ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/cardiosci.2022-93884

The Relationship of In-Hospital Mortality with Cardiac Injury in COVID-19 Patients: A Retrospective Cohort Study

COVID-19 Hastalarında Hastane İçi Mortalitenin Kardiyak Hasar ile İlişkisi: Retrospektif Kohort Çalışması

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ABSTRACT Objective: Coronavirus disease-2019 (COVID-19) emerged in late 2019 and has caused a pandemic, resulting in significant morbidity and mortality. However, the clinical significance of cardiac injury in patients affected by COVID-19 is still unknown. Therefore, our objective was to explore the association between cardiac injury and mortality in hospitalized patients with COVID-19. **Material and Methods:** The study included four hundred forty-three patients with laboratory values for troponin and follow-up. The mean age was 57.3±16.0 years. The male to female ratio was 1.53. Fever (45.6%) and cough (42.7%) were the most frequent sign and symptom at admission. Hypertension was the most common comorbidity, identified in 140 patients (31.6%). **Results:** In 143 (32.2%) patients, we determined cardiac injury. The median length of hospital stay was ten days. The mortality rate was 14.4%. The median length of hospital stay was longer in patients with cardiac injury (14 days vs. 9 days, respectively) (p<0.001). The mortality rate was 3.7% in the patients without cardiac injury, whereas the mortality rate was significantly higher among the patients with cardiac injury (37.7%, p<0.001). The multivariable model showed that cardiac injury was the only independent risk factor for death. There was a higher risk of death in patients with cardiac injury than in those without cardiac injury [hazard ratio, 4.01 (95% confidence interval, 1.85-8.72, p<0.001)]. **Conclusion:** In conclusion, cardiac injury is a common condition among hospitalized patients with COVID-19 and is associated with an elevated risk of in-hospital mortality. In addition, it is significantly more common in patients with known heart disease, complicating the treatment process.

Keywords: COVID-19; mortality; troponin I

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], 2019 yılının sonlarında ortaya çıktı ve önemli bir morbidite ve mortalite ile sonuçlanan bir pandemiye neden oldu. Bununla birlikte COVID-19'dan etkilenen hastalarda kardiyak hasarın klinik önemi hâlâ bilinmemektedir. Bu nedenle amacımız, hastanede yatan COVID-19 hastalarında kardiyak hasar ile mortalite arasındaki ilişkiyi araştırmaktı. **Gereç ve Yöntemler:** Çalışmaya troponin, diğer laboratuvar değerleri olan 443 hasta dâhil edildi. Ortalama yaş 57,3±16,0 yıl idi. Erkek-kadın oranı 1,53 saptandı. Ateş (%45,6) ve öksürük (%42,7) başvuru anında en sık görülen belirti ve semptomdu. Yüz kırk (%31,6) hastada tanımlanan en sık komorbidite hipertansiyon olarak izlendi. **Bulgular:** Yüz kırk üç (%32,2) hastada troponin artışı tespit ettik. Ortalama hastanede kalış süresi 10 gündü. Mortalite oranı %14,4 olarak tespit edildi. Ortanca hastanede kalış süresi kardiyak hasar olan hastalarda daha uzundu (sırasıyla 14 gün ve 9 gün) (p<0,001). Kardiyak hasar olmayan hastalarda ölüm oranı %3,7 iken, kardiyak hasar olan grupta ölüm oranı anlamlı olarak daha yüksekti (%37,7, p<0,001). Çok değişkenli model, kardiyak hasarın ölüm için tek bağımsız risk faktörü olduğunu gösterdi. Kardiyak hasarı olan hastalarda, hasar olmayanlara göre daha yüksek ölüm riski vardı (tehlike oranı, 4,01 [%95 güven aralığı, 1,85-8,72, p<0,001]). **Sonuç:** Sonuç olarak kardiyak hasar hastanede yatan COVID-19 hastalarında sık görülen bir durumdur ve yüksek hastane içi mortalite riski ile ilişkilidir. Ayrıca bilinen kalp hastalığı olan hastalarda belirgin şekilde daha sık görülür ve tedavi sürecini zorlaştırır.

Anahtar Kelimeler: COVID-19; mortalite; troponin I

The coronavirus disease-2019 (COVID-19) emerged in 2019; has become a pandemic since then. As a result, approximately 527 million confirmed cases and 6.2 million deaths were reported globally on May 23, 2022.[1] The clinical signs of COVID-19 include subclinical infection, pneumonia, mild upper

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Peer review under responsibility of Turkiye Klinikleri Cardiovascular Sciences.

Received: 15 Oct 2022 ***Received in revised form:*** 15 Dec 2022 ***Accepted:*** 03 Jan 2023 ***Available online:*** 06 Jan 2023

respiratory tract disease, acute respiratory distress syndrome (ARDS) that progresses to severe pneumonia and requires intensive care hospitalization, mechanical ventilation, and extracorporeal membrane oxygenation.[2] In addition, cardiovascular involvement and cardiac injury (CI) were associated with a more severe clinical course with a 10-30% rate in 2 studies conducted in China.[3,4]

OBJECTIVES

However, the intercourse between CI, the risk of death associated with COVID-19 still uncertain. For this reason, our study was planned to estimate the intercourse between CI and in-hospital mortality in COVID-19 patients.

MATERIAL AND METHODS

The patients who had presented to Bursa City Hospital between November 23, 2020, and January 23, 2021, and confirmed with a positive polymerase chain reaction test of the nasopharyngeal swab and patients upper 18 years of age were taken into this study. Pregnant women, confirmed diagnosis of acute coronary syndrome, were not included from this study. Also patients without mesurement high-sensitivity troponin I (hs-TNI) values also excluded. The approval was obtained from the Ethics Committee of Bursa City Hospital for this study (date: November 18, 2020; no: 2020-10/2). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients' demographic characteristics, clinical data were collected from medical records. The high-sensitivity cardiac troponin (troponin elecsysy troponin T hs , roche; 99. Persentil 14 ng/L) measured at the baseline visit was recorded. The radiological evaluations were made with chest radiography and computed tomography. The participants were divided into 2 groups according to the with or without of CI.

CI is the disruption of normal cardiac myocyte membrane integrity resulting in the release of intracellular cytosolic and structural proteins such as troponin, creatine kinase, myoglobin, heart-type fatty acid binding protein, and lactate dehydrogenase into the extracellular space (e.g. blood). Independent of electrocardiography and echocardiography, cardiac biomarkers (hs-TNI) exceeding the 99th percentile upper reference limit were described as CI. Clinical results were followed throughout the patients' hospital stay.

Descriptive statistics were provided as mean± standard deviation and median values for continuous variables depending on their distributions. The numerical variables' normal distributions were analyzed using the Shapiro-Wilk, Anderson-Darling, Kolmogorov-Smirnov tests. The Mann-Whitney U test was applied for variables without normal distribution. Kaplan-Meier survival analysis with the log-rank test was performed to determine the temporal relationship between CI and overall survival. Multivariate Cox regression models determined the independent demographic and clinical risk factors for death during hospitalization.

RESULTS

A total of 1,018 COVID-19 laboratory-confirmed patient files were scanned. Among these, 443 patients with laboratory values for troponin and follow-up were included. The flowchart is shown in Figure 1. The male to female ratio was 1.53. Fever (45.6%) and cough (42.7%) were the most frequent sign and symptom at admission. Hypertension was the most common comorbidity, identified in 140 (31.6%) patients. The participants' demographic, clinical characteristics are summarized in Table 1.

In 143 (32.2%) patients, we determined CI. The group with CI was significantly older than group without CI (mean, 69.6 years vs. 51.4 years, respectively) ($p<0.001$). Gender distributions of the patients with and without CI were similar ($p=0.999$). Shortness of breath was more likely seen in the patients with CI ($p=0.005$), whereas cough, sore throat, and headache were common in patients without CI ($p=0.001$, $p=0.017$, $p=0.021$). CI was observed more frequently in patients with comorbidities (Table 1).

We determined significant differences between the patients with and without CI regarding the laboratory investigations (Table 2). Bilateral involvement

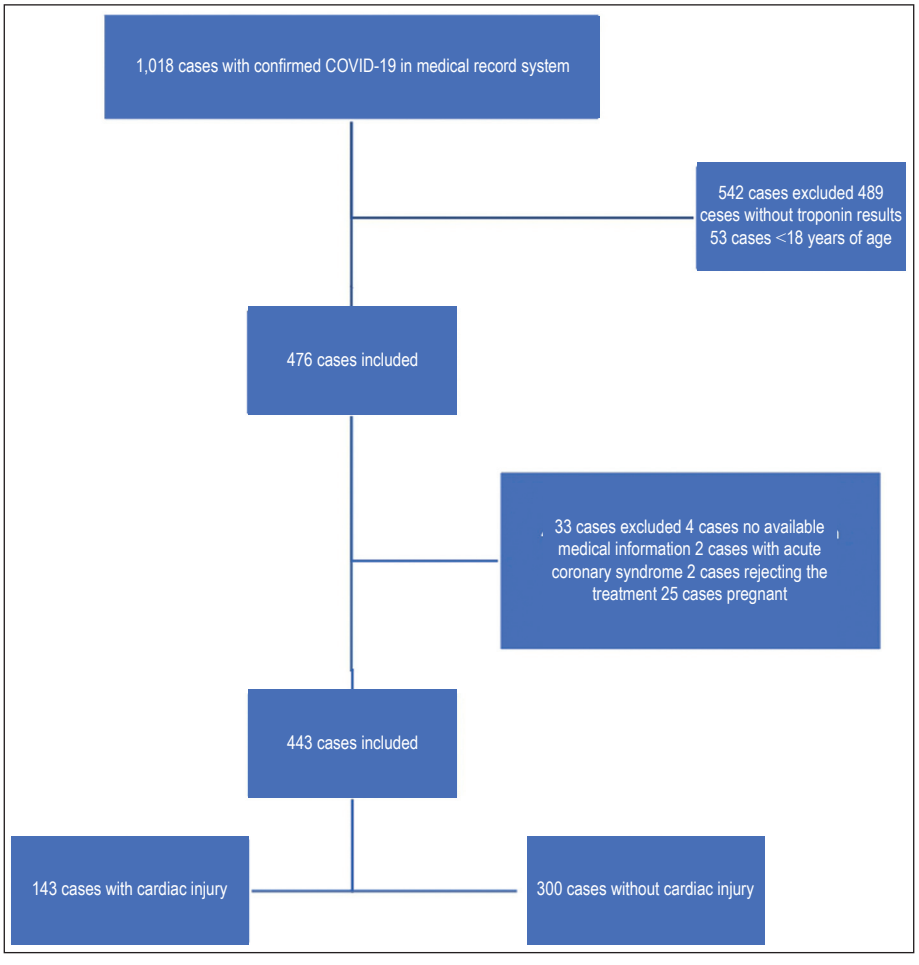

FIGURE 1: Flowchart of patient recruitment.

was present in 85.9% of the patients with CI and 76.4% of those without CI in computed tomography. The difference was insignificant (p=0.066) (Table 2).

Table 3 presents the details of the treatment modalities. Invasive ventilation (42.3% vs. 3.3%, p<0.001); renal replacement therapy (7.7%; zero, p<0.001) were more applied in the patients with CI when compared to those with no CI. Besides, the patients with CI were more likely to be treated with glucocorticoids and parenteral antibiotics (p<=0.004; p<0.001).

Electrolyte imbalance, ARDS were the most common two complications seen [67 (15.1%) and 58 (13.1%), respectively]. The median time of hospital stay was 10 days. The mortality rate was 14.4% (Table 4). In addition, we determined significantly more complications in group with CI compared to those group with no CI (p<0.05 for each type of complication) (Table 4).

The median hospital stay was significantly longer in the patients with high hs-TNI level (14 days vs. 9 days, p<0.001). In addition, the mortality rate was 3.7% in the patients with no CI, whereas mortality rate was significantly higher among the gruop with CI (37.7%, p<0.001).

Curve analysis showed that a cut-off value of ≤14.2 troponin level was predictive for in-hospital mortality in COVID-19 patients with 75.99% sensitivity and 84.37% specificity (area under the curve: 0.866, 95% CI: 0.831-0.896, p<0.001) (Table 5).

The Kaplan-Meier survival curves show a decreased overall survival in group with CI than in

TABLE 1: Demographic and clinical characteristics of the patients.

	Overall (n=443)	Cardiac injury		p value
		Present (n=143)	Absent (n=300)	
Age (year)†	57.3±16.0	69.6±12.4	51.4±14.1	**<0.001**
Gender‡				
Male	268 (60.5)	87 (60.8)	181 (60.3)	0.999
Female	175 (39.5)	56 (39.2)	119 (39.7)	
Signs and symptoms at admission‡				
Fever	202 (45.6)	66 (46.2)	136 (45.3)	0.952
Shortness of breath	141 (31.8)	59 (41.3)	82 (27.3)	**0.005**
Cough	189 (42.7)	44 (30.8)	145 (48.3)	**0.001**
Fatigue	108 (24.4)	34 (23.8)	74 (24.7)	0.838
Muscle ache	39 (8.8)	8 (5.6)	31 (10.3)	0.143
Diarrhea	23 (5.2)	7 (4.9)	16 (5.3)	0.999
Sore throat	33 (7.4)	4 (2.8)	29 (9.7)	**0.017**
Chest pain	21 (4.7)	3 (2.1)	18 (6.0)	0.117
Headache	28 (6.3)	3 (2.1)	25 (8.3)	**0.021**
Comorbidities‡				
Hypertension	140 (31.6)	67 (46.9)	73 (24.3)	**<0.001**
Diabetes mellitus	113 (25.5)	57 (39.9)	56 (18.7)	**<0.001**
Coronary artery disease	54 (12.2)	36 (25.2)	18 (6.0)	**<0.001**
Congestive heart failure	19 (4.3)	15 (10.5)	4 (1.3)	**<0.001**
Chronic renal failure	19 (4.3)	15 (10.5)	4 (1.3)	**<0.001**
Chronic obstructive pulmonary disease	20 (4.5)	14 (9.8)	6 (2.0)	**0.001**
Cerebrovascular accident	10 (2.3)	8 (5.6)	2 (0.7)	**0.002**
Cancer	13 (2.9)	7 (4.9)	6 (2.0)	0.129

†Mean±standard deviation; ‡n (%).

group without CI (p<0.001) (Figure 2). And the univariable Cox regression model revealed that the CI and age were the independent risk factors for death. However, the multivariable model showed that the presence of a CI was the only independent risk factor for death, and there was a significantly higher risk of death in patients with CI than in those without CI [hazard ratio, 4.01 (95% CI, 1.85-8.72, p<0.001)] (Table 6, Figure 3).

DISCUSSION

Our study showed a relationship between in-hospital mortality and CI in COVID-19 patients. According to the present study, in-hospital mortality was higher in patients with CI than patients with no CI.

It was shown that COVID-19 infection causes acute and chronic CI.[5] Although it is unknown how COVID-19 infection causes cardiac damage, treatment becomes difficult and complex in such a case.[6] Systemic inflammation, myocardial fibrosis, myocardial inflammation, exaggerated cytokine reply of Type-1 and Type-2 helper T cells, direct viral-mediated damage, hypercoagulopathy, overregulation of angiotensin-converting enzyme 2 receptors, coronary plaque destabilization, and hypoxia are among the mechanisms that cause cardiac damage in COVID-19 infection.[7-9] Although myocarditis caused by COVID-19 has not been fully defined, direct myocardial involvement cannot be ignored.

A recent study conducted with 138 patients hospitalized with COVID-19 reported that 7.2% of the patients developed an CI and the patients treated in intensive care unit (ICUs) had a 22.2% higher probability of developing cardiac injuries.[10] In the study carried out by Campo et al., cardiac damage was present in 46% of patients in the ICU.[11] Cardiac damage in COVID-19 infection was reported at a rate varying between 20% and 34% in retrospective studies, and it

TABLE 2: Laboratory and radiological findings of the patients.

	Cardiac injury		
	Present (n=143)	**Absent (n=300)**	**p value**
Laboratory parameters			
Hemoglobin (g/dL)†	12.6±2.0	13.5±1.8	**<0.001**
Leukocyte count (x109/L)ᵞ	7.1 (1.4-44.0)	6.0 (2.2-43.8)	**<0.001**
Platelet count (x103/μL)ᵞ	206.0 (63.0-677.0)	223.0 (12.6-654.0)	**0.027**
Aspartate aminotransferase (U/L)ᵞ	30.0 (4.7-131.0)	24.2 (1.9-230.0)	**0.002**
Alanine aminotransferase (U/L)ᵞ	22.0 (5.0-221.0)	25.0 (5.0-300.0]	**0.014**
Blood urea nitrogen (mg/dL)ᵞ	44.5 (0.5-331.0)	26.5 (0.0-398.0)	**<0.001**
Creatinine (mg/dL)ᵞ	1.1 (0.1-27.6)	0.8 (0.4-2.9)	**<0.001**
Albumin (g/dL)ᵞ	31.1 (2.1-42.8)	37.2 (24.4-399.0)	**<0.001**
C-reactive protein (mg/dL)ᵞ	128.8 (0.0-434.1)	34.3 (0.3-400.0)	**<0.001**
Troponin (μg/L)ᵞ	41.4 (0.6-2764.0)	5.3 (0.0-43.0)	**<0.001**
Creatinine kinase-myocardial band (ng/mL)ᵞ	2.2 (0.0-17.4)	1.0 (0.0-492.0)	**<0.001**
Myoglobin (μg/L)ᵞ	145.0 (27.5-1803.0)	51.0 (21.0-421000.0)	**0.036**
Ferritin (μg/L)ᵞ	736.0 (8.2-4259.0)	354.0 (4.6-2000.0)	**<0.001**
Pro-B type natriuretic peptide (pg/mL)ᵞ	1325.0 (1.0-35000.0)	98.6 (9.0-1331.0)	**<0.001**
Procalcitonin (ng/mL)ᵞ	0.2 (0.0-85.3)	0.1 (0.0-70.3)	**<0.001**
D-dimer (ng/mL)ᵞ	1.4 (0.0-307.0)	0.4 (0.2-16.9)	**<0.001**
Activated partial thromboplastin time (sec)ᵞ	32.2 (0.3-449.0)	29.6 (10.6-368.0)	**<0.001**
INRᵞ	1.0 (0.3-4.1)	1.0 (0.1-3.1)	**<0.001**
Computed tomography findings‡			
No involvement	9 (6.3)	34 (11.5)	0.066
Unilateral involvement	11 (7.7)	36 (12.2)	
Bilateral involvement	122 (85.9)	226 (76.4)	

†Mean±standard deviation; ‡n (%); ᵞMedian (minimum-maximum); INR: International normalized ratio.

TABLE 3: Distribution of the treatment modalities, complications, and clinical outcomes of the patients.

	Cardiac injury		
Treatment modalities‡	**Present (n=143)**	**Absent (n=300)**	**p value**
Oxygen supplementation	75 (52.8)	113 (37.8)	**0.004**
Noninvasive ventilation	23 (16.1)	19 (6.3)	**0.002**
Invasive ventilation	60 (42.3)	10 (3.3)	**<0.001**
Renal replacement therapy	11 (7.7)	0 (0.0)	**<0.001**
Antiviral medications	139 (97.2)	287 (95.7)	0.601
Glucocorticoids	62 (43.4)	87 (29.0)	0.004
Intravenous immunoglobulin	12 (8.5)	13 (4.3)	0.126
Antibiotics	137 (95.8)	244 (81.3)	**<0.001**
Complications‡			
Electrolyte imbalances	50 (35.0)	17 (5.7)	**<0.001**
ARDS	49 (34.3)	9 (3.0)	**<0.001**
Acute renal failure	23 (16.1)	3 (1.0)	**<0.001**
Anemia	13 (9.1)	2 (0.7)	**<0.001**
Hypoproteinemia	9 (6.3)	2 (0.7)	**0.001**
Coagulation disorders	8 (5.6)	0 (0.0)	**<0.001**
Length of hospital stay (days)ᵞ	14.0 (1.0-129.0)	9.0 (2.0-54.0)	**<0.001**
Mortality‡	53 (37.1)	11 (3.7)	**<0.001**

‡n (%); ᵞMedian (minimum-maximum); ARDS: Acute respiratory distress syndrome.

TABLE 4: Complications and clinical outcomes of the patients.

		Cardiac injury		
	Overall	Present (n=143)	Absent (n=300)	p value
Complications‡				
Electrolyte imbalances	67 (15.1)	50 (35.0)	17 (5.7)	**<0.001**
ARDS	58 (13.1)	49 (34.3)	9 (3.0)	**<0.001**
Acute renal failure	26 (5.9)	23 (16.1)	3 (1.0)	**<0.001**
Anemia	15 (3.4)	13 (9.1)	2 (0.7)	**<0.001**
Hypoproteinemia	11 (2.5)	9 (6.3)	2 (0.7)	**0.001**
Coagulation disorders	8 (1.8)	8 (5.6)	0 (0.0)	**<0.001**
Length of hospital stay (days)ᵀ	10.0 (1.0-129.0)	14.0 (1.0-129.0)	9.0 (2.0-54.0)	**<0.001**
Mortality‡	64 (14.4)	53 (37.1)	11 (3.7)	**<0.001**

‡n (%); ᵀMedian (minimum-maximum); ARDS: Acute respiratory distress syndrome.

TABLE 5: ROC analysis.

	AUC	Sensitivity	Specificity	Cut-off	95% CI	p value
Troponin (μg/L)	0.866	75.99	84.37	≤14.2	0.831-0.896	**<0.001**

ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval.

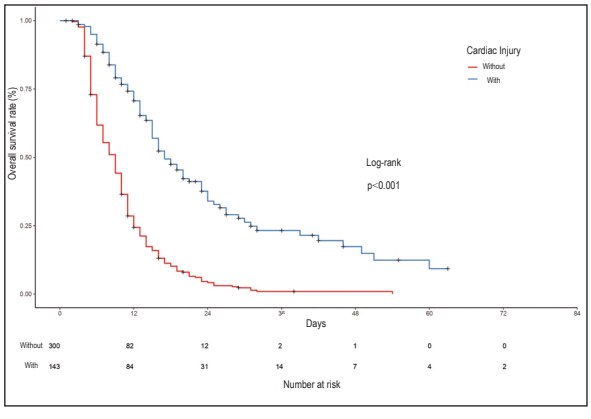

FIGURE 2: Kaplan-Meier survival curves for overall survival, starting from the admission of the patients with and without cardiac injury.

was also associated with mortality.[4,12-14] In the present study, the CI was determined in 143 of 443 patients, the rate was 32%, and similarly, it was shown that increased in-hospital mortality risk in COVID-19 patients was associated with CI. Troponin positivity was slightly higher in our patients compared to the literature. This result was considered to be related to the fact that our study included only hospitalized patients, and the relatively well patients in clinical terms were excluded because their troponin levels were not investigated. The COVID-19 patients with cardiac injuries were older in previous studies, similar to our study.[15,16]

TABLE 6: Univariable and multivariable Cox regression analysis on the independent risk factors associated with the development of death in the overall study group.

Risk factor	Univariable [HR (95% CI)]	Multivariable [HR (95% CI)]
Cardiac injury, present	4.34 (2.22-8.50, **p<0.001**)	4.01 (1.85-8.72, **p<0.001**)
Hypertension, present	1.00 (0.60-1.65, p=0.986)	0.65 (0.38-1.13, p=0.129)
Diabetes mellitus, present	1.24 (0.74-2.07, p=0.418)	1.05 (0.61-1.82, p=0.857)
Coronary artery disease, present	1.12 (0.60-2.11, p=0.723)	0.71 (0.36-1.40, p=0.327)
Congestive heart failure, present	2.35 (1.12-4.97, p=0.025)	1.71 (0.79-3.69, p=0.171)
Chronic renal failure, present	1.67 (0.74-3.77, p=0.219)	1.32 (0.57-3.08, p=0.521)
Chronic obstructive pulmonary disease, present	1.12 (0.50-2.51, p=0.789)	1.18 (0.47-2.93, p=0.726)
Cerebrovascular accident, present	0.75 (0.22-2.51, p=0.639)	0.43 (0.11-1.70, p=0.230)
Age, present	1.03 (1.01-1.05, **p=0.009**)	1.01 (0.99-1.03, p=0.320)

HR: Hazard ratio; CI: Confidence interval.

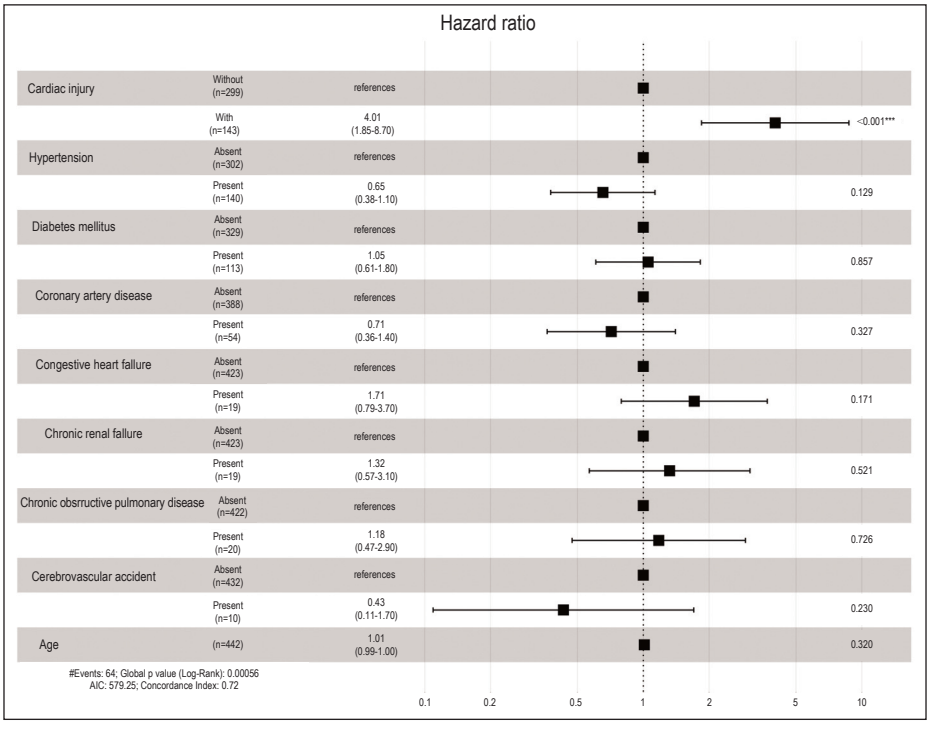

FIGURE 3: Graphic representation of Cox regression analysis for death in the overall study group.
***Denotes the p-value being less than 5 percent. AIC: Akaike information criterion.

There are studies in which troponin values were correlated with C-reactive protein (CRP) and pro-B type natriuretic peptide (pro-BNP) values in the medical literature.[4] Similarly, in the present study, laboratory values such as CRP, D-dimer, N-terminal- proBNP were higher in the patients with elevated Troponin levels. The most usually echocardiographic disorder in COVID-19 was right ventricle (RV) dilatation in a recent echocardiographic study. The authors interpreted this as monitoring more significant deterioration in RV parameters associated with pulmonary resistance. In COVID-19 patients, the mutual mechanism for troponin elevation was reported as acute RV dysfunction caused by parenchymal or vascular lung disease.[17] In the present study, severe complications such as electrolyte imbalance, acute renal failure, anemia, ARDS, and coagulation disorders were observed often in patients with elevated troponin levels than in patients without CI, and their hospital stay was longer. Because of the higher incidence of ARDS, managing the patients with intubation was more common in the presence of a CI, supporting that CI is associated with the clinic of COVID-19.

In the study carried out by Shi et al., it was found that approximately 30-60% of patients with CI had a history of heart disease.[3] The present study determined that patients with CI had a higher rate of heart failure and coronary artery disease. In this regard, COVID-19 patients with preexisting heart disease are more susceptible to CI. In addition, other comorbidities and advanced age seem to accompany more in such patients. For this reason, COVID-19 patients who have preexisting cardiac comorbidity can be predicted to be more susceptible to complications such as severe hypoxemia, inflammatory activation, and hypotension and may progress to cardiac damage, which will worsen the prognosis.

Because this study had a retrospective design, only the patients with troponin values were included. Creatine kinase myocardial band blood levels could not be found in a sufficient number of patients, so it

could not be evaluated in the study. Moreover, the COVID-19 virus mutation types were unknown. Also, the study could have been conducted with more patients in multiple centers to endorse the consequences of CI in this patients. Another limitation was that the data on the cardiac damage mechanism of COVID-19 was not collected and and myocarditis associated with COVID-19 could not be excluded.

CONCLUSION

Cardiac injury is a common among hospitalized patients with COVID-19 and is associated with elevated risks of in-hospital mortality. In addition, it is significantly more common in patients with known heart disease, complicating the treatment process. For this reason, the presence of a CI should be evaluated in the treatment of COVID-19, and an evaluation of the troponin level should be performed for risk assessment in patients followed up with COVID-19.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sevil Gülaştı;* ***Design:*** *Ferdi Gülaştı;* ***Control/Supervision:*** *Sevil Gülaştı;* ***Data Collection and/or Processing:*** *Sevil Gülaştı, Ferdi Gülaştı;* ***Analysis and/or Interpretation:*** *Sevil Gülaştı;* ***Literature Review:*** *Ferdi Gülaştı;* ***Writing the Article:*** *Sevil Gülaştı, Ferdi Gülaştı;* ***Critical Review:*** *Ferdi Gülaştı.*

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