

Prognostic significance of cardiac injury in COVID-19 patients with and without coronary artery disease

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Objective COVID-19 is a disease with high mortality, and risk factors for worse clinical outcome have not been well-defined yet. The aim of this study is to delineate the prognostic importance of presence of concomitant cardiac injury on admission in patients with COVID-19.

Methods For this multi-center retrospective study, data of consecutive patients who were treated for COVID-19 between 20 March and 20 April 2020 were collected. Clinical characteristics, laboratory findings and outcomes data were obtained from electronic medical records. In-hospital clinical outcome was compared between patients with and without cardiac injury.

Results A total of 607 hospitalized patients with COVID-19 were included in the study; the median age was 62.5 ± 14.3 years, and 334 (55%) were male. Cardiac injury was detected in 150 (24.7%) of patients included in the study. Mortality rate was higher in patients with cardiac injury (42% vs. 8%; $P < 0.01$). The frequency of patients who required ICU (72% vs. 19%), who developed acute kidney injury (14% vs. 1%) and acute respiratory distress syndrome (71% vs. 18%) were also higher in patients with cardiac injury. In multivariate analysis, age, coronary artery disease (CAD), elevated CRP levels, and presence of cardiac injury [odds ratio (OR) 10.58, 95% confidence interval (CI) 2.42–46.27; $P < 0.001$] were found to be

independent predictors of mortality. In subgroup analysis, including patients free of history of CAD, presence of cardiac injury on admission also predicted mortality (OR 2.52, 95% CI 1.17–5.45; $P = 0.018$).

Conclusion Cardiac injury on admission is associated with worse clinical outcome and higher mortality risk in COVID-19 patients including patients free of previous CAD diagnosis. *Coron Artery Dis* XXX: 000–000 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

SARS-CoV-2, which causes acute respiratory disease called COVID-19, is a new betacoronavirus and has been named ‘Severe Acute Respiratory Syndrome – Coronavirus-2’ (SARS-CoV-2) by the WHO. The disease it causes has been named coronavirus disease 2019 (COVID-19) and has been characterized as a pandemic since 11 March 2020 [1]. The spectrum of disease can vary from simple cold to severe acute respiratory distress syndrome (ARDS). COVID-19 is also associated with enteric, hepatic, nephrotic, neurological and cardiac involvement causing multiple organ failure and high risk of death [2]. COVID-19 associated mortality rates vary significantly between countries [2,3]. Presence of

co-morbid conditions and advanced age are accepted as high-risk indicators in COVID-19 infection [4]. Elevation of high sensitive Troponin I (hs-TnI) which is an indicator of myocardial damage is reported in a significant portion of patients with COVID-19 infection [4–7] but the prognostic value of this finding is not well-defined. In this multicenter study, we aimed to investigate the prognostic value of presence of myocardial damage in patients hospitalized with diagnosis of COVID-19.

Methods

Study population

The first COVID-19 case was defined on 11 March 2020 in Turkey. Since then, some government hospitals were

modified only to treat COVID-19 patients. For this multi-center retrospective study, data of 607 consecutive COVID-19 patients who were hospitalized in three government hospitals in Istanbul, Turkey between 20 March 2020 and 20 April 2020 were analyzed (Fig. 1). Epidemiological, demographic, clinical, laboratory parameters and outcome data were extracted from electronic medical records of individual hospitals. Patients younger than 18 years of age, with concurrent ST-segment elevation myocardial infarction, with history of advanced kidney failure [estimated glomerular filtration rate (eGFR) <30 ml/min] or hemodialysis and patients with missing laboratory parameters on admission including hs-TnI, and creatine kinase myocardial band (CK-MB) were excluded. The treatment of each case was left to the discretion of attending physician and was planned according to the national guidelines updated by the Turkish Ministry of Health. This study was approved by the institutional review board and Republic of Turkey Ministry of Health.

Laboratory analysis

Laboratory results of admission complete blood count, routine biochemical parameters including urea, creatinine, blood chemical analysis, assessment of liver and renal function and electrolytes, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), d-dimer and hs-TnI were collected from medical records. For

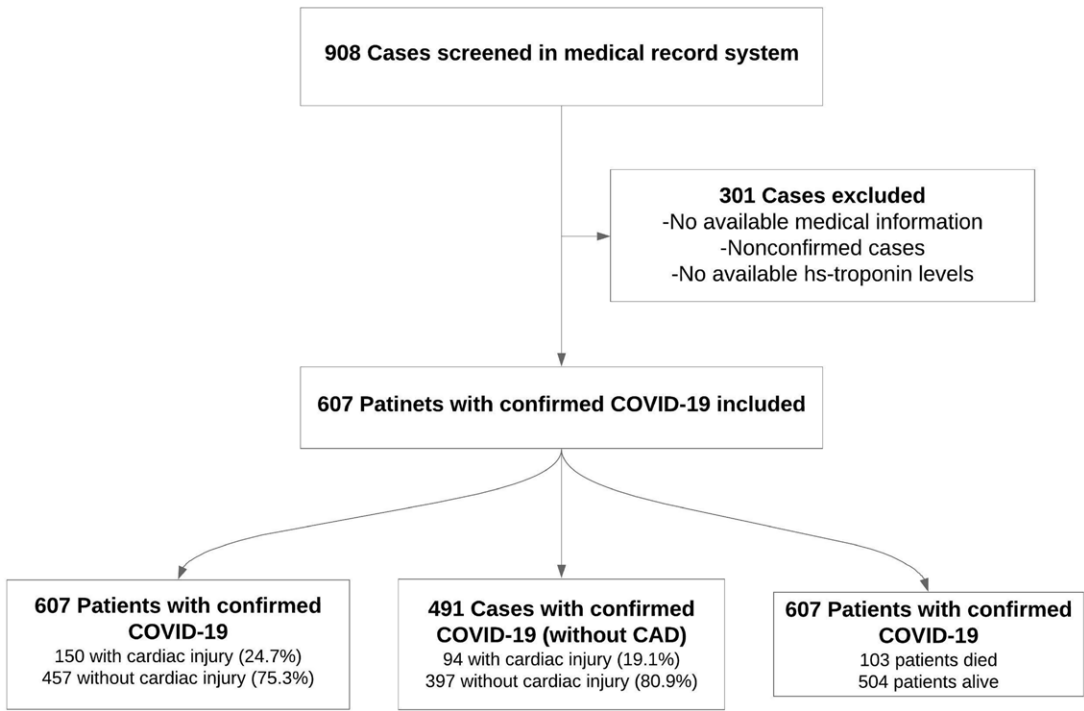
definition of myocardial damage admission hs-TnI and CK-MB levels were evaluated. The upper reference limit (99th percentile) ranges with an upper reference range of 14 pg/ml for patients.

SARS-CoV-2 RNA was detected by real-time reverse transcription-PCR (RT-PCR) method in the Public Health Microbiology Reference Laboratory of the Ministry of Health. First taking an oropharyngeal swab, then a nasal sample using the same swab and placed on the same transport broth. Nucleic acid amplification tests (NAAT) for SARS-CoV-2 virus Routine confirmation of COVID-19 cases was performed by determining specific sequences of virus RNA with a NAAT test such as real-time RT-PCR, and validating it by nucleic acid sequence analysis when necessary.

Definitions and clinical outcomes

The medical records of included patients were searched for development of adverse clinical events including length of stay, development of ARDS, ICU treatment, acute kidney injury (AKI) and mortality. The patients who had no fever and oxygen requirement in the last 48–72 hours and who had a throat-swab specimens SARS-CoV-2 real-time RT-PCR test two times negative were discharged. The last check of individual patient data was performed on 20 April 2020.

Fig. 1.



Flowchart of the study.

Acute cardiac injury was defined as high sensitivity cardiac troponin I serum levels above the 99th percentile upper reference limit, regardless of new abnormalities in ECG [8]. ARDS was defined according to the Berlin definition [9]. AKI was identified according to the Kidney Disease: Improving Global Outcomes definition [10]. The value of initial history chronic kidney disease (CKD) was defined as eGFR between 30 and 59%/1.73 m² [11]. Coronary artery disease (CAD) was diagnosed by the presence of documented previous myocardial infarction, or a history of percutaneous coronary intervention/coronary artery by-pass grafting surgery.

The clinical outcomes (AKI, ICU, ARDS, discharges, mortality and length of stay) were monitored up to 20 April 2020, the final date of follow-up.

Statistical analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to analyze normality of the data. Continuous data are expressed as mean $\pm$ SD, and categorical data are expressed as percentages. Chi-square test was used to assess differences in categorical variables between groups. Student's *t*-test or Mann–Whitney *U* test was

used to compare unpaired samples as needed. The possible factors identified with univariate analyses were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of death. The proportional hazards assumption and model fit was assessed by means of residual (Schoenfeld and Martingale) analysis. Cumulative survival curves were derived according to the Kaplan–Meier method and differences between curves were analyzed on log-rank statistics. Significance was assumed at a two-sided *P* < 0.05.

Results

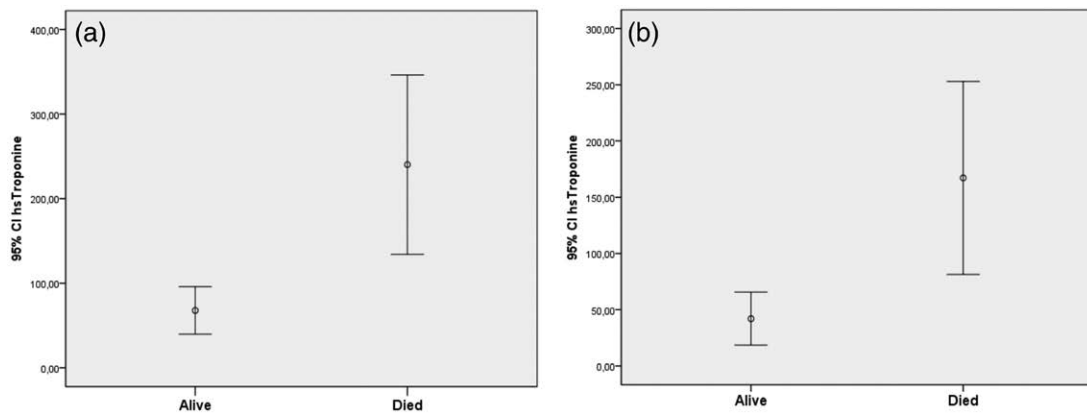
Of the 607 COVID-19 patients recruited for the study, 150 had concomitant cardiac injury on admission. Clinical and demographic characteristics of patients with and without cardiac injury are shown in Table 1. Patients with cardiac injury were older and the frequency of patients with CAD, hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease (COPD) and CKD was higher in this group. In addition, white blood cells (WBC), creatinine, uric acid, sodium, glucose, CRP, procalcitonin, hs-TnI, d-dimer, CK-MB, AST, LDH and ferritin levels were significantly higher in patients with cardiac injury (Fig. 2).

Table 1 Demographic and clinical characteristics of patients with and without cardiac injury

Characteristic	Cardiac injury (+) (n = 150)	Cardiac injury (–) (n = 457)	<i>P</i> value
Age (years)	68.5 $\pm$ 13.4	56.6 $\pm$ 15.2	<0.001
Male, n (%)	86 (57)	248 (54)	0.512
BMI (kg/m ²)	27 $\pm$ 7.1	26 $\pm$ 7.2	0.421
Chronic medical illness			
Hypertension, n (%)	88 (58)	178 (38)	<0.001
Diabetes mellitus, n (%)	62 (41)	130 (28)	0.003
HLD, n (%)	42 (28)	84 (18)	0.012
CAD, n (%)	56 (37)	60 (13)	<0.001
Smoking, n (%)	58 (38)	213 (46)	0.090
COPD, n (%)	29 (19)	44 (9)	0.002
CKD, n (%)	31 (20)	26 (5)	<0.001
Laboratory findings on admission hospital			
Hemoglobin (g/dl)	12.7 $\pm$ 1.8	12.8 $\pm$ 1.8	0.376
Platelet count (10 ³ /μl)	226.5 $\pm$ 105.3	214.1 $\pm$ 81.7	0.138
WBC (10 ³ /μl)	9.1 (6.2–13.8)	6.1 (4.7–8.1)	<0.001
Creatinine (mg/dl)	1.3 (0.9–2.9)	0.8 (0.6–1.0)	<0.001
Uric acid (mg/dl)	5.7 $\pm$ 2.8	4.9 $\pm$ 2.1	0.014
Sodium (mmol/L)	140.0 $\pm$ 8.9	136.1 $\pm$ 4.8	<0.001
Potassium (mmol/L)	4.2 $\pm$ 0.8	4.1 $\pm$ 0.6	0.196
Glucose (mg/dl)	135 (106–199)	113 (99–147)	<0.001
CRP (mg/dl)	118 (66–185)	61 (28–109)	<0.001
Procalcitonin (ng/ml)	0.8 (0.1–2.6)	0.12 (0.10–0.17)	<0.001
hsTroponin (pg/ml)	97 (42–300)	9 (5–13)	<0.001
D-dimer (ng/ml)	332 (106–2542)	59 (32–293)	<0.001
CK-MB (ng/ml)	5.0 (2.0–13.0)	1.3 (0.8–3.1)	<0.001
AST (U/L)	42 (26–66)	33 (23–46)	<0.001
ALT (U/L)	26 (17–43)	24 (17–39)	0.203
LDH (U/L)	464 (330–656)	341 (253–452)	<0.001
Ferritin (mg/L)	551 (306–1299)	256 (108–589)	<0.001
Complications and clinical outcome			
Hospital length of stay, days	12 (5–14)	9 (4–12)	<0.001
Acute kidney injury, n (%)	22 (14)	8 (1)	<0.001
ICU, n (%)	108 (72)	87 (19)	<0.001
ARDS, n (%)	107 (71)	84 (18)	<0.001
Death, n (%)	64 (42)	39 (8)	<0.001

ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CAD, coronary artery disease; CK, creatinine kinase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HLD, hyperlipidemia; LDH, lactate dehydrogenase; WBC, white blood cell.

Fig. 2.



High sensitive cardiac troponin I levels in all patients (a) and without CAD patients (b) who died and survived. CAD, coronary artery disease.

Table 2 Demographic and clinical characteristics of patients without coronary artery disease

Characteristic	Cardiac injury (+) (n = 94)	Cardiac injury (-) (n = 397)	P value
Age (years)	66.0 ± 14.5	55.3 ± 15.2	<0.001
Male, n (%)	51 (54)	210 (52)	0.812
BMI (kg/m ²)	26 ± 6.5	26 ± 7.4	0.954
Chronic medical illness			
Hypertension, n (%)	46 (49)	125 (31)	0.001
Diabetes mellitus, n (%)	32 (34)	98 (24)	0.064
HLD, n (%)	17 (18)	52 (13)	0.211
Smoking, n (%)	33 (35)	186 (46)	0.039
COPD, n (%)	16 (17)	35 (8)	0.019
CKD, n (%)	16 (17)	18 (4)	<0.001
Laboratory findings on admission hospital			
Hemoglobin (g/dl)	12.8 ± 1.8	12.8 ± 1.7	0.925
Platelet (10 ³ /μl)	223.7 ± 106.3	215.0 ± 83.1	0.393
WBC (10 ³ /μl)	9.0 (6.1–13.4)	6.0 (4.8–8.1)	<0.001
Creatinine (mg/dl)	1.3 (0.9–3.1)	0.8 (0.6–1.0)	<0.001
Uric acid (mg/dl)	5.8 ± 2.6	4.8 ± 2.0	0.012
Sodium (mmol/L)	140.6 ± 9.5	136.3 ± 4.7	<0.001
Potassium (mmol/L)	4.2 ± 0.8	4.1 ± 0.6	0.179
Glucose (mg/dl)	132 (98–182)	111 (98–144)	0.034
CRP (mg/dl)	118 (66–179)	61 (28–109)	<0.001
Procalcitonin (ng/ml)	0.9 (0.1–2.6)	0.12 (0.02–0.17)	<0.001
hsTroponin (pg/ml)	77 (38–219)	9 (5–12)	<0.001
D-dimer (ng/ml)	323 (99–2457)	59 (32–300)	<0.001
CK-MB (ng/ml)	4.8 (2.0–12.0)	1.3 (0.7–3.5)	<0.001
AST (U/L)	41 (26–62)	33 (22–46)	0.001
ALT (U/L)	25 (17–42)	24 (17–36)	0.285
LDH (U/L)	414 (242–589)	255 (210–387)	<0.001
Ferritin (mg/L)	610 (417–1435)	248 (108–585)	<0.001
Complications and clinical outcome			
Hospital length of stay, days	11 (5–16)	9 (4–11)	0.002
Acute kidney injury, n (%)	15 (16)	8 (2)	<0.001
ICU, n (%)	64 (68)	70 (17)	<0.001
ARDS, n (%)	64 (68)	67 (16)	<0.001
Death, n (%)	35 (37)	28 (7)	<0.001

ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CK, creatinine kinase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HLD, hyperlipidemia; LDH, lactate dehydrogenase; WBC, white blood cell.

After removing 116 patients with history of CAD, the remaining 491 patients were compared according to the presence of cardiac injury (Table 2). The average age of the group with cardiac injury was statistically higher ($P < 0.001$). There was a statistically significant difference between the groups in terms of hypertension, COPD and CKD ($P < 0.05$). Regarding laboratory tests, WBC,

creatinine, uric acid, sodium, glucose, CRP, procalcitonin, hs-TnI, d-dimer, CK-MB, AST, LDH and ferritin levels were significantly higher in the cardiac injury group ($P < 0.05$) (Fig. 2).

The length of hospital stay was longer in patients with cardiac injury. When in-hospital outcomes were compared frequency of patients who required ICU (72% vs.

Table 3 Baseline characteristics of patients who died and survived

Characteristic	Died (n = 103)	Alive (n = 504)	P value
Age (years)	69.3 ± 12.5	57.5 ± 15.4	<0.001
Male, n (%)	61 (59)	273 (54)	0.347
BMI (kg/m ²)	26 ± 4.3	27 ± 5.2	0.212
Chronic medical illness			
Hypertension, n (%)	60 (58)	206 (40)	0.001
Diabetes mellitus, n (%)	39 (37)	153 (30)	0.135
HLD, n (%)	24 (23)	102 (20)	0.485
CAD, n (%)	40 (38)	76 (15)	<0.001
Smoking, n (%)	50 (48)	221 (43)	0.383
COPD, n (%)	22 (21)	51 (10)	0.001
CKD, n (%)	15 (14)	42 (8)	0.048
Laboratory findings on admission hospital			
Hemoglobin (g/dl)	12.6 ± 1.9	12.8 ± 1.8	0.353
Platelet (10 ³ /μl)	221.7 ± 105.7	216.3 ± 84.4	0.578
WBC (10 ³ /μl)	9.8 (6.1–15.0)	6.3 (4.8–8.3)	<0.001
Creatinine (mg/dl)	1.4 (0.9–2.9)	0.8 (0.7–1.0)	<0.001
Uric acid (mg/dl)	6.3 ± 3.1	4.8 ± 2.1	<0.001
Sodium (mmol/L)	139.4 ± 9.6	136.6 ± 5.3	0.005
Potassium (mmol/L)	4.3 ± 0.9	4.1 ± 0.6	0.024
Glucose (mg/dl)	140 (109–230)	114 (99–148)	<0.001
CRP (mg/dl)	132 (85–194)	64 (29–110)	<0.001
Prokalsitonin (ng/ml)	1.1 (0.2–2.4)	0.1 (0.09–0.2)	<0.001
hs-Troponin (pg/ml)	41 (14–157)	10 (5–15)	<0.001
D-dimer (ng/ml)	305 (61–2950)	67 (34–358)	<0.001
CK-MB (ng/ml)	4.2 (2.0–10.0)	1.4 (0.8–5.0)	<0.001
AST (U/L)	55 (34–85)	32 (22–45)	<0.001
ALT (U/L)	28 (18–63)	24 (17–39)	0.011
LDH (U/L)	525 (383–792)	338 (249–447)	<0.001
Ferritin (mg/L)	586 (207–1367)	277 (112–591)	0.001
Complications and clinical outcome			
Hospital length of stay, days	12 (5–14)	9 (4–12)	0.022
Cardiac injury, n (%)	64 (62)	86 (17)	<0.001
Acute kidney injury, n (%)	19 (18)	11 (2)	<0.001
ICU, n (%)	102 (99)	93 (18)	<0.001
ARDS, n (%)	102 (99)	89 (17)	<0.001

ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CAD, coronary artery disease; CK, creatinine kinase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HLD, hyperlipidemia; LDH, lactate dehydrogenase; WBC, white blood cell.

19%), who developed AKI (14% vs. 1%) and ARDS (71% vs. 18%) and who died (42% vs. 8%) were significantly higher in patients with cardiac injury (Table 1). When patients with previous CAD were excluded, clinical outcome was still worse in patients with cardiac injury, with a mortality rate of 37% vs. 7% ($P < 0.001$) (Table 2).

When 103 deceased patients were compared to 504 survived patients, mean age, the frequency of hypertension, CAD, CKD and COPD were significantly higher in deceased group (Table 3). When laboratory tests were compared, WBC, creatinine, uric acid, sodium, potassium, glucose, CRP, procalcitonin, hs-TnI, d-dimer, CK-MB, AST, ALT, LDH and ferritin were statistically higher in deceased patients. The distribution of 103 deaths among groups by day, in the group with cardiac injury, 10.6% of deaths occurred in the first 5 days, 25.2% in the 5–10 days, and 14.5% in the 10–15 days, while in the group without cardiac injury, 11.6% in the first 5 days, 4.8% in the 5–10 days, and 11.6% in the 10–15 days deaths occurred. 50.4% of all deaths were observed in the group with Cardiac injury within the first 15 days (Fig. 3).

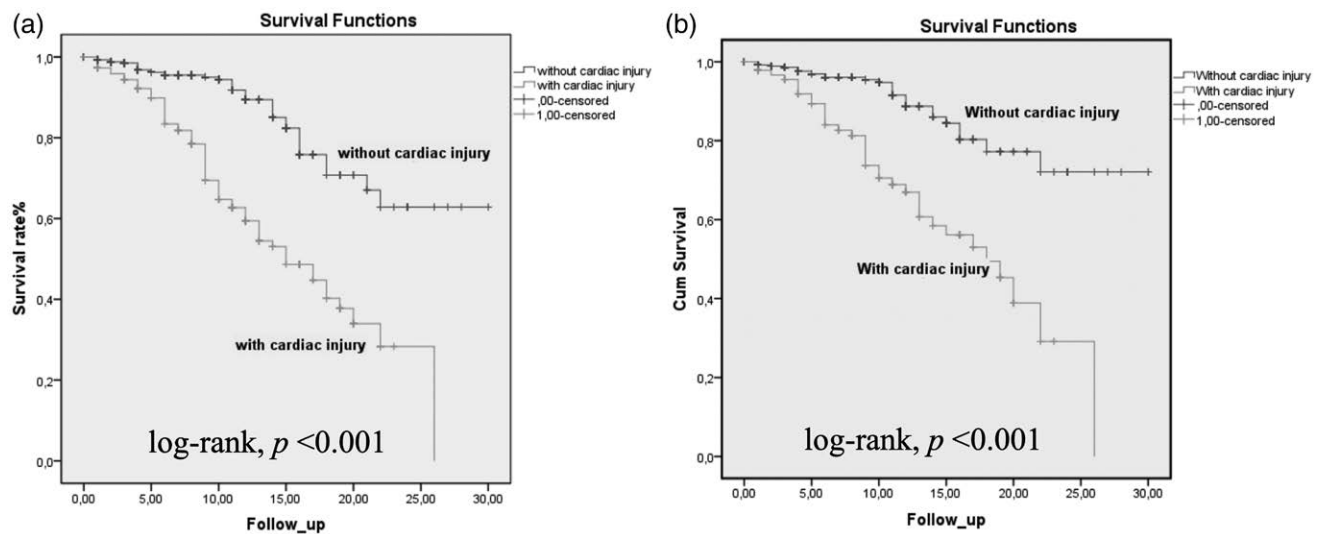
Possible predictors of mortality were evaluated with univariate and multivariate Cox-regression analyses. Clinical

and laboratory parameters such as age, sex, hypertension, diabetes mellitus, CAD, smoking, COPD, creatinine, uric acid, glucose, CRP, presence of cardiac injury and d-dimer were evaluated in univariate analysis. Age, hypertension, CAD, COPD, creatinine, uric acid, glucose, CRP, presence of cardiac injury and d-dimer ≥ 500 ng/ml were analyzed in multivariate analysis. Age, CAD, CRP and presence of cardiac injury were found to be independent predictors in terms of predicting mortality [age odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01–1.05; $P = 0.001$; CAD OR 1.26, 95% CI 1.06–1.50; $P = 0.009$; CRP OR 1.01, 95% CI 1.00–1.01; $P = 0.004$; presence of cardiac injury OR 10.58, 95% CI 2.42–46.27; $P < 0.001$] (Table 4). When patients with previous CAD were excluded from analyses, presence of cardiac injury was still an independent predictor of mortality (OR 2.52, 95% CI 1.17–5.45; $P = 0.018$). When the survival rates were analyzed with Kaplan–Meier survival curves, patients with cardiac injury had significantly higher mortality rates (Fig. 3).

Discussion

In the present study, the prognostic significance of admission hs-TnI levels was investigated in patients with COVID-19. The main findings of our study are as follows:

Fig. 3.



Kaplan–Meier survival curves for mortality during the time from admission. All patients (a) and patients without coronary artery disease (CAD) (b).

Table 4 Univariate and multivariate cox regression analysis on the risk factors associated with mortality in patients with COVID-19

Variable	All patients						Patients without coronary artery disease (CAD)					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	1.05	1.04–1.07	<0.001	1.03	1.01–1.05	0.001	1.05	1.03–1.07	<0.001	1.05	1.01–1.08	0.002
Sex	1.22	0.79–1.89	0.348				1.14	0.69–1.87	0.608			
Hypertension	2.01	1.31–3.10	0.001	1.26	0.60–2.62	0.531	1.34	0.81–2.20	0.249			
Diabetes mellitus	1.39	0.89–2.17	0.137				1.04	0.61–1.76	0.879			
CAD	1.25	1.14–1.38	<0.001	1.26	1.06–1.50	0.009						
Smoking	1.20	0.79–1.84	0.383				1.01	0.61–1.67	0.948			
COPD	2.41	1.38–4.19	0.002	2.99	0.34–25.96	0.319	1.65	0.89–3.06	0.108			
Creatinine	1.29	1.15–1.44	<0.001	1.13	0.81–1.58	0.453	1.11	1.01–1.21	0.031	1.05	0.80–1.38	0.682
Uric acid	3.57	2.24–5.69	<0.001	2.03	0.84–4.92	0.114	1.44	1.12–1.86	0.005	0.93	0.32–2.69	0.896
Glucose	1.00	1.00–1.01	<0.001	1.00	0.99–1.00	0.148	1.01	1.00–1.01	0.002	1.00	0.99–1.01	0.517
CRP	1.01	1.00–1.01	<0.001	1.01	1.00–1.01	0.004	1.01	1.00–1.01	<0.001	1.00	0.99–1.01	0.525
Cardiac injury	7.97	5.03–12.64	<0.001	10.58	2.42–46.27	<0.001	3.79	2.29–6.25	<0.001	2.52	1.17–5.45	0.018
D-dimer ≥500	3.07	1.97–4.78	<0.001	0.58	0.28–1.23	0.160	1.22	1.14–1.32	<0.001	1.20	1.03–1.39	0.015

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; OR, odds ratio.

- (1) Cardiac injury was detected in 24.7% of patients included in the study;
- (2) The frequency of patients who developed AKI, ARDS, who required ICU treatment and who died was significantly higher in patients with cardiac injury;
- (3) In multivariate regression analysis, presence of cardiac injury was found to be an independent predictor of mortality even in patients without history of CAD;
- (4) Between fifth and 15th days of hospitalization is a 'vulnerable period' for patients with cardiac injury, as most of the deaths occurred in this period.

As of 23 April 2020, the number of cases worldwide is 2.5 million due to COVID-19 infection, and the number of deaths is 165 000. To date, there is no disease-specific

treatment or vaccine. COVID-19 with many organ involvement, the most common cause of death in these patients is ARDS and accompanying cardiovascular complications including myocarditis, myocardial injury, arrhythmias, venous thromboembolism, heart failure and cardiogenic shock [2,12–14]. In patients admitted to the emergency department due to COVID-19 infection, both accompanying myocardial involvement, ECG changes due to microvascular damage (ST-elevation, ST-depression and nonspecific ST-T segment changes), and increased cardiac biomarkers (troponin and natriuretic peptide levels) are observed [15].

In a meta-analysis involving 13 studies, cardiac injury is associated with mortality, need for ICU care and severity

of disease in patients with COVID-19 [16]. In another meta-analysis of four different studies, the evaluation of 341 patients showed that high levels of troponin were measured in mortally severe patients compared to mild patients, and increased levels of troponin were associated with mortality [17]. In the retrospective analysis of 191 cases hospitalized for COVID-19 infection; hs-cTnI levels increased in >50% of the deceased patients while the rate of cases measured with hs-cTnI >28 pg/ml was 46% among the deceased patients, only 1% was reported in the survivor patients ($P < 0.0001$). Significant relationship was found between univariate analysis and hs-cTn I level increase and death (OR 80.1, 95% CI 10.3–620.4; $P < 0.0001$) [7].

In another study involving 416 patients hospitalized for COVID-19, one in five patients had cardiac injury (19.7%). Invasive-noninvasive mechanical ventilation requirement, ARDS and AKI injury were higher in patients with high troponin levels. Mortality was 10-fold higher in patients with myocardial injury (51% vs. 5%) [6]. In a study by Wang *et al.* [14], cardiac injury was found to be 16.7%, while in a study by Huang *et al.* [18], it was found to be 12.1%. Cardiac injury was detected in 24.7% of patients included in our study. AKI, ICU hospitalization, ARDS and mortality rate were higher in patients with cardiac injury compared to those without. hs-TnI levels have a higher OR rate than all laboratory parameters included in both univariate and multivariate analysis. In multivariate analyzes, hs-TnI levels were found to be independent predictors of death in COVID-19 patients with and without CAD. In our study, the reason for the high rate of cardiac injury is that only patients with hs-TnI levels were included.

It is known that d-dimer is an important indicator of mortality in severe infection and sepsis. In a recent study, d-dimer levels were significantly higher in patients who died due to COVID-19 than those who did not die (5.2 µg/ml vs. 0.6 µg/ml, $P < 0.0001$, respectively). D-dimer >1 µg/ml was found as an independent indicator of in-hospital mortality in multivariate regression analysis (OR 18.42, 2.64–128.55, $P = 0.0033$) [7]. In our study, d-dimer levels were found to be higher in patients who died compared to the survivors. D-dimer ≥500 ng/ml was determined as an independent predictor of mortality by univariate analysis. D-dimer increase may be due to increased systemic pro-inflammatory activation triggering the prothrombotic process.

Mortality rates are highest in elderly patients with COVID-19 infection (14.8% over 80 years old) and in patients with a history of underlying cardiovascular disease [2]. Similarly, in our study, age and history of CAD were determined as an independent predictor of in-hospital mortality by multivariate analysis.

The cause of the increase in troponin during COVID-19 infection is not fully elucidated. Acute severe respiratory failure syndrome alone may be the cause of increased cTn

[19]. In addition, type-I myocardial infarction, which is the result of prothrombotic system activation and plaque rupture triggered by serious inflammatory activation, or type-II myocardial infarction, which is caused due to either increased oxygen demand or decreased supply, as a result of severe myocardial inflammation, are among the possible scenarios [8,12]. In addition, it is suggested that the invasion of ACE-II, which is abundant in myocytes and vascular endothelial cells and is the region where the coronavirus attaches, may cause direct cardiac involvement due to viral myocarditis or stress cardiomyopathy [20]. In severe patients, the imbalance between oxygen demand and supply does not only affect the myocardium, multiple organ failure due to cellular damage may occur. Troponin levels can detect patients with impaired tissue oxygenation and perfusion at an early stage and allow early treatment of these patients.

The comparison of our study and other studies: our study was designed as multicenter and includes more patients than other studies in terms of the number of patients. It is important in terms of demonstrating the prognostic significance of troponin levels observed during the admission in the emergency department. While investigating the effect of cardiac injury in studies on COVID-19, patients with a history of CAD were also included, and the prognostic significance of troponin levels in non-CAD patients was not investigated. Our results demonstrated that the prognostic significance of cardiac injury was shown also in patients without a history of CAD.

In conclusion, it was observed that the cardiac troponin levels, which were found to be high on hospital admission, were associated with worse outcome and predicted in-hospital mortality. Accordingly, increased cardiac troponin levels may reflect the severity of the disease. It is thought that troponin levels frequently increase due to non-coronary events in COVID-19 patients [21] and therefore can be used as a prognostic marker. The clustering of deaths into the first 15 days of the hospital admission in COVID-19 patients has underlined the importance of first 15 days as the critical ‘vulnerable period’ in secondary prevention measures of these patients.

Study limitations

The study was conducted retrospectively, patients whose hs-TnI levels were measured on hospital admission were included in the study. Another limitation of our study is that IL-6 and BNP are not measured and lack of data regarding echocardiography findings. A prospective study involving SARS-CoV-2 infection and involving both symptomatic and asymptomatic patients will provide an accurate estimate of the prevalence of cardiac injury.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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