment. In this study, male gender, advanced age, comorbidities (DM, HT, CAD), pulmonary involvement, and severe clinical presentation were identified as significantly related factors associated with mortality.

Keywords: COVID-19, mortality, risk factors

INTRODUCTION

The novel coronavirus (SARS-CoV-2) causes COVID-19 disease. From December 31, 2019, to the present (July 2022), 545 million new cases have been detected, while the number of deaths due to the disease has reached 6.3 million. While 15 million new patients have been seen in Turkey since the beginning of the pandemic, the number of deaths due to the disease has reached ninety-nine thousand (1). Many studies have been conducted on the risk factors that cause mortality in COVID-19 patients. The most important risk factors in these studies were hypertension (HT), diabetes mellitus (DM), obesity, cardiovascular diseases (CAD), chronic obstructive pulmonary disease (COPD), and malignancies. Male gender and advanced age are other risk factors found in studies (2-5). In a multicenter study in Turkey, risk factors affecting mortality were advanced age, male gender, concomitant malignancy, and interstitial lung disease. In the same study, when laboratory values were examined, high blood urea nitrogen (BUN), lactate dehydrogenase (LDH), c-reactive protein (CRP), d-dimer, procalcitonin, neutrophil count, and low albumin and lymphocyte levels were associated with mortality (6). Romero-Gameros et al. (7) found a significant relationship between mortality and higher d-dimer, ferritin, LDH, and CRP levels.

This study aims to reveal mortality-related risk factors, including comorbid conditions, clinical course, imaging, and laboratory parameters in COVID-19 patients hospitalized in a tertiary hospital.

MATERIAL AND METHOD

An observational, retrospective study was conducted among hospitalized COVID-19 patients at the tertiary health center in Turkey between November 2020 and April 2021 after Ondokuz Mayıs University Clinical Researchs Ethics Committee approval (Date: 25.06.2021, Decision No: 2021/336). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration

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of Helsinki. Inclusion criteria for patients: 18 and older with a positive real-time polymerase chain reaction (RT-PCR) test; complete laboratory results are needed for the study protocol. A total of 601 patients were treated in this period and vaccinated 85 patients were excluded. The remaining 516 patients' demographical data, clinical severity [non-severe, severe (sPO2<90%, respiratory rate >30/min, signs of severe distress), and critical (requires life-sustaining treatment, acute respiratory distress syndrome, sepsis, septic shock)] (8) laboratory parameters (leukocyte, neutrophil, monocyte, platelet counts, hemoglobin levels, C reactive protein (CRP), D-dimer, ferritin, aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and procalcitonin levels), thorax computed tomography (CT) involvement, and mortalities were recorded. The patients were divided into two groups survivors and non-survivor. We compared the acquired data between the groups.

RESULTS

In the evaluation of the factors affecting COVID-19 mortality, it was observed that male gender and advanced age were significantly associated with mortality, and the mortality rate was higher in patients with involvement in thorax CT and patients with a clinically severe course. In the evaluation of the patients in terms of comorbidities, DM, HT, and CAD were significantly higher in the patients who died. It was determined that patients who died during hospitalization needed respiratory support at a higher rate (**Table 1**).

Table 1. The evaluation of demographics, comorbid conditions, and ventilation support on mortality

	Survivor (n=315)	Non-survivor (n=201)	p
Gender (Male), n (%)	167 (53.0)	127 (63.1)	0.023
Age (years)	58.69 ± 14.96	69.03 ± 12.64	0.000
Thorax CT (involved), n (%)	292 (92.6)	198 (98.5)	0.003
Clinical condition (Severe), n (%)	123 (39.0)	175 (87.0)	<0.001
Comorbidities			
DM, n (%)	81 (25.7)	72 (35.8)	0.014
HT, n (%)	128 (40.6)	120 (59.7)	<0.001
CAD, n (%)	54 (17.1)	65 (32.3)	<0.001
COPD, n (%)	22 (6.9)	22 (10.9)	0.116
Asthma, n (%)	22 (6.9)	15 (7.4)	0.837
Malignancy, n (%)	32 (10.1)	28 (13.9)	0.192
Smoking, n (%)	217 (68.8)	134 (66.6)	0.598
Ventilation Support			
No MV, n (%)	238 (75.5)	58 (28.8)	<0.001
HFNO, n (%)	66 (20.9)	92 (45.7)	<0.001
NIMV, n (%)	7 (2.2)	15 (7.4)	0.004
Intubation, n (%)	4 (1.2)	36 (17.9)	<0.001

CT: computerized tomography, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, MV: mechanical ventilation, HFNO: high-frequency nasal oxygenation, NIMV: non-invasive mechanical ventilation

In the evaluation of the effect of laboratory findings on mortality, it was observed that leukocyte and neutrophil levels were higher in patients who died. In contrast, lymphocyte count and hemoglobin level were significantly lower. It was noted that inflammation markers such as ferritin, d-dimer, CRP and procalcitonin, and AST and LDH levels were significantly higher in the mortal group (**Table 2**).

Table 2. The evaluation of laboratory values on mortality

	Survivor (n=315)	Non-survivor (n=201)	p
WBC (/μL)	7,380.21±3,927.33	9,457.11±5,949.47	0.001
Neutrophil (/μL)	5,637.71±3,646.41	7,829.2±5,586.82	0.000
Lymphocyte (/μL)	1,166.86±682.74	984.93±1,017.11	0.000
Hemoglobin (g/dL)	12.69±2.14	12.06±2.23	0.005
Monocyte (/μL)	505.4±775.82	565.32±1,162.17	0.826
Platelet (10^3/μL)	211.54±97.42	200.42±90.57	0.100
AST (U/L)	41.88±39.45	53.64±64.43	0.015
ALT (U/L)	35.64±43.24	35.57±39.37	0.734
GGT (U/L)	56.45±83.34	65.68±115.64	0.140
LDH (U/L)	377.63±192.11	577.8±404.92	0.000
Ferritin (ng/mL)	585.91±691.36	1,277.19±1,888.57	0.000
CRP (mg/L)	81.68±77.56	137.85±106.61	0.000
D-dimer (ng/mL)	1,467.16±2,100.42	3,391.62±3,454.3	0.000
Procalcitonin (ng/mL)	0.49±4.23	3.85±12.16	0.000

WBC: white blood cells, CRP: c-reactive protein, AST: aspartate transaminase, ALT: alanine transaminase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase

In the study, logistic regression analysis was performed to determine the risk factors affecting the mortality of COVID-19 patients. Patient's age, gender, comorbid diseases (DM, HT, CAD, COPD, Asthma, Malignancy), presence of involvement in thorax CT, clinical severity of the disease, need for mechanical ventilation, WBC, neutrophil, lymphocyte, monocyte, hemoglobin, thrombocyte, CRP, d-dimer, ferritin, AST, ALT, GGT, LDH, and procalcitonin levels were primarily analyzed by univariate logistic regression analysis. Age, gender, comorbid diseases (DM, HT, CAD), presence of involvement in thorax CT, clinical severity of the disease, need for mechanical ventilation, WBC, neutrophil, lymphocyte, hemoglobin, CRP, d -dimer, ferritin, AST, LDH and procalcitonin levels were included in the multivariate logistic regression analysis. In the multivariate logistic regression analysis, the variable selection was performed using the forward addition method. In the final step, the variables found to be significant in the model were age, clinical severity, NIMV, intubation, hemoglobin, ferritin, and LDH levels (**Table 3**). In the final step, it was determined that each unit's increase in age, ferritin, and LDH levels in the model increased mortality by 1.074, 1.001, and 1.002 times, respectively, and each unit's increase in hemoglobin level decreased mortality by 11%. Clinical severity, NIMV, and intubation increased the mortality risk by 7.37, 4.09, and 6.47 times, respectively.

Table 3. Logistic regression analysis

	Wald	p	OR	95% CI for EXP(B)	
				Lower	Upper
Age	51.600	0.000	1.074	1.054	1.096
Clinical Severity	47.780	0.000	7.367	4.182	12.978
NIMV	6.219	0.013	4.091	1.352	12.380
Intubation	8.728	0.003	6.473	1.875	22.344
Hemoglobin	4.171	0.041	0.887	0.791	0.995
Ferritin	12.615	0.000	1.001	1.000	1.001
LDH	10.076	0.002	1.002	1.001	1.003

NIMV: non-invasive mechanical ventilation, LDH: lactate dehydrogenase
Model χ^2= 256.432; p<0.001, Hosmer and Lemeshow Test: p=0.699

DISCUSSION

Our study revealed that male gender and advanced age were significantly effective in mortality. The mortality rate was higher in patients with pulmonary involvement and severe clinical course. Also, DM, HT, and CAD were effective comorbidities in mortality. Additionally, while leukocyte and neutrophil counts were higher, lymphocyte count and hemoglobin levels were significantly lower in dead patients. High inflammation markers such as ferritin, d-dimer, CRP, procalcitonin, and AST, LDH levels were associated with mortality.

Male sex and advanced age were frequently reported predictors of mortality. Zhou et al. (9) reported that advanced age, severe disease, and high levels of D-dimer were associated with the risk of in-hospital death. The UK OpenSAFELY study (3) also reported that increasing age, male gender, and comorbidities such as diabetes, severe asthma, liver disease, and kidney disease were associated with high mortality risk. A nationwide retrospective large cohort in Turkey also reported that older age, male sex, and severe disease were independent predictors of mortality (6). Jin et al. (10) also found that male gender and increased age were related to severe disease and mortality. The present study also demonstrated that male sex and advanced age were significantly associated with mortality in hospitalized COVID-19 patients. Age-related conditions such as comorbidities and frailty can affect disease progression. Additionally, aging affects the proper functioning of the adaptive and innate immune system, which can lead to vulnerability to several infections.

Yuan et al. (11) reported that patients with pulmonary involvement have a higher mortality rate. A meta-analysis including 7,106 COVID-19 patients also showed that thorax CT involvement in these patients could predict mortality (12). In accordance with the literature, our results showed a higher mortality rate with pulmonary involvement.

A meta-analysis, including 61 cohort studies with 31,089 patients about the negative impact of comorbidities on COVID-19, reported chronic kidney disease, cardiovascular disease, cerebrovascular disease, COPD, HT, malignancy, DM, and immunodeficiency were associated with increased risk of mortality (5). A large data set with 331,928 positive COVID-19 patients from Mexico analyzed that DM, obesity, HT, COPD, CKD, and immunocompromised patients were at greater risk for mortality (13). Similarly, in the current study, DM, HT, and CAD were significantly associated with mortality.

In many investigations; decreased white blood cell, platelet count, and increased d-dimer, AST, urea, creatinine, and LDH were associated with mortality (14-17). Romero-Gomeros et al. (7) reported that high levels of d-dimer, LDH, and CRP levels were related to mortality as in our study in which we observed CRP, d-dimer, LDH, and procalcitonin levels were significantly higher in the mortal group.

The exclusion of vaccinated patients, an essential factor influencing mortality, may represent the strength of our study. In contrast, retrospective design and the relatively small sample size in a single center may represent the limitations of the current study.

CONCLUSION

Identifying predicting factors is essential for the early recognition of vulnerable patients for hospitalization decisions and early aggressive treatment. In this study, male gender, advanced age, comorbidities (DM, HT, CAD), pulmonary involvement, and severe clinical presentation were identified as significantly related factors associated with mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Decision No: 2021/336).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and they have approved the final version.

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