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Orijinal Araştırma / Original Article

Risk Factors Associated with Severe Disease in COVID-19

COVID-19'da Ciddi Hastalıkla İlişkili Risk Faktörleri

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Abstract

Aim: This study aimed to determine the characteristics and risk factors associated with severe illness from COVID-19.

Material and Method: A total of 186 adult patients (97 female) hospitalized with a diagnosis of COVID-19 (laboratory-confirmed cases, SARS-CoV-2-RNA detected with the molecular method) between March 2020 and May 2020 were included in the study. The possible risk factors evaluated were age, gender, comorbidities, smoking, symptoms, and laboratory parameters at the time of admission to the hospital.

Results: A total of 186 patients were included in the final study; 43 (23.1%) were evaluated as having severe COVID-19 and 143 (76.9%) as having non-severe COVID-19. Multivariate logistic regression analysis identified risk factors for severe COVID-19 to be age >65 years (odds ratio [OR]=5.289, 95% confidence interval (CI):1.680–16.651, p=0.004), elevated levels of lactate dehydrogenase (LDH; OR=8.521, 95% CI:2.445–29.702, p=0.001), ferritin (OR=7.436, 95% CI:2.171–25.468, p=0.001), D-dimer (OR=10.076, 95% CI: 2.758–36.813, p<0.001), creatine kinase myocardial band (CK–MB; OR=5.916, 95% CI:1.833–19.089, p=0.003), and troponin (OR=9.201, 95% CI:11.886–44.888, p=0.006).

Conclusion: The results of this study examining possible risk factors for severe COVID-19 demonstrated that age >65 years and elevated LDH, ferritin, D-dimer, CK-MB, and troponin levels are independent risk factors. Clinicians should consider these potential risk factors for progression to severe illness when treating COVID-19 patients.

Keywords: COVID-19, pandemic, risk factor, severe illness

Öz

Amaç: Çalışmamızın amacı COVID-19'da şiddetli hastalık ile ilişkili özellikler ve risk faktörlerinin belirlenmesidir.

Gereç ve Yöntem: Mart 2020-Mayıs 2020 tarihleri arasında COVID-19 (moleküler yöntemle SARS-CoV-2-RNA tespit edilen olgular) tanısı ile hastaneye yatırılan toplam 186 yetişkin hasta (97 kadın) çalışmaya dahil edildi. Olası risk faktörleri olarak yaş, cinsiyet, komorbidite, sigara kullanımı, semptomlar ve yatış sırasındaki bazı laboratuvar parametreleri irdelendi.

Bulgular: Hastaların 97'si (%52,2) kadın olup, 43 (%23,1) olgu şiddetli COVID-19 ve 143 (%76,9) olgu şiddetli olmayan COVID-19 olarak değerlendirildi. Çoklu değişkenli lojistik regresyon analizinde; 65 yaş üzeri (odds oranı (OR)=5.289, %95 güven aralığı (CI) 1.680-16.651, p=0.004), artmış LDH (OR=8.521, 95% CI:2.445-29.702, p:0.001), ferritin (OR=7.436, 95% CI:2.171-25.468, p:0.001), D-dimer (OR=10.076, 95% CI: 2.758-36.813, p<0.001), CK-MB (OR=5.916, 95% CI:1.833-19.089, p:0.003) ve troponin seviyesi (OR=9.201, 95% CI:11.886-44.888, p:0.006) şiddetli COVID-19 için risk faktörleri olarak tanımlandı.

Sonuç: Ciddi COVID-19 için olası risk faktörlerini incelediğimiz bu çalışmada 65 yaş üstü, yükselmiş LDH, ferritin, D-dimer, CK-MB ve troponin düzeylerinin bağımsız risk faktörleri olduğunu bulduk. Klinisyenler, COVID-19 hastalarının tedavisi sırasında ciddi hastalığa ilerleme için bu potansiyel risk faktörlerini dikkate almalıdır.

Anahtar Kelimeler: COVID-19, pandemi, risk faktörü, şiddetli hastalık

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first recorded in December 2019 in Wuhan, China; the virus then rapidly spread throughout the world.[1] The disease is highly contagious, and its primary clinical symptoms are fever, dry cough, fatigue, myalgia, and shortness of breath. While COVID-19 often presents with only upper respiratory tract symptoms, it may also manifest itself through a broad spectrum of symptoms, such as mild pneumonia, severe pneumonia, acute respiratory failure, and multiple organ damage.[2] In a large cohort study conducted in China, the clinical status of the cases was evaluated as 81% mild, 14% severe, and 5% critical, and the overall case fatality rate (CFR) was reported to be 2.3%.[3] In most patients, the disease is mild and even asymptomatic, usually resolving spontaneously without the need for hospitalization. Although severe cases are rare, they are difficult to treat, and the mortality rate is high.[4] Identifying risk factors for COVID-19 progression is crucial to help diagnose severe cases early and improve prognosis. This study aimed to determine the characteristics and risk factors associated with severe illness in COVID-19. The results of this research will help in the early detection of patients at risk of developing severe illness and improve the outcomes of these patients.

MATERIAL AND METHOD

Study Setting

The retrospective cross-sectional study was conducted in the Health Sciences University Konya Training and Research Hospital, a 1200-bed tertiary hospital located in an area with a high prevalence of COVID-19 and accepted as a reference center for COVID-19 care. Patients over 18 years of age hospitalized in the Infectious Diseases Clinic and General Intensive Care Unit (ICU) of our hospital between March and May 2020 were included in the study.

Study Design

The study sample comprised a total of 186 adult patients (97 female) hospitalized with a laboratory-confirmed (RNA SARS-CoV-2 detected by molecular method) diagnosis of COVID-19 (World Health Organization confirmed case definition). Patients were excluded from the study if they were aged <18 years, were pregnant, had any hematological disease, had a history of thromboembolic events, or were using anticoagulant or antiaggregant treatments for any reason. According to the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, patients with COVID-19 were categorized into groups: Mild illness defines those individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging; moderate illness defines those individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level; and severe illness define those individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.[5] In accordance with this classification, 43 patients were included in the severe COVID-19 group and 143 in the non-severe (mild or moderate) group. The possible risk factors evaluated were age, gender, comorbidities, smoking history, symptoms, and laboratory parameters during hospitalization. Among the comorbidities considered were diabetes mellitus (DM), malignancy, chronic lung disease, hypertension (HT), and cardiovascular (CV) disease. The symptoms analyzed were fever, sore throat, headache, dizziness, weakness, myalgia, cough, shortness of breath, chest pain, palpitations, anorexia, abdominal pain, diarrhea, decreased sense of smell and taste, and nasal congestion. The laboratory parameters examined during hospitalization included neutrophil count, lymphocyte count, platelet count, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, troponin, and creatine kinase myocardial band (CK–MB). Comparisons were made between the severe and non-severe COVID-19 patient groups with respect to age, gender, smoking history, comorbidities, symptoms, and laboratory parameters.

Ethical Approval

Approval for the study was granted by the Local Ethics Committee of the Health Sciences University Konya Training and Research Hospital (Decision no: 08.05.2020/38-07). In addition, permission was obtained from the Ministry of Health on 05/01/2020 (Application no: 2020-04-30T14_23_49). The study was conducted in accordance with the principles of the Declaration of Helsinki 2013.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS V22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) values and categorical variables as number (n) and percentage (%). In the comparisons between the severe and non-severe COVID-19 patients, the independent samples t-test was applied to evaluate continuous data and the chi-square test to evaluate categorical data. Univariate and multivariate logistic regression analyses were performed to identify risk factors for severe COVID-19. All variables with a p value <0.1 on univariate analysis were entered into forward, stepwise multivariate logistic regression analysis. A value of < 0.05 was considered statistically significant.

RESULTS

According to the inclusion criteria (**Figure 1**), 186 patients hospitalized for laboratory-confirmed COVID-19 were included, and 97 (52.2%) were female. The severe COVID-19 group included 43 (23.1%) patients, and the non-severe COVID-19 group included 143 (76.9%) patients. The patient outcomes were recorded as recovery in 169 (90.9%) and death in 17 (9.1%). Comorbidities of the patients were recorded as 59 (31.7%) with HT, 19 (10.2%) with CV disease, 42 (22.6%) with DM, 18 (9.7%) with chronic lung disease, and 3 (1.6%) with malignancy. The three most common symptoms were cough (63.4%), weakness (55.9%), and anorexia (50.5%). Other symptoms were fever (37.6%), sore throat (34.9%), dyspnea (29%), headache (25.3%), myalgia (16.1%), nasal stuffiness (15.6%), loss of smell (14.5%), palpitations (12.9%), loss of taste (12.4%), dizziness (10.8%), diarrhea (9.7%), chest pain (8.1%), and abdominal pain (3.8%). In the examination of the antiviral and antibacterial treatments administered to patients for COVID-19, all patients received hydroxychloroquine and azithromycin, 155 (83.3%) received oseltamivir, 64 (34.4%) received favipiravir, and 8 (4.3%) received lopinavir/ritonavir. The demographic data and clinical characteristics of all patients with COVID-19 are summarized in **Table 1**.

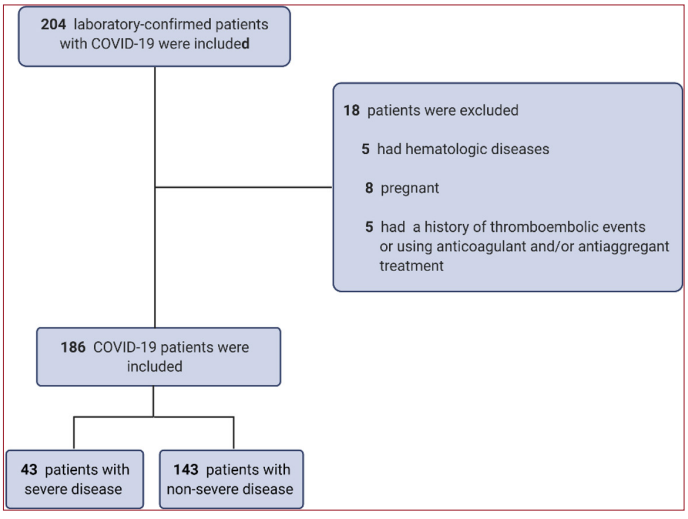

Figure 1. The study population.

Table 1. Demographics and clinical characteristics of patients with COVID-19 (n=186)

Characteristics	n (%)
Sex	
Male	89 (47.8)
Female	97 (52.2)
Disease severity	
Severe	43 (23.1)
Non-severe	143 (76.9)
Outcome	
Healing	169 (90.9)
Exitus	17 (9.1)
Comorbidity	
Malignancy	3 (1.6)
Chronic pulmonary disease	18 (9.7)
Cardiovascular disease	19 (10.2)
Hypertension	59 (31.7)
Diabetes mellitus	42 (22.6)
Symptoms at admission	
Fever	70 (37.6)
Sore throat	65 (34.9)
Headache	47 (25.3)
Dizziness	20 (10.8)
Weakness	104 (55.9)
Myalgia	30 (16.1)
Cough	118 (63.4)
Dyspnea	54 (29.0)
Chest pain	15 (8.1)
Palpitation	24 (12.9)
Anorexia	94 (50.5)
Abdominal pain	7 (3.8)
Diarrhea	18 (9.7)
Loss of smell	27 (14.5)
Loss of taste	23 (12.4)
Nasal stuffiness	29 (15.6)
Treatment	
Hydroxychloroquine	186 (100)
Favipiravir	64 (34.4)
Lopinavir/ritonavir	8 (4.3)
Oseltamivir	155 (83.3)
Azytromicin	186 (100)

No significant difference was determined between the severe and non-severe COVID-19 groups with respect to gender (p=0.882). When the two groups were compared in terms of age, the mean age of the severe patients was significantly higher than that of the non-severe patients (p=0.001). When the hemogram parameters were compared, the neutrophil count was considerably higher in the severe group than in the non-severe group (p=0.006). Lymphocyte and platelet counts were significantly lower in the severe versus non-severe group (p<0.001 and p=0.031, respectively). There was no significant difference between the two groups in terms of creatinine (p=0.184). The ALT, AST, and LDH levels were significantly higher in the severe group (p=0.040, p=0.005, and p=0.038, respectively). The ferritin level was determined to be significantly higher in the severe group (p=0.008). No significant difference was observed between the two groups in terms of ESR (p=0.255). CRP was found to be significantly higher in the severe group (p<0.001). There was no significant difference between the two groups in terms of CK–MB (p=0.197). Troponin and D-dimer were significantly higher in the severe group than in the non-severe group (p=0.029 and p=0.002, respectively). The demographic data and laboratory parameters of the severe and non-severe patients with COVID-19 are summarized in **Table 2.**

Table 2. Demographics and laboratory parameters between severe and non-severe patients with COVID-19

Characteristics (n, %/mean±SD)	Non-severe n=143	Severe n=43	P value
Demographics			
Age (years)	56.0±14.7	64.9±14.1	0.001
Sex (male)	68 (47.6)	21 (48.8)	0.882
Laboratory parameters			
Neutrophils (1800-6980/mm³)	3929±1924	5732±3926	0.006
Lymphocytes (1260-3350/mm³)	1723±663	1059±520	<0.001
Platelets (150000-450000/mm³)	214000±69953	186814±77689	0.031
Creatinine (0.84-1.25 mg/dl)	0.9±0.5	1.2±1.6	0.184
Alanine aminotransferase (0-50 U/L)	23±16	29±21	0.04
Aspartate aminotransferase (0-50 U/L)	29±15	40±24	0.005
Lactate dehydrogenase (0-248 U/L)	273±230	352±153	0.038
Ferritin (18.5-306.5 µg/L)	144±212	473±633	0.008
C reactive protein (0-5 mg/L)	23±34	70±72	<0.001
Erythrocyte sedimentation rate (mm/h)	32±23	40±29	0.255
D-dimer (0-2 mg/L)	0.5±0.4	2.0±2.7	0.002
Creatine kinase –MB (0-3.6 U/L)	16±8	13±9	0.197
Troponin (0-60 mg/L)	7±17	41±94	0.029

Risk Factors for Severe COVID-19

The results of univariate and multivariate logistic regression analyses associated with severe COVID-19 are shown in **Table 3**. In univariate regression analysis, risk factors for severe COVID-19 were found to be age >65 years and the presence of chronic pulmonary disease, DM, decreased lymphocyte count, and elevated levels of AST, LDH, ferritin, CRP, ESR, D-dimer, CK-MB, and troponin. All the variables with p-values <0.1 in univariate analysis were entered into the forward step-wise multivariate logistic regression analysis. As a result of the multivariate logistic regression analysis, the risk factors for severe COVID-19 were determined to be age >65 years (odds ratio (OR)=5.289, 95% confidence interval (CI) 1.680–16.651, p=0.004), elevated levels of LDH (OR=8.521, 95% CI 2.445–29.702, p=0.001), ferritin (OR=7.436, 95% CI 2.171–25.468, p=0.001), D-dimer (OR=10.076, 95% CI 2.758–36.813, p<0.001), CK–MB (OR=5.916, 95% CI 1.833–19.089, p=0.003), and troponin (OR=9.201, 95% CI 11.886–44.888, p=0.006; **Table 3**).

Table 3. Logistic regression analysis results of risk factors for severe COVID-19 (n=186)

	Univariate Analysis			Multivariate Analysis		
Variables	OR	95% CI	p	OR	95% CI	p
Gender (male vs. female)	1.053	0.532–2.082	0.882			
Age >65 y	3.441	1.697–6.978	0.001	5.289	1.680–16.651	0.004
Smoking	1.231	0.371–4.082	0.734			
Chronic pulmonary disease	3.040	1.117–8.276	0.030	3.220	0.509–20.388	0.214
Diabetes mellitus	2.546	1.206–5.373	0.014	2.136	0.642–7.108	0.216
Cardiovascular disease	1.814	0.642–3.698	0.122			
Hypertension	1.348	0.576-4.154	0.461			
Lymphocyte count decreased	3.754	1.845–7.640	<0.001	1.388	0.461–4.177	0.560
Creatinine increased	2.560	1.060–6.187	0.037			
Alanine aminotransferase increased	1.436	0.476–4.333	0.520			
Aspartate aminotransferase increased	3.308	1.316–8.317	0.011	0.599	0.118–3.045	0.537
Lactate dehydrogenase increased	4.389	2.048–9.408	<0.001	8.521	2.445–29.702	0.001
Ferritin increased	8.727	3.868–19.689	<0.001	7.436	2.171–25.468	0.001
C reactive protein increased	6.445	2.941–14.124	<0.001	1.664	0.454–6.102	0.442
Erythrocyte sedimentation rate increased	2.961	1.468–5.974	0.002	2.123	0.714–6.312	0.176
D-dimer	7.200	3.133–16.544	<0.001	10.076	2.758–36.813	<0.001
Creatine kinase myocardial band increased	3.192	1.537–6.629	0.002	5.916	1.833–19.089	0.003
Troponin increased	11.023	3.908–31.090	<0.001	9.201	1.886–44.888	0.006

DISCUSSION

The results of the current study demonstrated that the clinical features of age >65 years and elevated levels of LDH, ferritin, D-dimer, CK-MB, and troponin according to laboratory tests were associated with severe COVID-19. The clinical spectrum of COVID-19 may vary from asymptomatic to severe; respiratory failure requiring mechanical ventilation, sepsis, septic shock, metabolic acidosis, coagulation disorder, and multiorgan failure may be seen.[6] It is critical to analyze the clinical features of COVID-19 in different regions and identify risk factors to reduce severe and critical illness incidence at an early stage.

In light of data from many countries, the elderly population is known to be at a higher risk of severe consequences of COVID-19 and has the most significant risk of death.[7] In a series of multivariable-adjusted analyses based on COVID-19 patient cohorts, more severe illness cases have been associated with advanced age.[8-10] Physiological changes that develop with aging, such as the disruption of the barrier systems in the skin, the respiratory system, and the gastrointestinal system, and a decrease in mucociliary clearance create a predisposition to infections. The age-related weakening of the immune systems of elderly patients leads to more severe infections than that in younger individuals.[11] Elderly patients have a higher prevalence of frailty and comorbidity, which reduces their functional reserve. Furthermore, their capacity and flexibility against diseases and infections are decreased.[12] The results of this study allowed the conclusion that being over the age of 65 years increased the risk of serious COVID-19 5.2-fold.

Previous studies have shown that a high LDH level is a risk factor for mild patients to progress toward critical illness.[13] According to a meta-analysis of 3117 hospitalized COVID-19 patients, the mean LDH value of severe patients was 1.54-fold higher than in non-severe cases.[14] High basal LDH levels were significantly associated with the risk of acute respiratory distress syndrome (ARDS) and mortality.[15] According to the results of the current study, elevated LDH levels increase the risk of serious COVID-19 8.5-fold. High LDH levels in severe COVID-19 patients are thought to be associated with lung damage and tissue damage.[16,17]

Many studies have associated elevated serum ferritin levels with mortality and the development of severe consequences in COVID-19.[18] A meta-analysis of 25 studies and 5350 patients showed that high ferritin is associated with a poor outcome and ARDS development in COVID-19 patients.[19] Active ferritin production occurs during inflammatory diseases. Cytokine-producing macrophages, which make up most immune cells in the lung parenchyma, are thought to be responsible for serum ferritin secretion. In addition, ferritin synthesis can be induced by many inflammatory stimuli, including cytokines such as IL-6.[20] The results of the current study demonstrated that elevated ferritin levels increased the risk of serious COVID-19 7.4-fold.

A meta-analysis that included 5872 COVID-19 patients showed that higher D-dimer concentrations were associated with severe illness and death in these patients.[21] Another study of 343 hospitalized COVID-19 patients concluded that D-dimer levels >2.0 µg/mL at hospital admission were an independent predictor of in-hospital mortality.[22] Viral infections are usually accompanied by an aggressive pro-inflammatory response and an inadequate anti-inflammatory response. This can cause the dysfunction of endothelial cells, resulting in excess thrombin formation. Moreover, severe COVID-19 can increase blood viscosity and induce thrombosis via a hypoxia-inducible transcription factor-dependent signaling pathway. Coagulopathy and even diffuse intravascular coagulation may develop in some patients due to sepsis.[22] The results of the current study found that a high D-dimer level increased the risk of severe illness 10-fold.

COVID-19 is associated with many direct or indirect cardiovascular complications, such as myocarditis, myocardial damage, arrhythmia, and venous thromboembolism.[23] Troponin and CK-MB have been identified as biomarkers of cardiac injury. In a study examining 416 cases, the troponin level was significantly higher in COVID-19 patients who were followed up in the intensive care unit (ICU) than in those who were not.[24] The results of multivariate logistic regression analysis determined elevated troponin levels to be an independent risk factor for critical illness.[25] In a retrospective study conducted with 138 patients, troponin and CK-MB were significantly higher in all patients requiring ICU hospitalization, and it was suggested that CK-MB has predictive value.[26] A meta-analysis including 4189 patients found that troponin and CK-MB were significantly increased in those with severe illness compared to those with mild illness.[27] In the current study, it was concluded that elevated troponin increased the risk of serious COVID-19 9.2-fold, and elevated CK-MB increased the risk 5.9-fold. Different theories about the cardiac injury mechanism in COVID-19 have been proposed, and further studies are needed for clarification.

Limitations

This study had some limitations, primarily because the data of the two groups were not balanced, and the sample size of the severe group was relatively small. A second limitation was that no further examination was made to reveal the relationship between elevated laboratory parameters and related organ injury. Finally, only the values of the examined laboratory parameters on presentation were considered, and the changes in the following days were not evaluated.

CONCLUSION

In this study, which examined possible risk factors for severe COVID-19, the results showed that age >65 years and elevated levels of LDH, ferritin, D-dimer, CK-MB, and troponin were independent risk factors. Clinicians should consider these potential risk factors for progression to severe illness when treating COVID-19 patients. The determination of possible severe patients at early stages will influence the treatments to be applied and reduce the morbidity and mortality of these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Local Ethics Committee of the Health Sciences University Konya Training and Research Hospital (Decision no: 08.05.2020/38-07).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: 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 that they have approved the final version.

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