ELEVATED TROPONIN I TREND IS ASSOCIATED WITH POOR PROGNOSIS IN CRITICAL COVID-19 PATIENTS

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ABSTRACT

Introduction*: Cardiac etiology may play a role in deaths due to the Coronavirus disease 2019 (COVID-19). Therefore, the relationship between troponin I and mortality in critical COVID-19 patients is of interest. Troponin I, one of the heart-specific proteins, is used as a biomarker to detect myocardial necrosis. In the present study, our aim is to demonstrate the relationship of the Troponin I trend with mortality in critical COVID-19 patients.*

Materials and methods: *A retrospective analysis was carried out for critical COVID-19 patients who were admitted to the intensive care unit at Ankara City Hospital, a tertiary center, during the early period of the pandemic between March 18, 2020 and April 28, 2020. The patients, whose Troponin I were measured regularly and for the longest period, were selected in order to draw the trends. These patients were distributed into two groups as survivor and death groups according to mortality in the intensive care unit.*

Results: *It was found that 18 of the 66 critical COVID-19 patients, the troponin I concentration was measured regularly every day for a period of minimum 13 days. The mean age ± SEM (Standard error of mean) was 68.25±4.28 years in the survivor group and 70.83±2.58 years in the death group (P>0.05). The mean APACHE II ± SEM was 16.08±2.95 in the survivor group and 36.17±5.67 in the death group (P<0.05). The mean troponin I concentration ± SEM on day 13 was 63.26±39.90 ng/L in the death group, while the mean troponin I ± SEM was 12.01±5.03 ng/L (P<0.05) in the survivor group.*

Conclusion: *The elevation in the troponin I trend in patients with COVID-19 was associated with mortality. In critically ill patients who survived, the mean troponin I approximately 5 times lower on day 13 compared to the patients who did not survive. Despite all vital supportive treatments, some of the patients with COVID-19 rapidly progressed to death. Monitoring the changes in troponin I trend can indicate the severity and prognosis of the disease.*

Keywords: *SARS-CoV-2, COVID-19, troponin I, prognosis, intensive care units.*

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Introduction

Unfortunately, the COVID-19 pandemic has caused many deaths all over the world. It is not yet fully known whether the mortality in critical COVID-19 patients is caused by the involvement of the respiratory, cardiovascular, central nervous system or other systems. Cardiac involvement may be responsible for the rapid fatal progression of COVID-19 despite the rescue and supportive treatments.

High-sensitivity cardiac troponin I assays have been used for the diagnosis of cardiomyocyte injury. Troponin I is a protein specific to the cardiac muscle fibers. Troponin I elevates in the presence of the myocardial injury. Clinicians generally use the "troponin I serial sampling" to investigate whether the symptoms of chest pain, dyspnea, and fatigue are caused by acute myocardial ischemia or other causes of myocardial injury. In a recently published study, 41% of moderate and severely critical patients with COVID-19 were found to have elevated troponin levels[(1)]. Troponin I elevation in the coronavirus 2019 disease (COVID-19), which is caused by the SARS-CoV-2 virus, is associated with the poor prognosis. Another

study found a significant level of Troponin I elevation in about 20% of all hospitalized patients with COVID-19. Patients with high troponin levels had comorbidities such as coronary artery disease, heart failure, and hypertension[2]. Numerous factors including excessive inflammation, increased clotting, hemodynamic instability, and hypoxemia can affect the heart in critical COVID-19 patients. Pulmonary embolism and sepsis can affect the heart. Acute type 1 or type 2 myocardial infarction, nonischemic myocardial injury, chronic myocardial injury, myocarditis, cardiomyopathy, and acute heart failure may be responsible for the troponin elevations[3].

Measuring the troponin levels in cases of COVID-19 guides clinicians in the requirement for advanced cardiac evaluation (such as Echocardiography, cardiac catheterization, scintigraphy and magnetic resonance imaging). In addition, it helps to determine the fatal risks for the patients. Thus, the level of care required for the patients and the requirement for close follow-up in intensive care can be determined[4]. In the present study, we aimed to demonstrate the relationship between the course of troponin I trend over time and the mortality in critically ill patients. Prognosis can be predicted by demonstrating the relationship of troponin I trend with mortality.

Materials and methods

A retrospective cohort study was designed. Among the patients, who were admitted to the Ankara State Hospital general intensive care units between March 18, 2020 and April 28, 2020, those meeting the following criteria were included in the study:

- Over the age of 18 and in both genders.
- Reverse transcription polymerase chain reaction test positive for SARS-CoV-2 virus.
- Elevated fever, cough, shortness of breath, RR ≥30 breath/min, oxygen saturation ≤93% or PaO2/FiO2 ≤300 mm Hg.
- Typical thoracic computed tomography findings of viral pneumonia.
- Patients with mechanical ventilation requirement, multiple organ failure and/or clinical picture of shock were included in the study[5, 6].
- Patients whose high-sensitivity cardiac troponin I assay measured regularly every day after admission to the hospital.

Data were obtained from the HICAMP program of Ankara City Hospital, General Intensive Care Units. The age, gender, comorbid diseases, length of stay in the intensive care unit and hospital were recorded for the patients included in the study. The patients were hospitalized either from the Emergency Department or from the COVID-19 outpatient clinic. The leukocyte count, lymphocyte count, hemoglobin, platelet count, albumin, lactate dehydrogenase, aspartate aminotransferase, bilirubin, creatine kinase-MB, creatinine, high-sensitivity C reactive protein, procalcitonin, lactate, activated partial thromboplastin time, prothrombin time and D-dimer values measured at the time of admission to the hospital were recorded. During the follow-up and treatment in the emergency and other departments, critically ill patients were transferred to the intensive care unit depending on the triage.

The APACHE II score within the first 24 hours following the admission to the intensive care unit was recorded. The troponin concentrations, which were measured regularly on a daily basis after the patients were admitted to the hospital, were recorded. The mortality of the patients was determined during their stay in the intensive care unit; and accordingly, they were classified in two groups as survivor and death groups.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics for Windows v.20.0 (IBM Corp., Armonk, NY). Constant variables were presented as mean, standard error of mean, median, minimum and maximum, whereas categorical variables were presented as frequency and percentage. The Shapiro-Wilk's test was used to evaluate the normality of the distribution for the constant variables. Levene's test was used to determine the homogeneity of variance. When hypotheses were not met, the Mann-Whitney U test was used to compare the 2 groups. Pearson's chi-square test was used to compare the categorical variables between groups. The level of statistical significance was determined as $P<0.05$.

Results

A total of 66 critically ill patients, who met the first 5 of the study criteria, were identified. In 48 of 66 patients, there were not sufficient troponin I measurements to obtain statistical inference, hence these 48 patients were excluded from the study. For the excluded patients, the median length of stay in the intensive care unit was 8 (minimum 3, maximum 29) days, and the median length of stay in the hospital was 13.5 (minimum 3, maximum 54) days. 25 of 48

patients (52%) died in the intensive care unit, the 23 of 48 (48%) were discharged. Following up with the discharged patients on December 23, 2020, we were informed that 2 of 23 patients died, where one died from pneumonia on the 45th day after the discharge, and the other died from heart failure and acute kidney injury on the 50th day after the discharge.

On the other hand, it was found that troponin measurement was made regularly every day for at least 13 days in the 18 of 66 patients. Of these 18 patients, 6 died in the intensive care unit and 12 were discharged from the hospital. Following up with the 12 discharged patients on December 23, 2020, we were informed that one patient died from heart failure on the 39th day after the hospital discharge, two patients died from pneumonia on the 49th and 59th days, and one died from acute kidney injury and sepsis on the 75th day. Demographics and clinical characteristics of the 18 patients included in the study were presented in Table 1.

		Survivors (n = 12)	Non-survivors (n = 6)	P
Age, years	Mean±Standard error of mean	68.25±4.28	70.83±2.58	0.682[a]
	Median (Minimum-maximum)	68 (39-92)	71 (61-80)	
Gender	Male, n (%)	7 (64)	4 (36)	0.732[b]
	Female, n (%)	5 (71)	2 (29)	
APACHE II	Mean± Standard error of mean	16.08±2.95	36.17±5.67	0.003[a]
	Median (Minimum-maximum)	11(5-40)	34(22-54)	
Comorbidities	Diabetes mellitus, n (%)	7 (58)	1 (17)	0.094[b]
	Hypertension, n (%)	8 (67)	4 (67)	1.000 [b]
	Coronary artery disease, n (%)	6 (50)	1 (17)	0.171[b]
	Chronic heart failure, n (%)	2 (17)	1 (17)	1.000[b]
	Kidney disease, n (%)	1 (8)	2 (33)	0.180[b]
	Stroke, n (%)	1 (8)	1 (17)	0.596[b]
Length of ICU stay, days	Mean± Standard error of mean	14.33±2.26	18.00±1.18	0.125[a]
	Median (Minimum-maximum)	13 (4-29)	18 (14-22)	
Length of hospital stay, days	Mean± Standard error of mean	23.42±3.18	23.00±1.03	0.750[a]
	Median (Minimum-maximum)	20 (9-47)	23 (20-27)	

Table 1: Demographic and clinical characteristics of the survivor and death groups.
Note: P values were calculated by aMann-Whitney U test or bPearson's chi-square test.

The mean age ± SEM (Standard error of mean) was 68.25±4.28 years in the survivor group and 70.83±2.58 years in the death group; and this difference was not statistically significant (P=0.682). Among these patients, 36% of male patients and 29% of female patients died. The mean APACHE II ± SEM was 16.08±2.95 in the survivor group, while it was 36.17±5.67 in the death group.

This difference was statistically significant (P=0.003). There was no statistically significant difference between the survivor and death groups in terms of comorbid diseases, length of stay in the intensive care unit and hospital. The other laboratory results were presented in Table 2.

	Group	Mean	Standard error of mean	Median	Minimum	Maximum	P
Leukocyte count (x10^9/L)	Survivors	8.61	0.88	8.89	3.70	13.72	0.180
	Non-survivors	11.11	1.19	9.94	8.53	15.50	
Lymphocytes (x10^9/L)	Survivors	1.06	0.20	0.83	0.32	2.44	0.067
	Non-survivors	0.47	0.08	0.40	0.29	0.78	
Hemoglobin (g/dL)	Survivors	11.05	0.68	11.40	7.20	14.4	0.682
	Non-survivors	11.63	1.18	12.05	7.50	15.20	
Platelet count (x10^9/L)	Survivors	275.75	24.13	277.0	145.0	411.0	0.213
	Non-survivors	206.16	39.87	225.50	54.0	310.0	
Bilirubin (mg/dL)	Survivors	0.65	0.07	0.65	0.40	1.10	0.553
	Non-survivors	1.30	0.63	0.70	0.20	4.40	
Albumin (g/dL)	Survivors	34.16	1.71	33.50	25.0	45.0	0.250
	Non-survivors	30.50	2.04	30.0	24.0	38.0	
Lactate dehydrogenase (U/L)	Survivors	358.41	32.34	340.0	222.0	578.0	0.003
	Non-survivors	657.50	103.94	548.0	453.0	1113.0	
Aspartate aminotransferase (U/L)	Survivors	42.33	12.39	23.00	13.0	154.0	0.083
	Non-survivors	55.50	6.04	53.00	41.0	80.0	
Bilirubin (mg/dL)	Survivors	0.65	0.07	0.65	0.40	1.10	0.553
	Non-survivors	1.30	0.63	0.70	0.20	4.40	
Creatine kinase-MB (μg/L)	Survivors	2.24	0.42	1.66	0.20	5.44	0.616
	Non-survivors	5.26	2.97	2.63	0.61	19.68	
Creatinine (mg/dL)	Survivors	1.12	0.20	0.92	0.46	3.10	0.553
	Non-survivors	1.37	0.38	1.23	0.51	3.19	
High-sensitivity C-reactive protein (g/L)	Survivors	0.13	0.02	0.11	0.04	0.28	0.494
	Non-survivors	0.17	0.04	0.16	0.04	0.33	
Procalcitonin (μg/L)	Survivors	1.39	0.80	0.32	0,04	9.76	0.437
	Non-survivors	1.75	0.87	1.18	0.05	5.7	
Lactate (mmol/L)	Survivors	1.97	0.17	1.81	0.84	3.06	0.616
	Non-survivors	2.35	0.40	2.01	1.52	4.22	
Activated partial thromboplastin time (seconds)	Survivors	34.47	7.96	24.80	20.40	120.00	0.213
	Non-survivors	29.25	2.07	27.50	24.70	37.50	
Prothrombin time (seconds)	Survivors	16.25	2.22	13.45	11.50	39.20	0.102
	Non-survivors	27.03	9.53	15.25	13.10	72.60	
D-dimer (mg/L)	Survivors	5.53	2.85	1.76	0.41	34.96	0.385
	Non-survivors	9.41	5.52	2.15	1.16	35.20	

Table 2: Laboratory test results of patients at admission to hospital.
Note: P values were calculated by Mann-Whitney U test.

The mean lactate dehydrogenase ± SEM was statistically significantly higher in the death group (657.50±103.94 U/L versus 358.41±32.34 U/L; P=0.003). The lymphocyte count of the death group were lower compared to that of the survivors; however, this difference was not statistically significant.

The graphs plotted according to the mean high-sensitivity cardiac troponin I concentrations in the survivor and death groups of critical COVID-19 patients were presented in Figure 1.

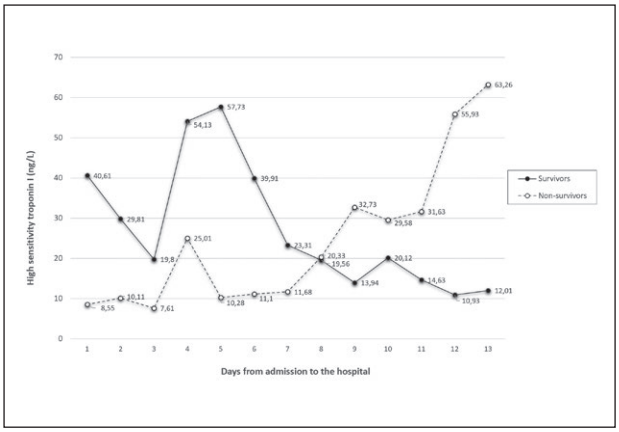

Figure 1: Troponin I trend was observed to elevate gradually on the last days in patients who died, while it declined in the survivors.

The mean troponin I ± SEM on the first day following the admission was 40.61±29.49 ng/L in the survivor group. On day 5, it elevated to 57.73±51.41 ng/L and then declined on the following days. The mean troponin I concentration of the survivors at day 13 was 12.01±5.03 ng/L. The mean troponin I ±SEM on the first day following the admission was 8.55±5.61 ng/L in the death group. On day 13, the mean troponin I ± SEM was 63.26±39.90 ng/L. In terms of troponin I concentration, there was an approximately 5-fold difference between the two groups on day 13 (P<0.05).

All patients were given hydroxychloroquine, favipiravir, antibiotics, low molecular weight heparin and proton pump inhibitor. No drug side effects were reported in any of the patients.

Discussion

In the present study, it was demonstrated that the troponin I trend elevated gradually in the non-surviving critical COVID-19 patients, while it declined in the surviving patients. Troponin I trend was higher in the surviving patients at the time of admission to the hospital and it declined within the second week, and it was lower in the non-survivors at the time of admission and it elevated later. Performing long-term regular laboratory tests will shed light on the unknown points of COVID-19. However, most of the critically ill patients admitted to the hospital either die or they recover in a short time and are discharged from the hospital. In addition to this, laboratory tests cannot be performed sufficiently due to reasons such as limited resources and increased workload during the pandemic period.

Chen et al. compared the laboratory results of the non-surviving and surviving patients with COVID-19, and found that the troponin I median (IQR) was 40.8 (14.7-157.8) ng/ L in 113 non-surviving COVID-19 patients, compared to a median (IQR) of 3.3 (1.9-7.0) ng/L in 161 surviving patients[1]. In a retrospective study conducted in the Wuhan State of China, Zhou et al. compared the median value of troponin I in 54 non-surviving and 137 surviving patients with COVID-19.

They found that the median Troponin I was approximately 7 times higher in the non-survivors compared to the survivors (P<0.0001[7]. Guo et al. detected comorbid diseases such as hypertension, coronary heart disease and cardiomyopathy in 66 (35%) of 187 hospitalized patients with COVID-19[8]. In our study, all of the patients were critically ill and they were admitted to the intensive care unit. This may be the reason why there was no statistical difference between the survivors and non-survivors in terms of comorbid diseases.

Han et al. reported that 3 (20%) of the 15 critical COVID-19 patients in the ICU had troponin I levels above 0.04 ng/mL and the mortality rate was 4-fold higher in patients with high cardiac parameters compared to the patients with normal parameters[9]. Shi et al. mentioned that the requirement for invasive mechanical ventilation was 5 times higher and the mortality rate was 10 times higher in the patients with COVID-19, who had elevated troponin levels, compared to patients without elevated troponin levels. They demonstrated that 8% to 28% of the patients with Covid-19 had elevated troponin and cardiac injury[2]. In addition, evidence of cardiomyopathy was reported in some cases with COVID-19(10). Cardiac arrest may occur in critical COVID-19 patients as a result of cardiac involvement. Direct cardiac involvement can result in clinical pictures such as myocarditis, cardiomyopathy, arrhythmias or heart failure. Unfortunately, this disease can indirectly affect the heart by systemic inflammation, severe hypoxia, multiple organ failure or other reasons and patients die rapidly[11].

The limitations of our study were the small sample size and its retrospective design. COVID-19 is an emerging disease with very limited information. New large-scale studies are needed to elucidate the etiology of troponin I elevation in cases of COVID-19 and the effect of possible treatments on troponin concentration.

In conclusion, monitoring troponin I trend can demonstrate the severity and prognosis of COVID-19. It is important to measure troponin I concentration regularly. When the elevation is observed, possible etiological factors that cause myocardial injury can be investigated. Despite vital supportive treatments, some of the patients with COVID-19 rapidly progress to death. In future studies, the effectiveness of potential COVID-19 treatments can be evaluated based on the change in troponin I trend.

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