European Review for Medical and Pharmacological Sciences 2021; 25: 2425-2434

Impact of acute myocardial injury on prognosis in patients with COVID-19

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Abstract. – OBJECTIVE: The primary objective of this study was to evaluate the frequency and impact of acute myocardial injury on prognosis in hospitalized COVID-19 patients.

PATIENTS AND METHODS: This was a retrospective study that included consecutive hospitalized patients with COVID-19. Clinic-demographic characteristics, laboratory values, and high-sensitivity troponin I were extracted from the electronic database. Mortality and other clinical complications, including respiratory failure requiring invasive mechanical ventilation and acute kidney injury were recorded. Myocardial injury was defined as having a serum troponin I value >19.8 ng/mL. We performed Kaplan-Meier survival analysis and Cox regression to determine survival times and independent predictors of mortality.

RESULTS: A total of 324 patients were included. Seventy-seven patients (23.8%) had acute myocardial injury. The primary outcome measure, namely death, occurred in 54.5% and 3.2% of the patients with and without myocardial injury, respectively. Notably, 75.3% of the patients with myocardial injury and 6.5% of the patients without myocardial injury developed ARDS. Overall, 50 out of 324 patients (15.4%) died during the study period. The mortality rate was 54.5% in patients with myocardial injury and 3.2% in patients without myocardial injury. Mean survival times were significantly different between the groups (15.1±0.9 days in patients with myocardial injury and 24.4±0.7 days in patients without myocardial injury, log-rank test p-value <0.001).

CONCLUSIONS: The presence of chronic kidney disease and application of invasive mechanical ventilation were found to be independent predictors of in-hospital mortality. The presence of acute myocardial injury was common but not independently associated with mortality among hospitalized COVID-19 patients.

Key Words:
COVID-19, Mortality, Myocardial injury, Prognosis, Troponin I.

Introduction

Coronavirus disease 2019 (COVID-19) name has been given to the disease caused by a novel coronavirus, now known as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2). First appeared in the Hubei province of China, COVID-19 became a pandemic in a short time and ravaged most of the world with case fatality rates up to 13.5%[1,2].

SARS-CoV2 enters human cells via the human angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed by type 2 alveolar cells in the lung. Thus, lungs are the principal target and the most important cause of mortality in COVID-19 disease[3,4]. Although myocardial cells scarcely express ACE 2 receptors under physiologic conditions, the situation changes in case of the presence of cardiovascular disease[2]. As lending clinical support for this molecular observation, several studies[5-8] have shown the vulnerability of patients who had underlying cardiovascular disease to COVID-19. At this point, it should be emphasized that the results of studies investigating determinants of severe COVID-19 and mortality are not unanimous in this regard. In addition, the expression of ACE2 in vascular endothelium and kidney may also account for the extra pulmonary complications leading to multiorgan dysfunction syndrome observed in patients with severe COVID-19.

The precise mechanism(s) by which SARS-CoV2 causes myocardial injury is yet to be elucidated. However, several putative mechanisms have been put forward, among which are unmasking of underlying cardiovascular comorbid disease, acute coronary syndrome, cytokine release syndrome, myocarditis, and stress cardiomyopathy[9]. Tavazzi et al[10] could isolate SARS-CoV2 from myocardium in a patient with COVID-19

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Cardiogenic Shock. Several studies[11,12] to date have shown that myocardial injury that was described as an elevation of serum troponin values over the 99th percentile of the laboratory upper limit was quite common among hospitalized patients with COVID-19. Moreover, myocardial injury is not merely a bystander of a cytokine storm; rather it seems a strong factor independently and unfavorably affects mortality. Several studies[13-18] reported that the presence of myocardial injury was an independent predictor of all-cause in-hospital mortality in COVID-19 patients.

However, to date, all of the studies reporting the association of myocardial injury with mortality in COVID-19, except a small report[19], have been reported from China. It is apparent that case fatality rates vary across different countries and populations because of many factors, including racial differences. Thus, it is of utmost importance to know the rate of myocardial injury and its impact on mortality and other adverse clinical outcomes in a specific population to characterize the involvement of the cardiovascular system in this disease.

In our study, we aimed to evaluate the frequency of myocardial injury and its association with in-hospital mortality in a Turkish cohort of patients who were hospitalized due to COVID-19.

Patients and Methods

Study Participants

The present study was carried out according to international agreements (Declaration of Helsinki and World Medical Association). The study protocol was approved by our Hospital's Clinical Studies Ethics Committee (220.05.2.08.064). This study was a retrospective analysis of consecutive patients who were admitted either to the general hospital ward or to the intensive care unit of our hospital with the diagnosis of COVID-19 and were followed up to death or discharge from the hospital before April 15, 2020. All of the included patients were diagnosed as having SARS-CoV2 infection with a reverse transcriptase-polymerase chain reaction-based test (RT-PCR) from samples taken with nasal swabs. All patients with PCR-based COVID-19 diagnosis were enrolled. Patients who were below 18 years-old who did not have PCR-based COVID-19 diagnosis and who did not have serum troponin measurements were excluded from the study.

Data Collection

Demographic characteristics, comorbid conditions, laboratory values, including hemogram parameters, serum creatinine, C-reactive protein, albumin, and high-sensitivity troponin I were extracted from the electronic database of the hospital and recorded by two investigators after cross-check. Serum troponin I was studied by the double-antibody sandwich ELISA method. All laboratory values except troponin I were studied from the venous bloods taken when the patients were admitted to the floor or the ICU. Serum troponin I value was selected as the highest value among the measurements of patients who had more than one troponin I measurement during the course of the hospitalization.

Clinical Outcomes and Definitions

The primary outcome measure of the present study was all-cause mortality. We also collected data regarding other clinical complications, including acute respiratory distress syndrome (ARDS) and acute kidney injury. The length of hospital stay was calculated for each patient. Presence of acute kidney injury, ARDS, requirements of hemodialysis, noninvasive oxygen treatment, noninvasive mechanical ventilation (NIMV), and invasive mechanical ventilation were recorded for each participant. Myocardial injury was defined as having a serum troponin I value that was higher than the 99th percentile of the upper limit of the laboratory reference range. As per this definition, if a patient had a serum troponin I value >19.8 ng/mL, he or she was deemed to have myocardial injury[20]. Troponin I value performed on the Beckman Coulter AccuTnI assay immunoanalyzers (Beckman Laboratories, Germany). We divided the whole study cohort according to this value as patients with and without myocardial injury. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition[21]. Acute kidney injury and chronic kidney disease were defined based on the KDIGO guidelines[22,23]. Neutrophil to lymphocyte ratio (NLR) was calculated as the peripheral blood neutrophil count divided by the lymphocyte count.

Statistical Analysis

In summarization of the data derived from the study, descriptive statistics were expressed as mean ± standard deviation and median (interquartile range) where appropriate. Categorical variables were presented as numbers and percentages. The Kolmogorov-Smirnov test and Q-Q plots were used to check the distribution type of the numerical variables. We divided all study cohort according to serum troponin I values; patients with and without myocardial injury. Comparison of these two groups and in other intergroup comparisons, we used either Chi-squared and Fisher's Exact test or the Mann-Whitney U test depending on the type of distribution of the variables. Kaplan-Meier curves were constructed to illustrate differences between the patients with and without myocardial injury. Log Rank test was used to compare the survival times of the groups. We also created univariate and multivariate Cox proportional hazards models to determine independent predictors of all-cause mortality. We performed univariate and multivariate Cox regression analyses to determine independent predictors of in-hospital mortality. We included all laboratory values, comorbidities, and complications as covariates of the outcome variable. We included variables that appeared significantly associated with the outcome variable in the multivariate method. On the other hand, among variables that are clearly related and had a high correlation, only one of them was included in the multivariate Cox model. We calculated hazard ratios and presented them along with 95% confidence intervals. All statistical analyses were performed with SPSS 24 (IBM, Armonk, NY, USA) statistical software package. A p-value below 0.05 was considered as statistically significant.

Results

Baseline Clinical Characteristics and Admission Laboratory Values

A total of 324 patients (171 male (52.8%), mean age 58.4 ± 15.2 years), were included in this retrospective study. The percentages of patients who had hypertension, congestive heart failure, and chronic kidney disease were 43.2%, 5.6%, and 11.7%, respectively. The median serum troponin I value was 3.6 ng/mL (IQR, 1.5 - 14.8). Baseline clinic-demographic characteristics and admission laboratory values of the patients were shown in Table I.

Comparison of Laboratory Values and Clinical Outcomes between Patients with and Without Myocardial Injury

Seventy-seven patients (23.8%) had acute myocardial injury. Patients who developed myocardial injury were significantly older than patients without myocardial injury (mean ages 64 ± 12.96 *vs.* 56.3 ± 15.2 years, respectively). In the myocardial injury group, coronary artery disease, hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and congestive heart failure were significantly more frequent compared with the patients without myocardial injury. Median white blood cell and neutrophil counts were significantly higher, whereas lymphocyte count was significantly lower in patients with myocardial injury compared with the patients without myocardial injury. Median NLR was also significantly higher in patients with myocardial injury compared to patients without myocardial injury. Median serum troponin I levels were significantly higher in patients with myocardial injury compared with patients without myocardial injury (306 ng/mL (72-852) *vs.* 3.6 ng/mL (3.26-3.9), p <0.001).

Patients with myocardial injury had a significantly longer hospital stay compared with the patients without myocardial injury. The primary outcome measure, namely death, occurred in 54.5% and 3.2% of the patients with and without myocardial injury, respectively. Notably, 75.3% of the patients with myocardial injury and 6.5% of the patients without myocardial injury developed ARDS. Acute kidney injury was observed in one-fourth of patients with myocardial injury. On the other hand, only 8.5% of patients without myocardial injury developed acute kidney injury. The comparison of clinical outcomes and laboratory parameters of the patients with and without myocardial injury was shown in Table II.

Comparison of Laboratory Values and Clinical Outcomes between Deceased and Surviving Patients

In total, 50 out of 324 patients (15.4%) died during the study period. The deceased patient group was significantly older compared with surviving patients (64±12.9 *vs.* 56.3±15.2 years, respectively, p <0.001). Only hypertension and CKD were significantly more common among the deceased compared with surviving patients. There was no significant difference between the groups in terms of other comorbid conditions. The comparison of the laboratory parameters between the groups was depicted in Table III. Myocardial injury was present in 84% of the deceased group, whereas 12.8% of the surviving patients had myocardial injury (p <0.001). The median serum troponin I levels were 306 ng/mL (72-852) and 2.5 ng/mL (1.3-5.5) in the deceased and surviving patients, respectively (p <0.001). Acute kidney

Table I. Clinic-demographic characteristics and baseline laboratory values of the study subjects.

	All patients (n=324)
Age (years) (mean ± SD)	58.4±15.2
Sex [n (%)]	
Female	153 (47.2%)
Male	171 (52.8%)
Comorbidities [n (%)]	
Coronary artery disease	52 (16%)
Hypertension	140 (43.2%)
Dyslipidemia	56 (17.3%)
Diabetes mellitus	99 (30.6%)
Cerebrovascular accident	10 (3.1%)
COPD	44 (13.6%)
Malignancy	19 (5.9%)
Smoking	92 (28.4%)
Chronic kidney disease	38 (11.7%)
Chronic atrial fibrillation	15 (4.6%)
Congestive heart failure	18 (5.6%)
Laboratory parameters [median (IQR)]	
Creatinine (mg/dL)	0.8 (0.6-1.03)
Hemoglobin (g/dL)	12.7 (11.4-13.8)
Neutrophil count (10^3/µL)	4.2 (2.84-6.04)
Lymphocyte count (10^3/µL)	1.18 (0.85-1.56)
White blood cell count (10^3/µL)	6.07 (4.56-7.8)
Platelet count (10^3/µL)	208.5 (168-263.5)
NLR	3.45 (2.06-5.78)
PLR	176.4 (124.4-244.3)
C-reactive protein (mg/L)	34.3 (13.2-99.2)
Troponin I (ng/mL)	3.6 (1.5-14.8)
Albumin (g/dL)	3.5 (3.1-3.9)
Clinical outcomes [n (%)]	
Length of hospital stay	8 (5-12)
Death	50 (15.4%)
Acute kidney injury	40 (12.3%)
Dialysis treatment	10 (3.1%)
ARDS	74 (22.8%)
Noninvasive mechanical ventilation	31 (9.6%)
Invasive mechanical ventilation	47 (14.5%)
Myocardial injury	
Absent (troponin I ≤19.8)	247 (76.2%)
Present (troponin I >19.8)	77 (23.8%)

ARDS: Acute respiratory distress syndrome, COPD: Chronic Obstructive pulmonary disease, ICU: Intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, NIMV: Noninvasive mechanical ventilation, PLR: Platelet-to-lymphocyte ratio.

injury and ARDS developed in significantly more patients in deceased group compared with the patients in the surviving group.

Survival Analysis

The mortality data were available for 324 patients. In total, 50 patients (15.4%) died during the study period. The mortality rate was 54.5% (n= 42) in patients with myocardial injury and 3.2% (n= 8) in patients without myocardial injury. Mean survival times were significantly different between the groups (15.1 ± 0.9 days in patients with myocardial injury and 24.4 ± 0.7 days in patients without myocardial injury, log-rank test p-value <0.001) (Table IV and Figure 1).

Independent Predictors of Mortality

According to the univariate and multivariate Cox regression analyses, the presence of chronic kidney disease and the application of invasive mechanical ventilation were found to be independent predictors of all-cause mortality. The presence of chronic kidney disease increased the risk of mortality 3.9 times (95% CI 1.839-8.239). If the patient had to be connected to the invasive mechanical ventilator, the risk of mortality increased by 14 times (95% CI 4.475-45.178). Interestingly, none of the chronic comorbid diseases other than chronic kidney disease and congestive heart failure were significantly associated with in-hospital mortality (Table V).

Discussion

The salient findings of the present study were as follows: (i) myocardial injury was not uncommon among hospitalized patients with COVID-19. Almost one-fourth of all patients had myocardial injury. (ii) Patients with myocardial injury had significantly more complication rates (acute kidney injury and ARDS) than patients without myocardial

Table II. Comparison of clinical outcomes and laboratory parameters of patients with and without myocardial injury.

	Patients with myocardial injury [n=77 (23.8%)]	Patients without myocardial injury [n=247 (76.2%)]	*p*
Age (year) (mean ± SD)	64 ± 12.96	56.3 ±15.2	**<0.001**
Sex [n (%)]			
Female	26 (33.8%)	127 (51.4%)	
Male	51 (66.2%)	120 (48.6%)	**0.009**
Comorbidities [n (%)]			
Coronary artery disease	23 (29.9%)	29 (11.7%)	**<0.001**
Hypertension	48 (62.3%)	92 (37.2%)	**<0.001**
Dyslipidemia	21 (27.3%)	35 (14.2%)	**0.008**
Diabetes mellitus	25 (32.5%)	74 (30.0%)	0.677
Cerebrovascular accident	4 (5.2%)	6 (2.4%)	0.256
COPD	17 (22.1%)	27 (10.9%)	**0.013**
Malignancy	8 (10.4%)	11 (4.5%)	0.090
Smoking	32 (41.6%)	60 (24.3%)	**0.003**
Chronic kidney disease	18 (7.3%)	20 (26%)	**<0.001**
Chronic atrial fibrillation	10 (13.0%)	5 (2.0%)	**<0.001**
Congestive heart failure	69 (89.6%)	10 (4.0%)	**0.045**
Laboratory parameters [median (IQR)]			
Creatinine (mg/dL)	0.8 (0.5-1.0)	0.76 (0.6-0.94)	**<0.001**
Hemoglobin (g/dL)	12 (10-13)	12.9 (11.8-13.9)	**0.001**
Neutrophil count (10^3/μL)	5.7 (4.2-8.12)	3.96 (2.6-5.18)	**<0.001**
Lymphocyte count (10^3/μL)	0.9 (0.6-1.5)	1.26 (0.9-1.57)	**0.001**
White blood cell count (10^3/μL)	7.6 (5.67-9.6)	5.7 (4.38-7.26)	**<0.001**
Platelet count (10^3/μL)	207 (168-285)	209 (168-261)	0.430
NLR	6.1 (3.3-10.8)	3.08 (1.86-5.1)	**<0.001**
PLR	207.0 (132.5-371.4)	170 (122.7-231.5)	**0.002**
C-reactive protein (mg/L)	124.1 (49-203)	24.9 (11.1-80.8)	**<0.001**
Troponin I (ng/mL)	306 (72-852)	2.5 (1.3-5.5)	**<0.001**
Albumin (g/dL)	3.1 (2.8-3.4)	3.6 (3.26-3.9)	**<0.001**
Clinical outcomes [n (%)]			
Length of hospital stay	11 (6.5-15)	8 (5-11)	**<0.001**
Death	42 (54.5%)	8 (3.2%)	**<0.001**
Acute kidney injury	19 (24.7%)	21 (8.5%)	**<0.001**
Dialysis treatment	5 (6.5%)	5 (2.0%)	0.062
ARDS	58 (75.3%)	16 (6.5%)	**<0.001**
Noninvasive mechanical ventilation	17 (22.1%)	14 (5.7%)	**<0.001**
Invasive mechanical ventilation	43 (55.8%)	4 (1.6%)	**<0.001**

ARDS: Acute respiratory distress syndrome, COPD: Chronic Obstructive pulmonary disease, NLR: Neutrophil-to-lymphocyte ratio, NIMV: Noninvasive mechanical ventilation, PLR: Platelet-to-lymphocyte ratio.

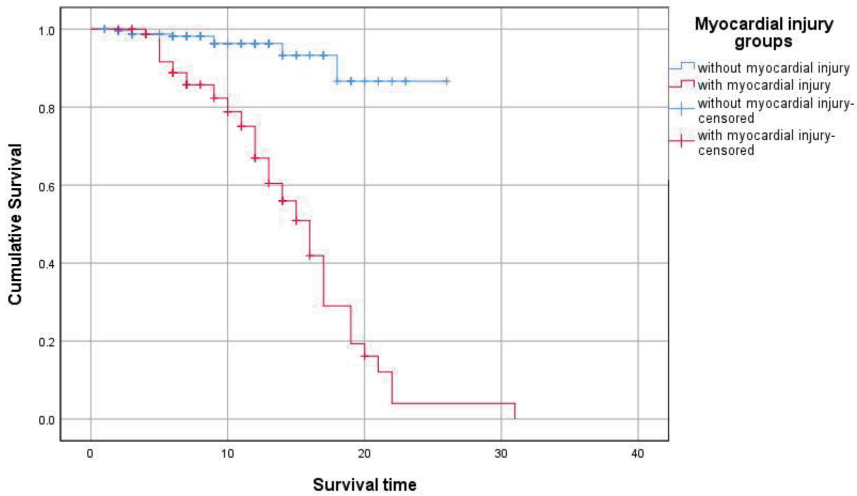

Figure 1. Kaplan-Meier curve showing survival ratios of COVID-19 patients with and without myocardial injury.

injury. (iii) The presence of myocardial injury was associated with lower survival times and higher mortality compared with patients without myocardial injury. (iv) The presence of underlying chronic kidney disease and the need for invasive mechanical ventilation emerged as independent predictors of in-hospital mortality. Interestingly, none of the other comorbid diseases, including heart disease, was independently associated with in-hospital mortality.

The myocardial injury on clinical outcomes in COVID-19 patients has been deeply analyzed. Shi et al[18] conducted the most extensive retrospective evaluation of the impact of COVID-19 on clinical outcomes. The authors included 671 patients hospitalized with PCR-based COVID-19 diagnosis. The results of the study showed that high serum troponin I levels could predict the in-hospital mortality. In another retrospective study[17], the same authors included 416 hospitalized patients with COVID-19 and evaluated clinical outcomes. Cardiac injury was detected in 19.7% of the participants. Complications such as acute kidney injury, ARDS, and coagulation disorders were significantly more common among patients with myocardial injury compared with patients without myocardial injury. Having myocardial injury increased the risk of death 3.41 times (95% CI 1.62-7.16). A recent meta-analysis[13], including 10 studies with 3118 patients assessed the impact of myocardial injury on mortality in COVID-19 patients. Acute myocardial injury, defined as having a serum troponin I value higher than the 99th percentile of the upper limit of the laboratory reference range, was associated with an unadjusted odds ratio of 21.15 for in-hospital mortality. Another meta-analysis by Santoso et al[24] included 13 studies comprising 2389 patients that evaluated only acute myocardial injury on mortality. The authors confirmed the findings of the latter meta-analysis mentioned above. Cardiac injury was associated with a relative risk of 7.95 for mortality (p <0.001). All studies in these two meta-analyses were conducted in the Chinese population and reported from China. To the best of our knowledge, only one small study reported the impact of the presence of myocardial injury on mortality outside of China from the United States of America[19]. In this respect, our study is the first large study reported outside of China investigating the effects of myocardial injury on clinical outcomes, including in-hospital mortality.

Our results were generally in agreement with the previous studies. Acute myocardial injury was detected in 23.8% of our study cohort. In previous studies, this rate varied from 2.6% up to 23.1%, possibly due to the differences in the study setting and population characteristics regarding underlying comorbid diseases[25-27]. In our study, patients with acute myocardial injury had significantly shorter survival times compared with patients who did not have acute myocardial injury. Despite this, the development of acute myocardial injury was not an independent predictor of in-hospital mortality.

In a number of previous studies, it was shown that having underlying cardiovascular disease, hypertension or diabetes mellitus significantly increased the risk of severe COVID-19 disease as well as mortality[6,28]. However, not all studies reported such a relationship between underlying chronic cardiovascular and metabolic disease and increased mortality in COVID-19 patients[15,17,18]. Similar to the latter studies, our results did not show any independent association of underlying cardiovascular disease, diabetes, and hypertension with all-cause mortality. Only hypertension, chronic atrial fibrillation and chronic kidney disease were more common among the deceased patients compared with the surviving patients. On the other hand, the frequencies of congestive heart failure, coronary artery disease, malignancy, and COPD were not different between the groups.

In the present study, the only underlying chronic disease in COVID-19 patients that was significantly associated with all-cause mortality

Table III. Comparison of clinical characteristics and laboratory values of deceased and survivor patients.

	Deceased Patients (n=50	**Surviving Patients (n=274)**	***p*-value**
Age (years) (mean ± SD)	64±12.9	56.3±15.2	**<0.001**
Sex (n (%))			
Female	23 (46.0%)	130 (47.4%)	
Male	27 (54.0%)	144 (52.6%)	0.851
Comorbidities [n (%)]			
Coronary artery disease	13 (26.0%)	30 (14.2 %)	0.057
Hypertension	36 (72.0%)	104 (38.0%)	**<0.001**
Dyslipidemia	13 (26%)	43 (15.7%)	0.076
Diabetes mellitus	18 (36.0%)	81 (29.6%)	0.363
Cerebrovascular accident	3 (6.0%)	7 (2.6%)	0.189
COPD	10 (20.0%)	34 (12.4%)	0.150
Malignancy	6 (12%)	13 (4.7%)	0.092
Smoking	18 (36.0%)	74 (27.0%)	0.195
Chronic kidney disease	16 (32.0%)	22 (8.0)	**<0.001**
Chronic atrial fibrillation	6 (12.0%)	9 (3.3%)	**0.017**
Congestive heart failure	4 (8.0%)	14 (5.1%)	0.497
Laboratory parameters [median (IQR)]			
Creatinine (mg/dL)	1.0 (0.8-1.55)	0.76 (0.6-0.92)	0.018
Hemoglobin (g/dL)	12 (10-13)	12.9 (11.8-13.9)	<0.001
Neutrophil count ($10^3/\mu L$)	6.05 (4.2-8.6)	4.0 (2.7-5.27)	<0.001
Lymphocyte count ($10^3/\mu L$)	0.9 (0.63-1.6)	1.22 (0.9-1.54)	<0.001
White blood cell count ($10^3/\mu L$)	8.0 (6.1-10.8)	5.71 (4.4-7.29)	<0.001
Platelet count ($10^3/\mu L$)	207 (168-285)	209 (168-261)	0.857
NLR	6.1 (3.3-10.8)	3.08 (1.86-5.1)	<0.001
PLR	207 (132.5-371.4)	170 (122.7-231.5)	0.002
C-reactive protein (mg/L)	124.1 (49-203)	24.9 811.1-80.8)	<0.001
Troponin I (ng/mL)	306 (72-852)	2.5 (1.3-5.5)	<0.001
Albumin (g/dL)	3.1 (2.8-3.4)	3.6 (3.26-3.9)	<0.001
Clinical outcomes [n (%)]			
Length of hospital stay	11 (6.5-15)	8 (5-11)	**<0.001**
Myocardial injury			
Absent (troponin I ≤19.8)	8 (16.0%)	239 (87.2%)	**<0.001**
Present (troponin I >19.8)	42 (84.0%)	35 (12.8%)	
Acute kidney injury	15 (30.0%)	25 (9.1%)	**<0.001**
Dialysis treatment	4 (8.0%)	6 (2.2%)	0.052
ARDS	45 (90.0%)	29 (10.6 %)	**<0.001**
Noninvasive mechanical ventilation	5 (10.0%)	26 (9.5%)	1.000
Invasive mechanical ventilation	40 (80.0%)	7 (2.6%)	**<0.001**

ARDS: Acute respiratory distress syndrome, COPD: Chronic Obstructive pulmonary disease, NLR: Neutrophil-to-lymphocyte ratio, NIMV: Noninvasive mechanical ventilation, PLR: Platelet-to-lymphocyte ratio.

Table IV. Log-rank test showing the difference in survival times between patients with and without myocardial injury.

	Number of events/ number of patients (%)	Mean survival time (days)	95% Confidence interval	*p*-value*
Patients with myocardial injury	42/77 (54.5%)	15.1 ± 0.9	13.4-16.7	**<0.001**
Patients without myocardial injury	8/247 (3.2%)	24.4 ± 0.7	23.1-25.7	

ARDS: Acute respiratory distress syndrome, COPD: Chronic Obstructive pulmonary disease, NLR: Neutrophil-to-lymphocyte ratio, NIMV: Noninvasive mechanical ventilation, PLR: Platelet-to-lymphocyte ratio.

Table V. Univariate* and multivariate Cox regression analyses showing independent predictors of all-cause mortality.

COX regression						
	Univariate			Multivariate		
Parameters	Hazard Ratio	95% Confidence Interval	*p*-value	Hazard Ratio	95% Confidence Interval	*p*-value
Age	1.028	1.007-1.050	0.008			
Chronic kidney disease	3.007	1.634-5.534	<0.001	3.892	1.839-8.239	<0.001
Congestive heart failure	0.947	0.338-2.649	0.011			
Hemoglobin	0.868	0.762-0.987	0.031			
CRP	1.007	1.004-1.010	<0.001			
Troponin I	1.000	0.990-1.010	<0.001			
Albumin	0.414	0.235-0.729	0.002			
NLR	1.040	1.014-1.067	0.003			
PLR	1.001	1.000-1.003	0.009			
Myocardial injury (present/absent)	9.326	4.347-20.005	<0.001			
Mechanical ventilation	13.293	6.401-27.603	<0.001	14.219	4.475-45.178	<0.001
ARDS	18.398	7.263-18.398	<0.001			

*Only variables that showed significant association with mortality in univariate analysis were depicted. ARDS: Acute respiratory distress syndrome, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

was chronic kidney disease. Having CKD independently increased the risk of death (hazard ratio 3.892, 95% CI 1.839-8.239, p <0.001). Henry et al[29] in their four-study meta-analysis, reported that pooled analysis of the individual studies showed an independent association of CKD with severity of COVID-19. In their larger meta-analysis, Wang et al[28] confirmed the findings of the latter meta-analysis. However, the report did not specifically mention the association of presence of CKD and mortality. Oyelade et al[30] included 22 studies comprising 5595 COVID-19 patients in their meta-analysis that specifically looked at the effect of CKD and chronic liver disease on mortality. The overall prevalence of CKD was 1% among all patients. In patients with underlying CKD, 84% of patients had severe disease. Only 3 studies reported mortality, and the mortality rate was 53% in this meta-analysis[30]. In this regard, we think that our study presents novel data in that chronic kidney disease remains as an important independent determiner of in-hospital mortality. Considering the lack of independent association of underlying cardiovascular disease, diabetes, and hypertension with mortality in our study, this strong independent association of CKD with mortality seems remarkable. This aspect should be further clarified in future studies, considering the high prevalence of CKD in the general population, particularly among the elderly who are considered the most vulnerable age group in the COVID-19 pandemic.

Limitations

Several limitations of the current work deserve mention. First, because of the retrospective nature of the study, we cannot guarantee that independent associations are necessarily causal. Unknown factors (past drug use, echocardiography findings, etc.) that were not controlled might have affected our results. Second, we did not have the data regarding chronic drug use and COVID-19 treatments in our cohort. Especially, differences in the use of ACE inhibitors might have impacted our results to some extent. Third, we did not distinguish the specific causes of death. We only looked at all-cause mortality. Thus, we cannot extrapolate our results to the cardiovascular causes of death. Lastly, we did not have data regarding the specific etiology and subsequent treatment interventions for troponin I values. Since many different causes with differing prognoses might lead to increased serum troponin values, this might have affected the clinical outcomes of the study.

Current literature regarding the impact of acute myocardial injury on mortality in hospitalized COVID-19 patients seems under the dominance of Chinese studies that reported the results of the Chinese population. This is understandable, since China was the center of the COVID-19 outbreak. However, there are a lot of unknown factors that seem to affect the fatality rate among different populations in addition to known factors such as increased age and several comorbid conditions. Thus, the conduction of studies reporting determinants of mortality in different populations is of crucial importance to take necessary measures to face the challenges of COVID-19 pandemic in terms of public health and hospital systems perspectives.

Conclusions

Summarily, far as we have known, at the time of the writing of this manuscript, our study was the first to report determinants of mortality and survival among hospitalized COVID-19 patients outside China. In a research hospital setting with dedicated intensive care units and hospital wards, the overall frequency of acute myocardial injury was about 15% in a Turkish cohort of COVID-19 patients. One of the most important implications of the current study was that chronic kidney disease was an independent predictor of mortality while DM, COPD, hypertension, and congestive heart failure were not. Patients who had serum troponin I values above the upper limit of the laboratory reference range (myocardial injury) were disadvantages in terms of survival compared with patients who did not have myocardial injury. Thus, two features of our results should be emphasized: first, patients with CKD were significantly vulnerable to the systemic adverse effects of COVID-19. Second, despite its increased frequency in hospitalized COVID-19 patients, myocardial injury was not an independent predictor of in-hospital mortality.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Declaration

All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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