

Risk Factors for Mortality of Hospitalized Patients with Suspected Covid-19

Şüpheli Covid-19 ile Hastaneye Yatırılan Hastaların Mortalite Risk Faktörleri

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Summary

Objective: Covid-19 can lead to a wide range of conditions in individuals, ranging from flu-like illness to organ failure. The main aim of this study was to find of mortality associated risk factors for death among hospitalized patients of COVID-19.

Material and Method: This retrospective study consisted of patients who received a final diagnosis of "U07.3-Covid-19" in İzmir Kâtip Çelebi University Atatürk Training and Research Hospital between March 2020 and January 2021 and were followed up and treated. The sample size was calculated as 43 with the sample size formula with known universe, and 212 people were included in the study. The relationship of parameters with mortality was examined by Chi-Square Test.

Results: Of the 212 people included in the study, 60,4% were between the ages of 18-65 and 58,5% were male. A statistically significant relationship was found between Advanced age ($p=0.005$), antithrombotic use before admission ($p=0.039$), lymphopenia ($p=0.023$), creatinine elevation ($p=0.030$), C-reactive protein elevation ($p=0.003$), lactate dehydrogenase elevation ($p=0.005$), D-dimer elevation ($p=0.002$), troponin I elevation ($p=0.000$), typical reporting of patients 'thoracic tomography results in terms of Covid-19 ($p=0.032$), patients' consultation status after thoracic tomography ($p=0.025$) and mortality in Covid-19 patients.

Conclusion: In this study, a statistically significant relationship was found between advanced age, antithrombotic drug use before, some laboratory parameters and imaging results and mortality in patients diagnosed with Covid-19. It is necessary to investigate the risk factors affecting mortality in many studies in order to reduce the burden of the health sector during the SARS-CoV-2 pandemic and to ensure close follow-up of risky patients.

Key words: Covid-19, global health, mortality, risk factors

Özet

Amaç: Covid-19, grip benzeri hastalıktan organ yetmezliğine kadar bireylerde çok çeşitli durumlara yol açabilir. Bu çalışmanın temel amacı, COVID-19 nedeniyle hastaneye yatırılan hastalarda ölümle ilişkili risk faktörlerini saptamaktır.

Gereç veYöntem: Bu retrospektif çalışma, Mart 2020 ile Ocak 2021 arasında İzmir Kâtip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi'nde "U07.3-Covid-19" kesin tanısı alan ve takip ve tedavisi yapılan hastalarla gerçekleştirilmiştir. Örneklem büyüklüğü, evren sayısı bilinen örneklem formülü ile 43 olarak hesaplandı ve çalışmaya 212 kişi dahil edildi. Parametrelerin mortalite ile ilişkisi ki-kare testi ile incelendi.

Bulgular: Çalışmaya dahil edilen 212 kişiden %60,4'ü 18-65 yaş aralığında ve %58,5'i erkekti. İleri yaş ($p:0,005$), yatış öncesi antitrombotik kullanımı ($p:0,039$), lenfopeni ($p:0,023$), kreatinin yüksekliği ($p:0,030$), c-reaktif protein yüksekliği ($p:0,003$), laktat dehidrogenaz yüksekliği ($p:0,005$), D-Dimer yüksekliği ($p:0,002$), troponin I yüksekliği ($p:0,000$), hastaların toraks tomografi sonuçlarının Covid-19 açısından tipik olarak raporlanması ($p:0,032$), hastaların torasik tomografi sonrası konsültasyon durumu ($p:0,025$) ve Covid-19 hastalarında mortalite arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur.

Tartışma: Bu çalışmada ileri yaş, daha önce antitrombotik ilaç kullanımı, bazı laboratuvar parametreleri ve görüntüleme sonuçları ile Covid-19 tanısı almış hastalarda mortalite arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur. SARS-CoV-2 pandemisi sırasında sağlık sektörünün yükünü azaltmak ve riskli hastaların yakın takibini sağlamak için birçok çalışmada mortaliteyi etkileyen risk faktörlerinin araştırılması gerekmektedir.

Anahtar kelimeler: Covid-19, küresel sağlık, mortalite, risk faktörleri

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Introduction

The virus, initially labeled as Covid-19 by the China Center for Disease Control and Prevention(CDC) was declared a pandemic by the World Health Organization(WHO) on March 11, 2020 (1). Covid-19 can lead to a wide range of conditions in individuals, ranging from flu-like illness to organ failure (2). Antigen testing and reverse transcription polymerase chain reaction (RT-PCR) testing are used for the definitive diagnosis of the disease (3). As per the recommendation of the Republic of Turkey Ministry of Health, in cases without comorbid diseases or severe symptoms, and particularly in children, chest X-rays (CXRs) is initially preferred (4). The Turkish Ministry of Health has categorized chest CT (Computed Tomography) results into four categories. In the "typical" category, peripheral, bilateral, and multifocal ground-glass opacities are observed in CT imaging. In the "uncertain" category, the absence of typical findings and the presence of diffuse, perihilar, or unilateral ground-glass opacities are seen in CT imaging. In the "atypical" category, small nodules or cavitations are detected in CT imaging. In the "negative" category, no pneumonia-suggestive findings are observed in the CT imaging (5). Specific treatments for Covid-19 have not been developed yet. In various countries, there are primarily five types of vaccines being administered. Two of them are RNA vaccines, two are viral vector vaccines, and one is an inactivated vaccine (6). Different studies have shown that comorbidities can lead to a severe clinical course of Covid-19 and even death (7,8).

The aim of this study is to assess not only the sociodemographic characteristics but also laboratory and imaging parameters in relation to Covid-19 associated deaths.

Material and Method

This retrospective study was conducted following ethical approval and was carried out retrospectively by retrieving admission information of confirmed Covid-19 patients who were admitted and treated at İzmir Katip Çelebi University Atatürk Training and Research Hospital between February 26, 2020, and January 5, 2021, through the hospital's database system.

The ethical approval for this study was granted by the İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee, with approval number 851, during their meeting on July 23, 2020. The study was conducted in

accordance with the principles of the Helsinki Declaration, ensuring ethical standards in research.

The study population consists of a total of 1930 patients who received a definite diagnosis of Covid-19 and were hospitalized for follow-up and treatment at İzmir Katip Çelebi University Atatürk Training and Research Hospital. For the selection of the sample from this population, the disease's prevalence in our country was obtained from the Ministry of Health data, and the sample size was calculated using the known population formula. A total of 212 individuals were included in the research.

In the study, data on patients' sociodemographic information, as well as laboratory and imaging results at the time of their Covid-19 diagnosis, were collected from the hospital's database system. The status of patients' hospitalization, discharge, or mortality was also assessed based on their current condition.

Results

Of the patients included in the study, 41,5% were female (n:88), and 58,5% were male(n:124). The data collection form, consisting of a total of 20 questions, includes the first 7 questions for sociodemographic information (Table-1), and the subsequent 13 questions (Table-2) inquire about the patients' laboratory and imaging data at the time of diagnosis.

When the relationship between the sociodemographic data of the patients included in the study and mortality was examined, statistical significance was observed between age and mortality (p:0.005; d:0.268) as well as pre-existing antithrombotic use and mortality (p:0.039; d:0.171).

Significant statistical relationships were found between certain laboratory and imaging data of patients and mortality. These relationships include lymphocyte count and mortality (p:0.023; d:-0.112); creatinine level and mortality (p:0.030; d:0.207); CRP level and mortality (p:0.003; d:0.210); LDH level and mortality (p:0.005; d:0.167); D-dimer level and mortality (p:0.002; d:0.239); troponin I level and mortality (p:0.000; d:0.207); the typical reporting of chest CT results for COVID-19 and mortality (p:0.032; d:-0.016); and the relationship between the request for consultation after chest CT and mortality (p:0.025; d:-0.041) was found to be statistically significant.

Table 1. Sociodemographic data of patients included in the study

Sociodemographic Characteristics		N	%
Age	0-18 years (adolescent)	1	0.5
	18-65 years (young)	128	60.4
	65-74 years (young-old)	37	17.5
	74-84 years (elderyl)	31	14.6
	> 84 years (very elderly)	15	7.1
Gender	Male	124	58.5
	Female	88	41.5
Hypertension	No	132	62.3
	Yes	80	37.7
Diabetes Mellitus	No	150	70.8
	Yes	62	29.2
Cardiovascular Disease	No	170	80.2
	Yes	42	19.8
Prior Use of HCQ Medication	No	212	100
	Yes	0	0
Prior Use of Antithrombotic Medication	No	161	75.9
	Yes	51	24.1

HCQ: Hydroxychloroquine

Discussion

Among the patients included in the study, there was only one individual within the age range of 0-18 years. In contrast, the CDC has reported that the percentage of patients in the 0-18 age group among COVID-19 diagnosed cases is 1.7% (5). The reason for this difference may be the absence of a pediatric inpatient ward in the hospital where the study was conducted. In the research, a statistically significant relationship between age and mortality was found, and a meta-analysis revealed a significant increase in mortality risk with advancing age (9).

While 41.5% of the patients included in the study were female, and 58.5% were male, according to the data from the Turkish Statistical Institute (TÜİK), 50,2% of the Turkish population consists of males, and 49,8% consists of females (10). The reason for this situation may be, as indicated in some studies, that more males were hospitalized due to the possibility of a more severe course of COVID-19 in men (7,11).

37,7% of the patients included in the study had a diagnosis of hypertension. In a review conducted by Tadic et al.(12), the prevalence of hypertension in COVID-19 diagnosed patients varied between 4,5% and 30%. The reason for the higher rate observed in the presented study has been attributed to the fact that the study was conducted with hospitalized patients who were under continuous monitoring and treatment.

29,2% of the patients included in the study had a diagnosis of diabetes mellitus (DM). In a meta-analysis conducted by Wang et al. (13), the prevalence of DM in COVID-19 diagnosed patients ranged between 6-12%. The higher rate of DM observed in the study has been attributed to the possibility that COVID-19 may have a more severe course in individuals with a diagnosis of DM, which could have necessitated hospitalization during the course of the disease (9).

19.8% of the patients included in the study had a diagnosis of cardiovascular disease (CVD). In a review conducted by Tadic et al. (12), the prevalence of CVD in COVID-19 diagnosed patients ranged from 1% to 18%, and this range is consistent with our findings.

There were no patients who had used hydroxychloroquine (HCQ) for indications such as rheumatological diseases prior to the study. Several studies on this topic have demonstrated that prior use of HCQ is not protective against COVID-19 (14).

It is known that COVID-19 can cause hypercoagulability and the use of antithrombotic agents is recommended for its treatment. In the study, a statistically significant positive correlation was found between antithrombotic use and COVID-19-related mortality ($p=0.039$, $d=0.171$). However, in the literature, no statistically significant association was observed between the use of antithrombotic agents prior to admission and mortality in 192 patients, indicating that it did not have a protective effect (15).

Table 2. The specialized laboratory and imaging data of the patients included in the study

Laboratory and Imaging Data		N	%
Neutrophil Count	< 2000×10 ⁹ /L	17	8
	2000-10000×10 ⁹ /L	135	63.7
	> 10000×10 ⁹ /L	60	28.3
Lymphocyte Count	< 800×10 ⁹ /L	41	19.3
	800-4000×10 ⁹ /L	167	78.8
	> 4000×10 ⁹ /L	4	1.9
Platelet Count	< 150000×10 ⁹ /L	34	16
	150000-400000×10 ⁹ /L	172	81.1
	> 400000×10 ⁹ /L	6	2.8
Sedimentation Rate	No available data	126	59.4
	< 20 mm/h	35	16.5
	> 20 mm/h	51	24.1
Creatinine Level	< 0,6 mg/dl	9	4.2
	0,6-1,1 mg/dl	148	69.8
	> 1,1 mg/dl	55	25.9
ALT Level	0-55 u/dl	183	86.3
	> 55 u/dl	29	13.7
CRP Level	0-5 mg/dl	54	25.5
	> 5 mg/dl	158	74.5
LDH Level	No available data	59	27.8
	< 125 U/L	9	4.2
	125-220 U/L	58	27.4
	>220 U/L	86	40.6
D-Dimer Level	No available data	4	1.9
	< 243 ug/L	85	40.1
	> 243 ug/L	123	58.0
Troponin Level	No available data	68	32.1
	< 0,06 ng/ml	124	58.5
	> 0,06 ng/ml	20	9.4
Chest CT Result	No available data	22	10.4
	Typical	130	61.3
	Uncertain	11	5.2
	Atypical	11	5.2
	Negative	38	17.9
Presence of additional imaging methods requested after chest CT	No available data	21	9.9
	Yes	103	48.6
	No	88	41.5
Requested consultation following chest CT	No available data	22	10.4
	Yes	149	70.3
	No	41	19.3

ALT: Alanine Aminotransferase, CRP: C-Reactive Protein, CT: Computed Tomography, LDH: Lactate Dehydrogenase

In the research results, the number of patients with a neutrophil count below $2,000 \times 10^9/L$ constitutes 8% of the patients included in the study. There is limited research on the frequency of COVID-19 cases presenting with neutropenia. Many viral diseases, such as EBV, adenovirus, parvovirus, and influenza A, can cause neutropenia. In a case presentation prepared by López-Pereira et al.(16), a COVID-19 patient with severe neutropenia was discussed, and the hypothesis that COVID-19 may be associated with severe neutropenia was investigated, suggesting

that it is possible for COVID-19 to induce neutropenia.

In the study, the percentage of patients with a neutrophil count above $10,000 \times 10^9/L$ was observed to be 28,3%. In the literature, a statistically significant relationship has been shown between neutrophil count in COVID-19 diagnosed patients and the risk of developing ARDS and mortality (17). However, in the presented study, no significant difference was found between neutrophil levels and mortality. This may be due to the fact that the

neutrophil values considered in the study were measured at the time of diagnosis, and some parameters may have changed in the course of patient monitoring but were not taken into account.

In the research results, the percentage of patients with a lymphocyte count below $800 \times 10^9/L$ was found to be 19,3%. In a study conducted by Guan et al. (13) in China, the rate of lymphopenia was found to be 8.3%. The higher rate observed in this study may be attributed to the fact that the study was conducted with hospitalized patients. Another retrospective study conducted in Wuhan showed that the rate of lymphopenia in critical patients was 85% (2). In a study conducted by Wang et al. (18), demonstrated a significant relationship between lymphopenia and the need for intensive care in COVID-19 diagnosed patients. Similarly, in our study, lymphopenia was found to significantly increase the risk of mortality, consistent with the literature.

In the research, the percentage of patients with a platelet count below $150,000 \times 10^9/L$ was found to be 16%. In a different study, the rate of thrombocytopenia was reported as 36,2% (13). The reason for the lower rate observed in our study may be that the results were based on laboratory tests conducted at the onset of the disease. The exact cause of thrombocytopenia in COVID-19 patients is not fully understood, but it is believed that COVID-19 can trigger thrombocytopenia as a result of cytokine storms or directly suppress hematopoiesis through CD13/CD66a- mediated destructive effects. A meta-analysis of nine studies found a significant relationship between thrombocytopenia and the severity of COVID-19 (19).

In the research, the percentage of patients with an erythrocyte sedimentation rate (ESR) above 20 mm/h was found to be 24,1%. According to a meta-analysis conducted by Lapić et al. (20), which reviewed 23 studies examining the relationship between ESR and the severity of COVID-19, a statistically significant association was found between elevated ESR and disease severity. Another meta-analysis covering 14 studies demonstrated a significant association between ESR levels and mortality (21). However, in the present study, the lack of a statistically significant relationship between ESR levels and COVID-19 mortality may be attributed to the use of ESR values measured at the time of diagnosis.

In the research, the percentage of patients with creatinine levels greater than 1,1 mg/dl was found to be 25,9%. A meta-analysis that included 15 studies showed a statistically significant association

between elevated creatinine levels and poor outcomes in COVID-19 patients (22). Consistent with the literature, the study also revealed a significant positive relationship between elevated creatinine levels and mortality. Although the significant association of elevated creatinine levels in the study suggests that mortality may be significantly increased in patients with a history of chronic kidney disease, additional studies are needed due to the absence of inquiries regarding chronic kidney disease in the sociodemographic data.

In the research, the percentage of COVID-19 diagnosed patients with elevated ALT levels was found to be 13,7%. However, in a study conducted with 69 COVID-19 diagnosed patients, this percentage was reported as 33% (23). The difference may be attributed to the larger sample size in the latter study. In a study by Boregowda et al. (24), ALT and AST values were shown to have a statistically significant relationship with mortality. In contrast, in the presented study, no significant relationship was found between ALT levels and mortality, which may be due to the consideration of the hospital admission value for statistical significance.

In the study, the percentage of COVID-19 diagnosed patients with elevated CRP levels was found to be 74,5%. A meta-analysis conducted by Tian et al. (21), found a statistically significant relationship between CRP and mortality. In this study, when data were collected, the CRP parameter was examined, and a positive and statistically significant relationship was observed between CRP levels and mortality.

In the study, LDH levels were not assessed at the time of admission in 27,8% of the patients, while LDH elevation was detected in 40,6% of the patients. A positive and statistically significant relationship was observed between LDH levels and mortality. Consistent with the literature, a statistically significant relationship between LDH and mortality has been shown (21,25).

In the study, the percentage of patients with D-dimer levels above the normal range (243 ug/L and above) was found to be 58%. In the literature, a retrospective study reported a D-dimer elevation rate of 62,9%, which is higher than the rate observed in this study. A positive and statistically significant relationship was found between D-Dimer elevation and mortality in the study. Similarly, in the literature, there are studies demonstrating a statistically significant relationship between D-Dimer elevation and mortality (21,25).

In the study, the percentage of patients with elevated troponin I levels was found to be 9,4%, and a statistically significant positive relationship was observed between troponin I elevation and mortality. Similarly, in the literature, a study with 1449 patients and another study covering 4659 patients from 14 different studies have shown a statistically significant relationship between troponin I levels and COVID-19-related mortality (21,25).

In the study, chest CT was chosen as the imaging method in the data collection form. This decision was made to avoid potential misinterpretation in the results of other imaging methods, as the findings of COVID-19 on computerized tomography are categorized by the Ministry of Health. Chest CT was used as the imaging method in 89,6% of the patients in the study. In a previous research, abnormal findings were observed in 87,4% of those who underwent chest CT; however, no statistically significant relationship was found with mortality (25). In contrast, in the presented study, there was a statistically significant negative relationship between chest CT findings and mortality.

The need for consultation following chest CT was also queried in the data collection form, recognizing the requirement for a multidisciplinary approach in managing severe cases. The rate of consultation requests after chest CT was found to be 70,3% and a statistically significant relationship was identified with mortality. The direction of significance was negative.

Conclusions

In the study, some parameters have shown a statistically significant relationship consistent with other studies in the literature, while certain parameters have not shown a significant relationship with mortality, which differs from the literature. The aim of the study was to gain insights into the prognosis of COVID-19 diagnosed patients based on the tests conducted at the time of hospital admission. This way, it was envisaged that patients with a predicted poor prognosis could be admitted to the hospital, while those with a potentially good prognosis could be managed at home.

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