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TANAFFOS

A Cross-Sectional Study for Determining the Role of High-Sensitivity Cardiac Troponin T in Predicting 4-Month Mortality during the First Wave of the COVID-19 Pandemic

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Background: Positivity of cardiac troponins is common in hospitalized COVID-19 patients and may serve as an additional risk stratification tool in everyday clinical settings. Since patients with elevated troponins have a higher risk of in-hospital mortality, troponins have prognostic importance. As well as in-hospital mortality, high-sensitive troponin T may reflect 4-month mortality. We analyzed the relationship between cardiac troponin T levels and 4-month mortality of COVID-19.

Materials and Methods: It was conducted as a retrospective cross-sectional study in Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital Izmir, Turkey, with COVID-19 pneumonia patients during the first wave of the pandemic. We analyzed their comorbidities, C-reactive protein, ferritin, aspartate transaminase, alanine transaminase, cardiac troponin T, N-terminal-prohormone B-type-natriuretic peptide, international normalized ratio; duration of hospital stay, and survival status.

Results: Factors associated with mortality were cardiac troponin T > 0.53 pg/dl ($p = 0.009$) and aspartate transaminase > 26.5 U/l ($p = 0.012$). The threshold for cardiac troponin T to predict 4-month mortality was 5.83pg/ml. Its sensitivity was 82.8% and its specificity was 66.4%.

Conclusion: Cardiac troponin T and AST are indicators that can be used to predict 4-month mortality in addition to showing in-hospital mortality. The threshold for cardiac troponin T to predict 4-month all-cause mortality is 5.83pg/ml. The mortality difference persists at the beginning, middle, and end of the 4 months. Reference thresholds likely underestimate the true prognostic extent of cardiac injury and lower cutoff values may show mortality.

Keywords: COVID-19; Mortality; Pneumonia; Troponin T

INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) emerged in Wuhan city, China, in December 2019 and it was announced as a pandemic infection in 11 March 2020 (1). The first case in Turkey was reported on the same day (2).

Patients with COVID-19 primarily present with respiratory tract infection symptoms; however, previous studies show that COVID-19 may exacerbate cardiovascular risk factors and preexisting cardiovascular disease or may lead to cardiovascular complications (3). Therefore, it is essential to consider the cardiovascular system and to recognize those presenting with early signs of acute myocardial injury. Myocardial injury includes all conditions that cause cardiomyocyte death, and its

diagnostic marker is cardiac troponin (4). Myocardial injury is defined as the presence of at least one cardiac troponin value above the 99th percentile upper reference limit (URL) (4). Cardiac troponin 99th percentile URL levels have been defined for acute MI due to coronary artery occlusion. However, there are other conditions in which troponin levels increase. COVID-19 is one of those conditions which cause highly sensitive cardiac troponin elevations. Several potential causes of myocardial injury in patients with COVID-19 are overlapping or impossible to discriminate completely from each other. COVID-19 may result in troponin levels below the 99th percentile URL (5).

The risk of death is nearly four times higher in patients with myocardial injury at presentation. An elevated troponin level is associated with in-hospital death (6).

The positivity of cardiac troponins is common in hospitalized COVID-19 patients and may serve as an additional risk stratification tool in everyday clinical settings. Since patients with elevated troponins have a higher risk of in-hospital mortality, cardiac troponins have prognostic importance. As well as in-hospital mortality, high-sensitive cardiac troponin T may reflect 4-month mortality. Our study aimed to analyze the relationship between cTnT levels and the 4-month mortality of patients with COVID-19 pneumonia.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted in Health Sciences University of Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, which was a tertiary chest diseases pandemic hospital in Izmir, Turkey. The patients who were hospitalized for COVID-19 pneumonia were analyzed.

Study population

A total number of 389 consecutive patients with COVID-19 pneumonia, hospitalized in pandemic pulmonology wards on 11 March- 15 May 2020 period, were analyzed. This period was in the first wave of the pandemic. All patients were over 18 years old, and we analyzed them without taking gender differences into account. In our country, we used the same COVID-19 case definitions (probable and confirmed cases) that WHO proposed (1, 2). Thorax CT was used as a diagnostic tool at early stages of the disease and in PCR-negative patients. The patients with mild and unilateral pneumonia were not hospitalized, according to the recommendations. Hospitalization criteria for COVID-19 were compatible with WHO and National COVID-19 Treatment Guidelines (1,2).

Patients with multiple presentations for COVID-19 during the study period were considered as single entries, and the first hospitalization following confirmed diagnosis was used for data collection and analysis. Initial laboratory data were collected at the presentation. Patients who were directly admitted to the intensive care unit were not included in the study.

Laboratory testing methods

Polymerase chain reaction (PCR) testing:

Respiratory (oropharyngeal and/or nasal) swabs of all patients were analyzed in Public Health Department Microbiology Reference Laboratories for COVID-19. Verification of COVID-19 was done by nucleic acid amplification test which was a real-time polymerase chain reaction (rRT-PCR) and specific sequences were determined. The results were reported as "positive" if the COVID-19 sequence was confirmed.

High sensitive cardiac Troponin T (cTnT):

Blood samples for cTnT were taken at the presentation. Serum levels of cTnT were analyzed by using the Roche cobas e601 system (an automated immunoassay system using electrochemiluminescence) (Roche Diagnostics, Germany). It has a coefficient of variation of < 10% at the reported 99th percentile of a normal, healthy population. 14.0 pg/ml is reported as the threshold for the 99th percentile of a normal population. In those without an acute myocardial infarction, cTnT values using this system have demonstrated significant variability between studies and manufacturer claims that this may be related to differences in populations studied (7). For these reasons, we used the median value in our study population for the cTnT analysis.

Inclusion criteria and analyzed criteria

We recorded demographic data, presence of comorbidity, PCR results, complete blood counts, C-reactive protein (CRP), ferritin, aspartate transaminase (AST), and alanine transaminase (ALT), high sensitive cardiac troponin T (cTnT), N-terminal prohormone B-type natriuretic peptide (ProBNP), INR (International Normalized ratio), chest X-ray and thorax CT lesions, total duration of hospital stay, duration of follow-up, in-hospital mortality, and dates of death after discharge in a standardized database.

Follow-up and data analysis

All patients were followed up by telephone for vital status from the date of discharge until the 16th of September 2020. The programmed minimum length of follow-up was 3 months.

Statistical methods

Analyses were performed with SPSS software version 25.5 (IBM, NY, USA). Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used to determine whether the parameters used in the comparison of the groups were normally distributed. Mann Whitney U test and Student's t-test were used for the comparison of continuous variables, and Chi-square and Fisher's exact test were used for the comparison of categorical data. The optimal cut-off value, sensitivity and specificity values, and odds ratios to be used in mortality prediction of the Troponin-T were calculated by ROC analysis according to the area under the curve and Youden index. The effect of Troponin-T on overall survival was demonstrated by Kaplan-Meier analysis. The predictive values of the parameters for mortality were calculated with univariate and multivariate Cox regression analyses. The results were presented with 95% confidence intervals. In all analyses, p-value < 0.05 was considered statistically significant.

The study was approved by the Scientific Research and Thesis Evaluation Board of Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (EPK date / No:12.06.2020/10/19). The study was in accordance with the ethical standards of the institutional and national committees. The study was retrospective and informed consent was not necessary.

RESULTS

We studied all 389 consecutive patients with COVID-19 pneumonia who were admitted in all pandemic wards, during the 11 March-15 May 2020 period. When the exclusions were applied according to our methodology, 291 patients remained eligible for the final analysis. Figure 1 shows the study flowchart.

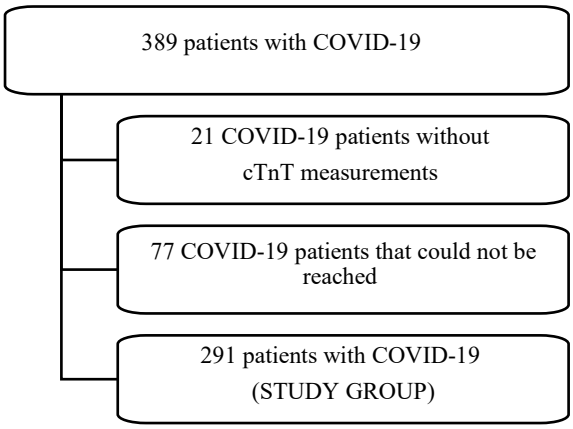

Figure 1. Study flowchart

Table 1 shows the demographic, laboratory, and clinical findings of 291 patients whose troponin was measured. Within a period of four months, 10% of our patients died. We compared characteristics of the deceased and surviving patients in Table 2. Age, presence of co-morbidity, median cTnT, ProBNP, leukocyte, platelets, AST, CRP, and INR values were higher in patients who died in four months. We analyzed the optimal cut-off values for age, cTnT, leucocytes, platelets, CRP, and AST and presented their sensitivity and specificity values in Table 3. Univariable Cox Regression analysis showed that age >49.5 (p =0.003), presence of comorbidity (p = 0.002), cTnT (p < 0.001), leukocyte (p = 0.002), platelet counts (p = 0.002), AST (p = 0.003), and CRP (p =0.015) showed significance for mortality. In multivariable Cox Regression analysis, cTnT (p=0.009) (HR=4.069) (95% CI 1.410-11.739) and AST (p =

0.012) (HR = 2.754) (95% CI 1.248-6.081) remained as the factors affecting overall survival (Table 4).

We analyzed the optimal cut-off value, sensitivity and specificity values, and hazard ratios used in the 4-month mortality prediction of the cTnT and calculated them using ROC analysis (Figure 2).

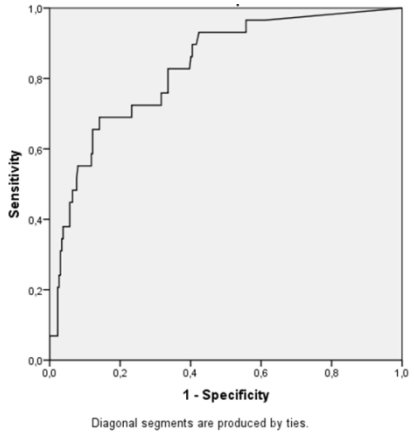

Figure 2. ROC analysis of cTnT

The optimal cut-off value for cTnT with a sensitivity of 82.8% and a specificity of 66.4% was 5.83 pg/ml. 112 of the patients had cardiac troponin values over 5.83 and therefore the exact prevalence of "new defined high" cardiac troponin COVID-19 patients was 38.5%. Figure 3 shows the Kaplan Meier survival time analysis of the patients with high and low cTnT for a cut-off value of 5.83 pg/ml. There was a significant survival time difference ($p < 0.001$) between those two groups. This survival time difference was further analyzed using Log Rank, Breslow, and Tarone-Ware analysis to clarify whether it varied in the 4 months. There was a consistently significant survival time difference in the beginning, during, and at the end of the study period.

The optimal cut-off value for AST was 26.5 U/l, its sensitivity was 62.1%, and the specificity was 67.8%. (with an AUC of 0.66).

Table 1. Demographic, laboratory and clinical findings of all 291 patients whose troponin was measured.

Variables		
Age (Mean ± SD) (min – max)		52.8 ± 14.9 (19 – 94)
Gender n (%) Female / Male		118/173 (41/59)
Patients with comorbidity n (%)		153 (53.7)
	Never smoker	113 (54.3)
Smoking (n = 208) n (%)	Prior smoker	59 (28.4)
	Current smoker	36 (17.3)
PCR status n (%)	Negative	127 (43.6)
	Positive	164 (56.4)
Leukocyte (x 10^3 / µl) (Mean ± SD) (min – max)		7.6 ± 4.3 (2.6 – 31.9)
Hemoglobin (g / dl) (Mean ± SD) (min – max)		13.2 ± 1.8 (7.8 – 17.7)
Platelets (x 10^3 / µl) (Mean ± SD) (min – max)		251.4 ± 113.3 (65 - 840)
CRP (mg / dl) (Mean ± SD) (min – max)		17.9 ± 46.0 (0 – 377.5)
Ferritin (ng / ml) (n = 233) (Mean ± SD) (min – max)		387.8 ± 468.0 (7.6 - 2465.5)
AST (U / l) (Mean ± SD) (min – max)		26.6 ± 18.4 (6 – 134)
ALT (U / l) (Mean ± SD) (min – max)		27.9 ± 23.7 (4 – 255)
cTnT (pg / ml) (Mean ± SD) (min – max)		26.0 ± 198.3 (3 – 3089)
Pro BNP (pg / ml) (n = 87) (Mean ± SD) (min – max)		1718.3 ± 4931.0 (5 – 36000)
INR (n = 198) (Mean ± SD) (min – max)		1.1 ± 0.2 (0.8 – 3.7)
Patients with chest X-ray presentation n (%)		197 (67.7)
Patients with thorax CT presentation n (%)		269 (95.4)
Mean length of hospital stay (days) (Mean ± SD)		8.9 ± 0.4
Mean follow-up period (days) (Mean ± SD) (min – max)		140.4 ± 2.3 (2 – 182)
Mortality n (%)		29 (10)

PCR: Polymerase chain reaction; AST: Aspartate transaminase; ALT: Alanine transaminase; cTnT: High sensitive cardiac troponin T; CRP: C- reactive protein; Pro BNP: N-terminal prohormone B-type natriuretic peptide; INR: International Normalized ratio; aPTT: Activated partial thromboplastin time; CT: Computerized tomography

Table 2. Comparison of clinical and demographic data of patients who died and survived. (n=291)

Variables		Died n = 29	Survived n = 262	P value
Age (mean ± sd) (min - max)		64.6 ± 12.7	51.5 ± 14.6	**< 0.001**
Gender n (%)	Female	9 (31.0)	109 (41.6)	0.271
	Male	20 (69.9)	153 (58.4)	
Patients with comorbidity n (%)		24 (85.7)	129 (50.2)	**< 0.001**
PCR status n (%)	Negative	10 (34.5)	117 (44.7)	0.295
	Positive	19 (65.5)	145 (55.3)	
Median cTnT (pg / ml)		16.4 (3.0 - 3089.0)	3.9 (3.0 – 355.7)	**< 0.001**
Median Pro BNP (n = 87) (min - max)		947.7 (92.0 - 36000.0)	83,3 (5,0 – 17924.0)	**0.001**
Median leukocyte (x 10^3 / ul) (min - max)		9.1 (3.8 - 31.6)	6.3 (2.6 - 30.9)	**0.002**
Median Platelets (x 10^3 / ul) (min - max)		295 (65 - 645)	226 (75 - 840)	**0.019**
Median AST (U / l) (min - max)		29.0 (10.0 – 132.0)	19.0 (6.0 – 134.0)	**0.005**
Median ALT (U / l) (min - max)		23.0 (4.0 – 81.0)	24.9 (5.0 – 255.0)	0.994
Median CRP (mg / dl) (min - max)		13.4 (0.6 – 340.5)	4.1 (0.0 – 377.5)	**< 0.001**
Median INR (n = 198) (min - max)		1.1 (0.9 – 1.5)	1.0 (0.8 – 3.7)	**0.001**
Median length of hos. stays (days) (min - max)		12.0 (1.0 - 45.0)	6,0 (1.0 – 38.0)	**< 0.001**
Median follow-up period (days) (min - max)		28.0 (2.0 – 125.0)	153.0 (31.0-182.0)	**< 0.001**

PCR: Polymerase chain reaction; AST: Aspartate transaminase; cTnT: High sensitive cardiac troponin T; ALT: Alanine transaminase; CRP: C- reactive protein; Pro BNP: N-terminal prohormone B-type natriuretic peptide

Table 3. Diagnostic value of cTnT and other parameters to predict mortality (ROC analysis)

Variables	AUC	95%CI	P value	Cut-off	sensitivity	specificity
Age	0.750	0.664-0.836	<0.001	49.50	89.7%	43.5%
cTnT	0.831	0.755-0.907	<0.001	5.83	82.8%	66.4%
Leucocyte	0.673	0.566-0.779	0.002	7750.0	65.5%	65.3%
Platelet	0.632	0.505-0.760	0.019	267500	62.1%	68.3%
CRP	0.682	0.579-0.785	0.001	8.46	58.6%	66.8%
AST	0.660	0.555-0.765	0.005	26.50	62.1%	67.8%

cTnT: Cardiac troponin T; CRP: C-reactive protein

Table 4. Cox regression analysis for the predictive values of the parameters for mortality

	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age						
<49.5 vs >49.5	6.179	1.870-20.416	0.003	3.167	0.676-14.830	0.184
Comorbidity (+) vs (-)	5.551	1.912-15.885	0.002	2.297	0.747-7.067	0.147
cTnT						
<5.83 vs.>5.83	8.457	3.226-22.171	<0.001	4.069	1.410-11.739	**0.009**
Leucocyte						
<7750 vs. >7750	3.333	1.550-7.169	0.002	1.655	0.677-4.048	0.269
Platelets						
<267.5 vs.>267.5	3.219	1.520-6.819	0.002	1.815	0.766-4.303	0.176
CRP						
<8.46 vs. >8.46	2.576	1.198-5.540	0.015	1.252	0.563-2.763	0.582
AST						
<26.5 vs >26.5	3.179	1.501-6.732	0.003	2.754	1.248-6.081	**0.012**

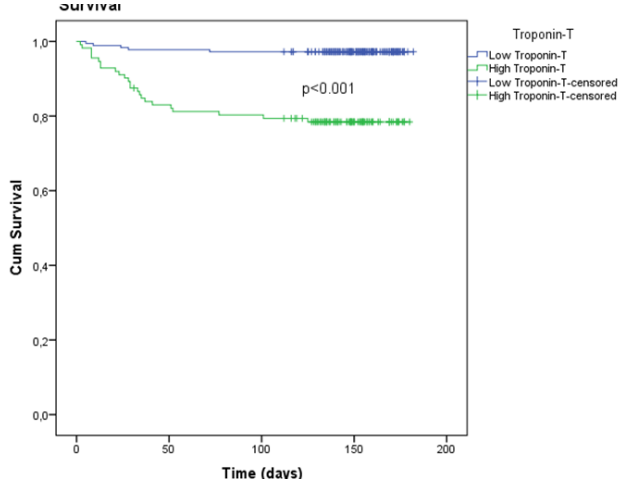

Figure 3. Kaplan-Meier analysis for patients with high and low cTnT (for cut-off value = 5.83 pg / mL)

DISCUSSION

This retrospective study was a comprehensive evaluation of serum cTnT with respect to 4-month all-cause mortality of COVID-19. All-cause mortality rate in four months was 10%. Age, presence of co-morbidity, median cTnT, ProBNP, leukocyte, platelets, AST, CRP, and INR values were higher in patients who died in four months. The prognostic parameters for mortality in 4 months were cTnT and AST. The threshold for cTnT to predict 4-month all-cause mortality was 5.83 pg/ml, which is 41.6% of the reference value, with a sensitivity of 82.8% and specificity of 66.4% (OR: 9.5, 95% CI 3.5-25.7, $p < 0.001$). The patients with cTnT higher than 5.83 pg/ml had shorter survival times. This trait was present for all four months. The threshold for AST to predict 4-month all-cause mortality was 26.5 U/l.

One of the first series reported from Wuhan (6), shows that patients with high cTnI are older and have more comorbidities, more laboratory abnormalities (higher levels of CRP, procalcitonin, and AST) and higher mortality rates (51.2 vs. 4.5%). The risk of death is four times higher in patients with myocardial injury at presentation. Other studies have shown that hospitalized patients with more severe disease and worse outcomes (including death, severe presentation, hospitalization in the intensive care unit, and/or mechanical ventilation), have greater frequency and magnitude of troponin elevations (3, 6, 8). Similarly, our study showed that the cTnT and AST values of patients who died were remarkably higher than the ones who survived and these results were compatible with the previous studies.

Cardiac troponin 99th percentile URL levels have been defined for acute MI due to coronary artery occlusion. However, there are other conditions in which troponin levels increase. Potential causes of myocardial injury in patients with COVID-19 are myocarditis (9); hypoxic injury; stress (takotsubo) cardiomyopathy (10); ischemic injury caused by cardiac microvascular dysfunction or epicardial coronary artery disease; right heart strain (acute cor pulmonale due to pulmonary embolism (11), adult respiratory distress syndrome or pneumonia); and systemic inflammatory response syndrome (cytokine storm) (12). However, the contribution of each of these potential causes to myocardial injury has not been determined. Also, there is substantial evidence of an association between preexisting cardiovascular disease and the risk and severity of COVID-19 infection (3). All these potential causes of myocardial injury may be overlapping, and elevated cardiac troponin does not help to differentiate these causes. Usually, the magnitude of troponin elevation in these conditions is often less than what is seen with acute MI due to coronary artery occlusion. We also analyzed the threshold for COVID-19 pneumonia in our study.

Increased cardiac troponin levels have been observed in 7-36% of COVID-19 inpatients (6, 8). Troponin elevation may be initially detected before, simultaneously, or after hospital admission (8). Most commonly, troponin elevation is mild and there are no associated cardiac symptoms (13). Moderate time-limited troponin elevation is seen in patients with clinically suspected myocarditis or stress cardiomyopathy (14). The Clinical status of some patients with moderate troponin elevation deteriorates and respiratory failure and progressive troponin elevation is seen after the second week of hospitalization (13).

There is limited data about prognoses and cardiovascular complications after recovery from COVID-

19. In addition, although reference laboratory cutoff values of cTnT are highly prognostic for in-hospital mortality, COVID-19 proceeds with cardiomyocyte death but causes troponin levels below the reference threshold. Qin et al. (5) shows that the cut-off threshold of 28-day mortality of cTnI is 0.66, which is a value 49% lower than the standard laboratory cut-off value. Similarly, reference laboratory cTnT cut-off value of the assay we used in our study was 14.0 pg/mL. However, the cutoff threshold of cTnT to predict 4-month all-cause mortality was 5.83 pg/mL, which was 41.6% of the reference value.

Some COVID-19 patients have other cardiac test abnormalities without concurrent troponin elevations (15). This may be due to conditions not associated with myocardial injury such as preexisting cardiac diseases or renal failure. Another reason may be a missed troponin level elevation due to troponin elevation below 99^{th} percentile URL thresholds (15). Using standard reference laboratory cutoffs may underestimate the extent of cardiac injury and the prognostic yield of this assay may be reduced. Our study showed that lower thresholds should be considered in COVID-19 pneumonia.

The parameters for 4-month mortality in our study were cTnT concentration and AST value. Although Guo et al. observed a significant positive linear correlation between serum cTnT and plasma C-reactive protein, suggesting a link between the severity of inflammation observed in COVID-19 and myocardial injury (16), we did not find any link between plasma CRP and cTnT concerning mortality in four months. This implied that the mortality was not due to progressive inflammation. It may be because of complications such as arrhythmia, embolism, or right heart strain.

Previous studies also showed that an elevated troponin level was also one of the clinical features associated with in-hospital death. When we analyzed the survival time, we wanted to learn whether the difference in survival time was only due to a higher in-hospital death rate or not. We analyzed this difference between the two groups for their interval in the survival curve and showed that there was a consistently significant survival time decrease in all thirds of the Kaplan-Meier curve. Survival difference was not associated with in-hospital deaths.

The patients who were directly admitted to the intensive care unit in the study were excluded from the study. In the first wave of the pandemics, patients admitted to intensive care unit received therapies such as convalescence plasma, tocilizumab, recombinant IL-1 antagonists, and corticosteroids. They were more severe, hypoxemic, and usually had sepsis and were on mechanical ventilation, hemodialysis and ECMO, which all might be, and cause, confounding factors for cardiac problems. We wanted to have a more homogenous study group. Also, we wanted to analyze patients admitted in the pneumonology wards for COVID-19 pneumonia.

Our study had some limitations. First, this was a single center study, but we included all consecutive patients with COVID-19 pneumonia at the start of pandemic. We conducted the study in a specific pulmonary disease ward of a tertiary hospital in the Aegean region. Therefore, our study group demonstrates mostly moderate and severe COVID-19 patients. Secondly, it was a retrospective non-interventional study; therefore, some of the laboratory data was absent in some of the patients and we could not include them in the study. Thirdly, we did not elaborate on co-morbidities in our analysis. We included chronic obstructive pulmonary disease, coronary heart disease, hypertension, diabetes mellitus, asthma, cerebrovascular disease, and cancer in the "co-morbidity" subtitle; but we analyzed comorbidities as a categorical variable. Fourthly, the study was conducted during the first wave of the pandemic. At that point, the effect of hypercoagulation was not defined, and only after $3\text{-}4^{th}$ months of the pandemic, this point was more emphasized. The patients we studied were those before the routine use of anticoagulation or steroids. Therefore, we studied the records of all initial patients, which were 389 in total, and finally, 291 patients remained eligible. This was the main reason that we chose the "4-month period", not more, to determine the role of hs-cTnT. The patients were followed

up by telephone for vital status, however, we could not obtain information about the heart-specific cause of death, or mode of their death (for example sudden, cardiac, or non-cardiovascular). Thus, we analyzed all-cause mortality and survival durations. Another limitation was that we should have presented other confounding factors. However, we presented the available factors. The study should have been designed to elaborate on these factors.

CONCLUSION

As a result of emerging studies, new data is continuously added to our knowledge about the clinical course of COVID-19. Also, the long-term effects of COVID-19 infection have become increasingly recognized and concerning. Our study provides some information about the long-term effects of COVID-19 infection. In conclusion, the all-cause mortality rate in four months is 10%. cTnT and AST are parameters that predict mortality. The cutoff value for cTnT to predict 4-month all-cause mortality is 5.83 pg/ml and it is 41.6% of the reference value. The patients with cTnT values higher than 5.83 pg/ml have shorter survival times and this trait remains the same for all four months. . The threshold for AST to predict 4-month all-cause mortality was 26.5 U/l. It is interesting that outcomes of a pulmonary disease are predicted by cardiac biomarkers, but cardiovascular system should not be ignored when evaluating the long-term effects and prognosis of COVID-19 infection.

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