Correlation of Cardiac Biomarkers with Computed Tomography Severity Score in Covid-19 Patients

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Abstract

INTRODUCTION: A vast number of COVID-19 cases have been reported worldwide since the initial outbreak in China, and the disease has since become a global pandemic. Knowledge on this predominantly respiratory illness is evolving with studies suggesting myocardial injury reflected by elevated cardiac enzymes portending to more severe disease. CT scoring indices provide visual, semi-quantitative assessment of lung involvement and have aided in determining extent of COVID-19 pneumonia but, none have been validated for prognostication. Establishing a relationship between these non-invasive diagnostic parameters could provide timely identification and proper allocation of limited medical resources to patients in need of more aggressive therapy.

METHODS AND RESULTS: A total of 50 COVID-19 patients were retrospectively enrolled and their clinical parameters collected from an electronic medical database. There was a total of 31 patients with troponin I-HS with chest CT scan done and another 42 patients for NT-proBNP and chest CT. The levels of both cardiac biomarkers in patients with clinically severe COVID pneumonia were higher than those with mild and moderate disease. Rank-order analysis showed that both troponin I-HS (moderate, $p=0.0003174$) and NT-proBNP (moderate, $p=0.006255$) correlated positively with CT severity scores. Furthermore, there is a significant relationship between mortality and septic shock with both Troponin I-HS ($p<0.001$; $p=0.002$) and NT-proBNP ($p=0.004$; $p=0.031$).

CONCLUSION: The cardiac markers troponin I-HS and NT-proBNP increased significantly at more severe CT scores and more notably, these biomarkers predicted the development of septic shock and mortality in COVID-19 pneumonia.

KEYWORDS: Cardiac Biomarkers, Chest CT, COVID-19, CT Severity, NT-proBNP, Troponin I

INTRODUCTION

COVID-19 is the most recent health crisis affecting the world today. It is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first reported in Wuhan, the capital city of Hubei province in China late last year. Since then, it has spread worldwide, resulting in a continuing pandemic. While most patients show mild symptoms, there have been a number of severe cases warranting ventilatory support and prolonged hospital stays – posing major challenges for the healthcare system globally.[1]

The virus is mainly spread between people during close contact through aerosolized droplets produced by talking, coughing or sneezing. Most patients with COVID-19 are either asymptomatic or present with fever and respiratory symptoms like shortness of breath or coughing. DOH has established a management algorithm classifying the infection based on clinical severity describing mild disease as having a 1) respiratory rate (RR) of <30 breaths/min, 2) oxygen saturations (spO_2) ≥ 93% without external oxygen support, and 3) without any signs of sepsis or respiratory distress while any other infection that doesn't satisfy these three criteria are classified as severe COVID-19 infection.[2-6]

Knowledge on this predominantly respiratory illness is evolving with some studies suggesting myocardial injury as reflected by elevated cardiac enzymes portending to more severe disease and a more protracted course of illness.[3,4] An observational study in Wuhan, China, reported approximately 20% of COVID-19 patients with cardiac injury which was seen as an independent cause of in-hospital mortality. Death in those with cardiac injury was substantially higher (51.2%) relative to patients without cardiac involvement (4.5%).[7] However, the underlying reasons for the increase of these often-assayed laboratory tests are poorly understood; and, there have been no published data as of this writing that correlates CT severity scores with these cardiac biomarkers (troponin I-HS and BNP/NT-proBNP).

Chest CT scans have been used for the early detection of the viral pneumonia and assessment of disease progression.[6] CT involvement scores provide visual, semi-quantitative assessment of lung involvement. There have been several modifications of the scoring indices and all of them have used visual estimates (in percentages) of the lungs as a whole or by lobe to help determine the extent of COVID-19 pneumonia.[2] But, none have been validated for the diagnosis or in the risk-stratification of the disease.

Establishing a relationship between these two diagnostic parameters (Computed Tomography imaging manifestations and myocardial injury based on cardiac biomarkers) in COVID-19 patients could help predict the course of the disease which in turn provides prompt classification and improvement of the prognosis of patients.

METHODS

Study Design and Sample Population

Approval from the hospital's Clinical and Translational Research Institute (CTRI) as well as the Institutional Review Board (IRB) was obtained prior to conduct of the study. A total of 386 medical records of COVID-19 RT-PCR positive adults admitted in the hospital from March 2020 up to July 2020 were retrospectively reviewed. After all the patients who had 1) debilitating diseases prior to admission causing them to be chronically bed-bound, 2) terminal cancer, 3) end-stage liver disease, 4) end-stage kidney disease 5) pregnant patients, and 6) those who have been recently admitted (within 3 months) due to an acute cardiovascular event had been excluded, data on 50 patients with a chest CT scan done along with either a serum Troponin I-HS or BNP/NT-proBNP level requested were gathered.

Data Collection

Pre-recorded data on the patients' history of exposure, demographics, symptoms, co-morbidities, chest CT scan findings and clinical outcomes were collected. The hospital system's pre-designated personal identification numbers were used as patient identifiers along with their respective birthdates and ages. COVID-19 severity was classified as mild or severe based on the current definitions from the Department of Health which take into account the respiratory rate, oxygen saturations at room air, the need for oxygen support, clinical signs of respiratory distress, age, presence or absence of sepsis, and co-morbid conditions.

Chest CT severity scoring parameters were adapted from previous investigations for COVID-19 which involved assigning points based on qualitative estimation of lung involvement. This involved assigning corresponding points based on estimated lung involvement: 0 points for no involvement, 1 point for less than 5% involvement, 2 points for 5% to 25% involvement, 3 points for 26% to 49% involvement, 4 points for 50 to 75% involvement, and 5 points for more than 75% involvement. The semi-quantitative radiographic scoring was determined by a boarded radiologist blinded from any of the other collected chart data.

All requested troponin I-HS and BNP/NT-proBNP levels were collected. Final clinical data were followed up until July 31, 2020.

Statistical Analysis

The Raosoft sample size calculator, at a 95% confidence level and 50% response distribution, determined a minimum required sample size of 46 to test significant correlation between CT severity score and level of cardiac biomarkers.

Categorical variables are presented in percentages or frequencies as appropriate. Independent samples t-test was used to compare the significant differences of troponin and BNP/NT-proBNP levels per category of chest CT score. The correlation of troponin I-HS and BNP/NT-proBNP with the CT

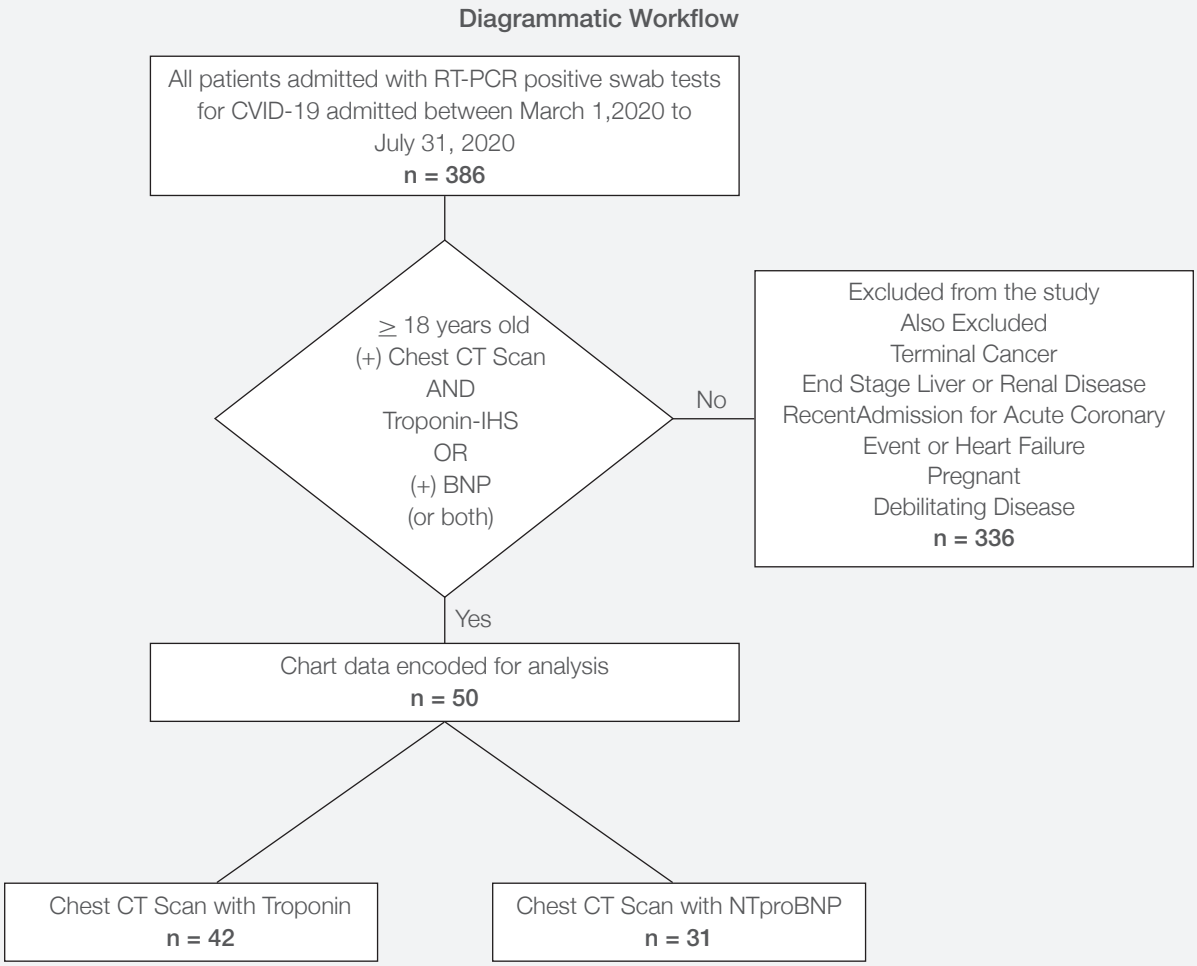

Figure 1. Diagrammatic Workflow of the Study.

percentages index scores was analyzed using Spearman's rank-order correlation test and assessed via scatterplot. All tests of significance are at $P < 0.05$ level. Medcalc Statistical Software was used to carry out all statistical analyses.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 50 COVID-19 positive patients were retrospectively enrolled in the study. As shown in Table 1, the average age of the admitted patients is 62. A majority (62%) were male. Most of the patients acquired the viral illness from community exposure (76%) with cough (66%), fever (54%) and shortness of breath (38%) as the most common presenting symptoms.

The overall BMI is slightly above normal at 25 kg/m^2. The predominant comorbidity is hypertension found in 60% of the cases followed by diabetes (42%) and kidney disease (24%). Majority of the cases initially presented with moderate disease (72%). A total of 24 patients went into respiratory failure over the course of their admission (48%) while 15 patients (30%) experienced shock from sepsis. Most of the cases were discharged (60%) while 40% of the patients enrolled in the study eventually expired.

3.2 Relationship Between Clinical Severity and Outcomes with Cardiac Biomarkers

Table 2 illustrates that there is no significant relationship between clinical severity upon admission and troponin I-HS. There is however, a significant relationship between mortality and an elevated level of troponin I-HS based on a predetermined laboratory cutoff of the 99th percentile upper limit of normal ($p < 0.001$). This implies that there are more patients who died when their troponin I-HS was above 15ng/mL. The same relationship can be appreciated between elevated troponin and the development of septic shock during the course of admission.

Similar results are seen in COVID-19 patients with NT-proBNP values above a predetermined cutoff of 200 pg/mL (Table 3). The data shows that both mortality and septic shock are significantly dependent with the level of NT-proBNP. There were 21 patients with NT-proBNP levels below 200 pg/mL who did not go into septic shock while 40% of the patients who had a NT-proBNP value of 200 pg/mL and below ended up alive and discharged ($p = 0.031$).

Relationship Between Clinical Severity and Outcomes with CT Severity Score

As shown in table 4, the CT Severity Score has a significant relationship with clinical severity on admission (p = 0.003) Most of the patients presenting with moderate COVID-19 disease had CT level 1 scores (38%). There were five patients with CT level 2 scores (15%), 6 patients with CT level 3 scores (15%) and 2 patients with level 4 CT scores (5%) who came in initially presenting with moderate COVID-19.

There were 6 patients with a level 3 CT severity score who were managed as septic shock during their course of admission

Table 1. Demographics and laboratory characteristics of patients with COVID-19 who had a CT Scan and cardiac biomarkers done during their hospital stay.

Demographic/Laboratory Characteristics	Trop I-HS n = 42	NT-proBNP n = 31	Overall n = 50
Age (in years)			
Median	61.5	64.0	62.0
Range	65.0	65.0	65.0
Sex			
Male	25 (50%)	20 (40%)	31 (62%)
Female	17 (34%)	11 (22%)	19 (38%)
Body Mass Index			
Median	24.5	25.8	25.0
Range	19.6	17.4	19.6
Comorbidities			
Diabetes	18 (36%)	12 (24%)	21 (42%)
Hypertension	24 (48%)	22 (44%)**	30 (60%)
Coronary Artery Disease	5 (1%)	3 (6%)	5 (10%)
Chronic Kidney Disease	11 (22%)	5 (1%)	12 (24%)
Others	26 (52%)	19 (38%)	29 (58%)
Exposure History			
Travel	1 (2%)	1 (2%)	1 (2%)
Household	3 (6%)	2 (4%)	3 (6%)
Healthcare	1 (2%)	1 (2%)	2 (4%)
Community	31 (32%)	24 (48%)	38 (76%)
Unknown	6 (12%)	3 (6%)	6 (12%)
Presenting Symptoms (Upon Admission)			
Fever	21 (42%)**	19 (38%)**	27 (54%)
Cough	30 (60%)**	22 (44%)	33 (66%)
Shortness of Breath	16 (32%)**	11 (22%)	19 (38%)
Diarrhea	6 (12%)	2 (4%)	7 (14%)
Others	18 (36%)**	11 (22%)	21 (42%)
D-Dimer			
Median	0.81	0.87	0.84
Range	3.8	3.8	3.8
Severe Disease			
Invasive Ventilation	20 (40%)	17 (34%)	24 (48%)
Septic Shock	13 (26%)	11 (22%)	15 (30%)
COVID-19 Clinical Severity (on Admission)			
Mild	3 (6%)	2 (4%)	3 (6%)
Moderate	29 (58%)	20 (40%)	36 (72%)
Severe	7 (14%)	6 (12%)	8 (16%)
Clinical Outcome			
Discharged	25 (50%)	16 (32%)	30 (60%)
Death	17 (34%)	15 (30%)	20 (40%)
*Significantly different medians at 0.05 level, Mann-Whitney U **Significantly dependent at 0.05 level, Chi-square			

Table 2. Relationship of Clinical Severity and Outcomes with Troponin I-HS

Laboratory Characteristic	Troponin I-HS		*p*-value
	15 and below	Above 15	
COVID-19 Clinical Severity			
Mild	1 (2.1%)	2 (4.3%)	0.140
Moderate	22 (46.8%)	14 (29.8%)	
Severe	2 (4.3%)	6 (12.8%)	
Mortality			
Alive	22 (44%)	8 (16%)	< 0.001*
Deceased	5 (10%)	15 (30%)	
Septic Shock			
Present	3 (6%)	12 (24%)	0.002*
Absent	24 (48%)	11 (22%)	
*Significantly dependent at 0.05 level, Chi-square			

Table 3. Relationship of Clinical Severity and Outcomes with NT-proBNP

Laboratory Characteristic	NT-proBNP		*p*-value
	200 and below	Above 200	
COVID-19 Clinical Severity			
Mild	3 (6.4%)	0 (0%)	0.072
Moderate	20 (42.6%)	16 (34%)	
Severe	2 (4.3%)	6 (12.8%)	
Mortality			
Alive	20 (40%)	10 (20%)	0.004*
Deceased	5 (10%)	15 (30%)	
Septic Shock			
Present	4 (8%)	11 (22%)	0.031*
Absent	21 (42%)	14 (28%)	
*Significantly dependent at 0.05 level, Chi-square			

Table 4. Relationship of Clinical Severity and Outcomes with CT Severity Score

Laboratory Characteristic	CT Severity						p-value
	0 (0%)	1 (1 to 5%)	2 (>5 to 25%)	3 (>25 to 50%)	4 (>50 to 75%)	5 (>75%)	
COVID-19 Clinical Severity							
Mild	0 (0%)	3 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.003*
Moderate	2 (5%)	15 (38%)	5 (15%)	6 (15%)	2 (5%)	0 (0%)	
Severe	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (10%)	
Mortality							
Alive	2 (5%)	18 (42%)	3 (7%)	1 (2%)	1 (2%)	0 (0%)	< 0.001*
Deceased	0 (0%)	2 (5%)	4 (9%)	6 (14%)	1 (2%)	5 (12%)	
Septic Shock							
Present	0 (0%)	1 (2%)	3 (7%)	6 (14%)	0 (0%)	4 (9%)	< 0.001*
Absent	2 (5%)	19 (44%)	4 (9%)	1 (2%)	2 (5%)	1 (2%)	
*Significantly dependent at 0.05 level, Chi-square							

Table 5. Correlation of Cardiac Biomarkers (Troponin I-HS, BNP/NT-proBNP) with the Chest CT Severity Score of COVID 19 patients

Cardiac Biomarkers	Spearman *rho*	Direction	Strength	*p*-value
Troponin I-HS	0.53	Positive	Moderate	0.0003174*
BNP/NT-proBNP	0.54	Positive	Moderate	0.006255*
*Significant *p*-value at 0.05 level				

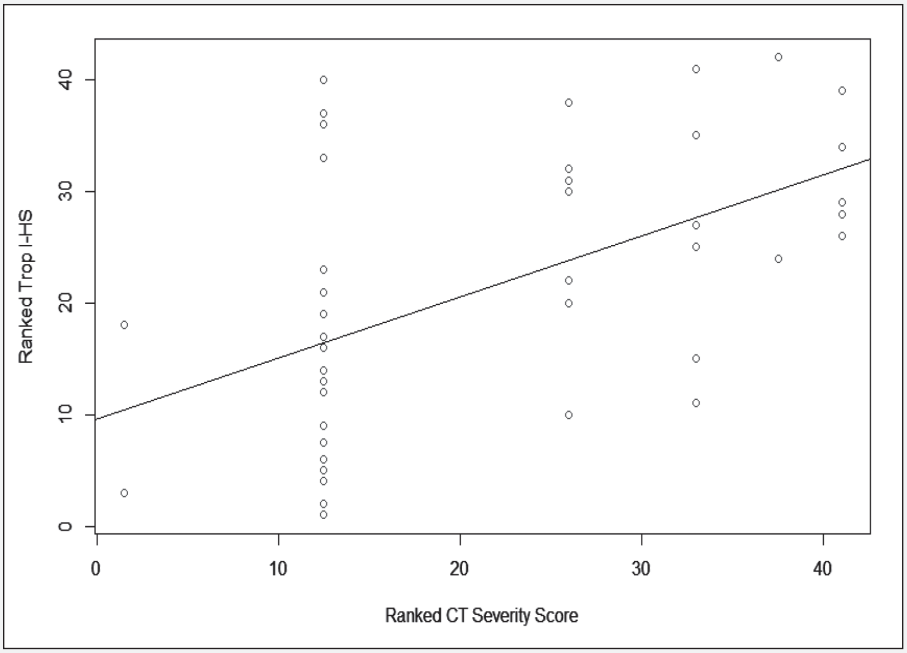

Figure 2. Correlation analysis between CT severity scores and Troponin I-HS

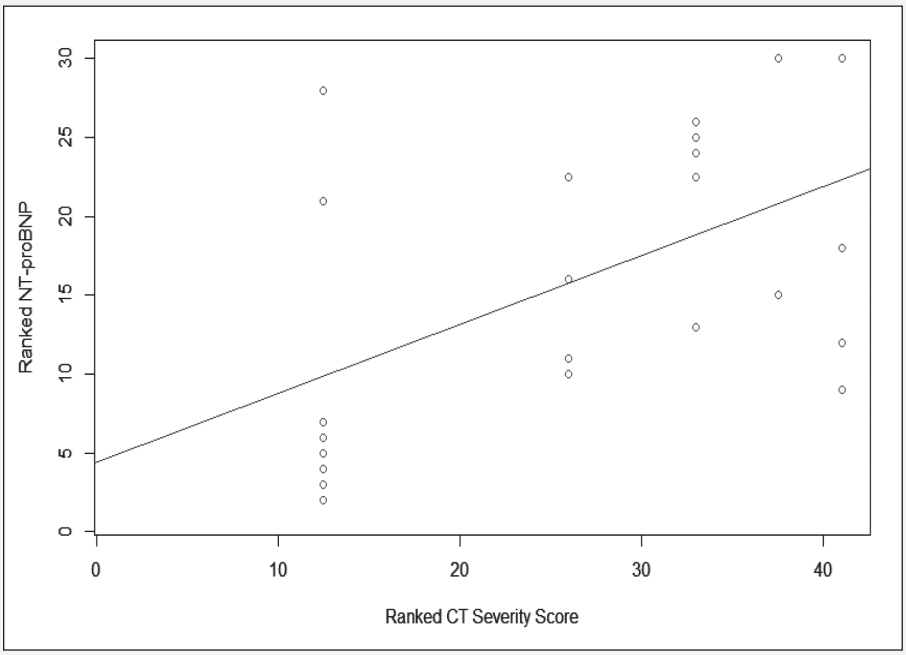

Figure 3. Correlation analysis between CT severity scores and NT-proBNP/BNP

while 18 patients (42%) with level 1 CT severity scores did not experience septic shock. It can be inferred that the higher the level of CT severity (level 2 to 5), the more likely the patient experiences septic shock ($p < 0.001$).

There were 18 patients (42%) who were eventually discharged with a level 1 CT severity score while those who wound up dead during the hospital course mostly had CT severity scores of 3 or 5 (14% and 12% respectively). There was a significant correlation between CT severity score and mortality ($p < 0.001$).

Analysis of Correlation between CT Severity Scores and Cardiac Biomarkers

Spearman's rank analysis was done to investigate the relationship between the Troponin I-HS (Table 5 and Figure 2) and the semi-quantitative CT Score as well as BNP/NT-proBNP levels and the CT Severity Score (Table 5 and Figure 3) Data clearly shows a positive and significant relationship between either cardiac biomarker (Troponin I-HS and NTproBNP) and the patients' chest CT severity score ($p = 0.0003174$ and $p = 0.006255$ respectively).

DISCUSSION

One of the most effective strategies to address the global COVID-19 predicament is delivering timely diagnosis and treatment which has been shown to reduce the time to resolution of COVID-19.[8] It is therefore crucial to establish validated clinical and laboratory parameters that can help in diagnosing the disease and predicting disease severity.

This observational study has shown that elevated levels of troponin I-HS did not predict clinical severity on admission. However, it did have a significant correlation with the development of septic shock and mortality which is consistent with most of the aforementioned studies in China. This implies

that this cardiac biomarker has the potential to predict disease outcomes during the course of admission regardless of the clinical status on initial presentation.

Similar inferences can be drawn out from the statistical analysis of COVID-19 patients and NT-proBNP values. Elevated levels of this cardiac biomarker did not translate to more severe illness upon admission. Though, it did have a significant relationship with the development of septic shock and death. Analogous to elevated troponin I-HS, NT-proBNP also has the potential to provide a means of prognosticating patients coming in for admission regardless of initial disease severity.

The Chest CT Scoring Index on the other hand, did have a significant relationship with COVID-19 severity upon admission as well as predict patients who would eventually go into septic shock or expire.

Rank correlation analysis of either troponin I-HS or NT-proBNP to their respective chest CT severity scores showed a positive, significant relationship ($p = 0.0003174$ and $p = 0.006255$ respectively). This implies that as either biomarker goes higher, the CT severity score also increases. It can be hypothesized based on this observation that there is myocardial involvement in some COVID-19 pneumonia cases which consequently portends to a poorer prognosis.

LIMITATIONS

Data patterns that were analyzed could have been confounded given the observational and retrospective nature of the study. Information drawn from the study would have been more impactful if the CT scans and cardiac biomarkers were done at similar points over the course of the patients' hospital stays. Also, this study retrospectively reviewed patients who were managed during the earlier stages of the pandemic where there were no structured algorithms for treating, establishing therapeutic targets, or prognosticating cases. The lack of standardized management of COVID-19 at the time could have potentially skewed the clinical outcomes as well as dramatically limiting the sample size. Furthermore, statistical analysis did not account for the risk factors that have been recently established as contributors to prognosis i.e. diabetes, obesity, and age.

CONCLUSION

In patients with COVID-19 pneumonia, elevation of troponin I-HS and NT-proBNP were associated with more severe CT scores, development of septic shock, and higher mortality.

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