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The assessment of high sensitivity cardiac troponin in patients with COVID-19: A multicenter study

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ABSTRACT

Background: Recent studies have shown that patients diagnosed with coronarivus disease 2019 (COVID-19) and also with previous cardiovascular diseases have a higher mortality due to worsening heart disease. At the same time, patients without previous cardiovascular disease may also have cardiac complications. The aim of this multicenter study was to assess high sensitivity cardiac troponin T (hs-cTnT) in patients with COVID-19 and to evaluate the incidence of myocardial injury.
Methods: In this multicenter study we enrolled 543 patients, 57.8% males, median age 63 years (range 18–99) from three selected hospitals: University Hospital Tor Vergata in Rome, Fondazione IRCCS Ca 'Granda Ospedale Maggiore Policlinico, in Milan, S Chiara Hospital in Trento. We measured hs-cTnT in all patients to assess myocardial injury and correlations with patient's age, symptoms and disease course.
Results: The data showed that, among the 543 patients studied, 257 patients (47.3%) had hs-cTnT values higher than the upper reference limit (URL) of 14 ng/L. Patients with high hs-cTnT had more frequently fever ($p < 0.01$) and respiratory symptoms ($p < 0.01$), compared to the group with hs-cTnT values below URL. The results showed also that patients with hs-cTnT above URL had a higher frequency of previous cardiovascular disease ($p < 0.01$) as well as of hypertension ($p < 0.01$). Instead, among 231 patients with no previous cardiovascular disease, 81 (31.5%) had hs-cTnT values above the URL. Finally. the majority of the patients with high hs-cTnT were admitted to the intensive care unit ($p < 0.01$).
Conclusion: Our data suggest the assessment of high sensitivity cardiac troponin in patients with COVID-19 for early diagnosis of cardiac involvement.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a severe pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has led to 435,000 deaths worldwide today [1]. In 15% of infected patients the clinical course of this pathology can be complicated by the onset of a serious form of interstitial pneumonia, which can therefore progress towards acute respiratory distress syndrome (ARDS), multi-organ failure (MOF) and death [2]. Italy was one of the countries most affected by COVID-19 with 238,000 infections and 34,400 deaths [3].

Although at the beginning of the pandemic the cardiovascular system appeared not to be particularly affected by the virus, more recent studies have shown that patients with previous cardiovascular diseases or with cardiovascular risk factors had a higher mortality rate than patients without previous cardiovascular diseases [4,5]. Furthermore, several studies have shown that also patients with COVID-19, who had no heart disease before the infection, can have cardiac complications [6–8].

Early diagnosis of cardiac complications in these patients is possible through the measurement of cardiac troponin which is considered the gold standard marker for myocardial injury [9]. In fact, since their discovery, cardiac troponins have gradually acquired greater clinical relevance in the diagnosis, treatment and prognosis of patients with cardiovascular diseases [9,10]. In particular, the most recent international guidelines recommend the use of high sensitivity cardiac troponin I (hs-cTnI) and T (hs-cTnT) in the

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diagnosis of myocardial damage and acute myocardial infarction [11,12]. However, there are still few studies on the role of high sensitivity cardiac troponins in patients with COVID-19 and although Italy is one of the countries most affected by this health emergency, very few studies so far has evaluated the concentration of high sensitivity cardiac troponin in Italian patients diagnosed with COVID-19. The aim of this study was to evaluate hs-cTnT in patients with COVID-19 and estimate myocardial injury in these patients.

2. Methods

In this multicenter study we enrolled 543 patients, 57.8% males, median age 63 years (range 18–99) from three selected hospitals: University Hospital Tor Vergata in Rome, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, in Milan, S. Chiara Hospital in Trento between 1 and 31 March 2020. All patients had an ascertained diagnosis of COVID-19 with rhinopharyngeal swab and molecular biology (RT-PCR) methods to search for virus RNA. All patients underwent hs-cTnT evaluation. At the time of the collection, the patients were hospitalized in intensive care or in a COVID unit (hospital wards dedicated to the non-invasive treatment of patients with COVID-19 or in the observation unit of the emergency department where, following a positive diagnosis, proceeded short observation [24–43] after which, according to the symptoms, hospitalization or home monitoring was scheduled. The collection of blood samples was carried out by venipuncture, and the sample was immediately transported to the department of laboratory medicine where it was centrifuged and immediately analyzed. The concentration of hs-cTnT was assessed by means of a high sensitivity immunoassay (limit of detection 3 ng/L, 10% CV at a concentration of 6.1 ng/L) on the Cobas platform (Roche Diagnostics, Mannheim, Germany). The study was approved by the local ethics committee and all patients entering the hospital signed an informed consent. The study was conducted in accordance with the Declaration of Helsinki

3. Statistic analysis

Data from groups of patients were analysis using a statistical software package (MedCalc, version 10.2.0.0, bvba, Ostend, Belgium). Chi-square test was used to compare the incidences of different parameters between the groups of patients. A p-value < 0.05 was considered statistically significant.

4. Results

The hs-cTnT concentration was measured in all patients after hospital admission, immediately after the diagnosis of COVID-19 with the nasopharyngeal swab. Based on the clinical conditions, the patients were hospitalized in the different wards. The data showed that, among the 543 patients studied, 257 patients (47.3%) had hs-cTnT values higher than the 99th percentile upper reference limit (URL) of 14 ng/L. Table I shows the different cardiovascular complications of patients with hs-cTnT values above URL. We then compared the two groups of patients (hs-cTnT values below URL vs values above URL). In the group of patients with hs-cTnT below URL only 12 (4.19%) had hs-cTnT values < 3 ng/L (limit of detection). Statistical analysis showed that the age of the patients was significantly higher in the troponin T group above the URL (median age 73 vs 56 years, range 18–99 and 18–95; $p < 0.01$). We therefore analyzed the symptoms of the patients and the correlation with the levels of hs-cTnT. Our data showed that patients in the group with high hs-cTnT had more frequently fever ($p < 0.01$) and respiratory symptoms ($p < 0.01$), compared to the group with hs-cTnT values below URL. At the same time, we also found a significant difference in the number of patients with anosmia/dysgeusia between patients with high troponin T, compared to the other group ($p < 0.05$). While we did not find significant differences between the two groups regarding the other symptoms (gastrointestinal symptoms, dermatological rush) (Fig. 1). Another interesting result of our study is that patients with hs-cTnT above URL had a higher frequency of previous cardiovascular disease ($p < 0.01$) as well as of hypertension ($p < 0.01$) (Fig. 2A). While data showed that among 231 patients with no previous cardiovascular disease, 81 (31.5%) had hs-cTnT values above the URL (Fig. 2A). We also analyzed the wards where the patients were hospitalized and the majority of the patients with hs-cTnT above URL were admitted to the intensive care unit ($p < 0.01$) (Fig. 2B). In fact, among 111 patients admitted to intensive care, 96 (86.5%) showed high levels of hs-cTnT. Finally, we analyzed the epidemiological data on mortality provided by the health management of our hospitals. Among the 543 patients studied, 34 (6.2%) died. Among these patients 22 (64.7%) were part of the group with cardiac troponin values above URL, while the other 12 (35.3%) were part of the group of patients with normal troponin levels. In particular, among the 22 patients in the group with hs-cTnT above URL 11 (50%) had heart failure/cardiogenic shock, 2 (9%) myocarditis, 5 (22.8%) arrhythmias, 3 (13.7%) pulmonary thromboembolism, 1 (4.5%) acute coronary syndrome.

5. Discussion

The aim of our study was to investigate the role of hs-cTnT measurement in patients diagnosed with COVID-19.

Among 543 patients studied we found that 257 patients (47.3%) had hs-cTnT values above the 99th percentile upper reference limit (URL) of 14 ng/L. The document Fourth Universal Definition of Myocardial Infarction [13] states that "the term myocardial injury should be used when there is evidence of elevated cardiac troponin values with at least one value above the 99th percentile upper reference limit (URL)". Therefore, we have shown that according to this document almost half of our patients had cardiovascular involvement.

Table 1 shows the cardiovascular complications in the patients studied. Not all patients, due to clinical conditions, underwent multimodal imaging techniques (echocardiogram, cardiac magnetic resonance, cardiac CT, coronary angiography). Patients with cardiac troponin elevation in the absence of obvious differential diagnosis were considered to have myocardial injury in accordance with the document Fourth Universal Definition of Myocardial Infarction [13]

Our data showed that patients with hs-cTnT above URL were more frequently hospitalized in intensive care, demonstrating a more critical course of the disease. At the same time, we showed that patients with high hs-cTnT were older, and more frequently affected by previous cardiovascular diseases and hypertension. Several studies have shown that patients with previous cardiovascular disease had a more severe course of COVID19 [4,5,14]. In particular, the recent study by the Chinese Center for Disease Control and Prevention on 72.314 COVID-19 cases, reported a 10.5% mortality in patients with pre-existing cardiovascular disease, a 7.3% in those with diabetes versus an overall mortality of 2.3% [15]. In heart patients coronavirus infection and systemic inflammation can lead to cardiac complications through numerous mechanisms, such as the instability of a pre-existing coronary atherosclerotic plaque, tachycardia with increased wall stress, hypoxia, the release of inflammatory cytokines (cytokine storm), sympathetic hypertonia with consequent effects on vascular tone, arrhythmias and a

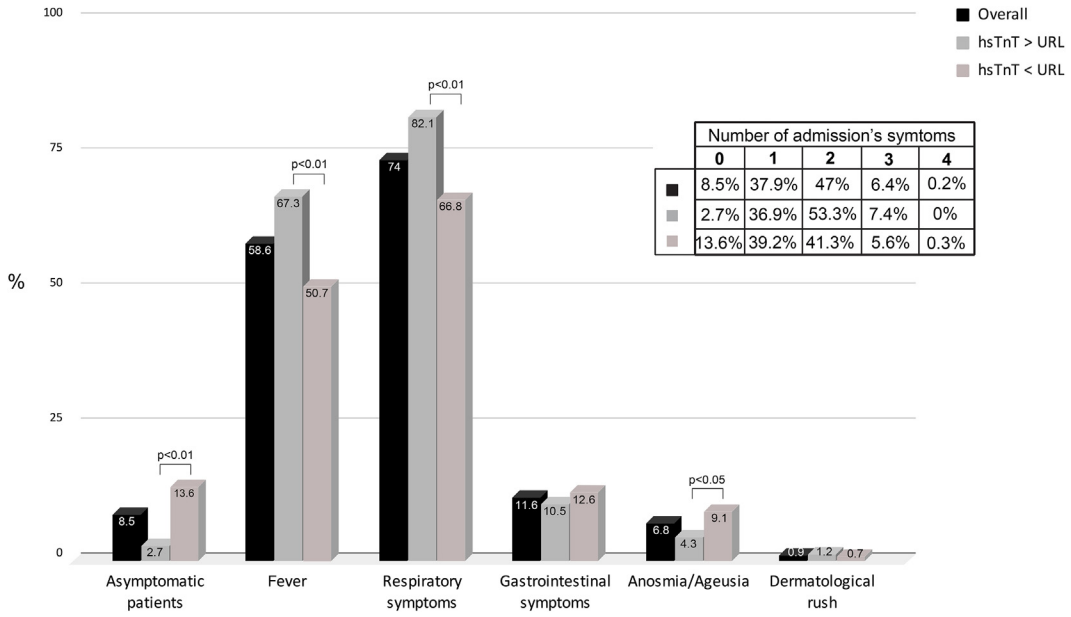

Fig. 1. Differences in symptoms in Covid19 patients based on hs-cTnT values.

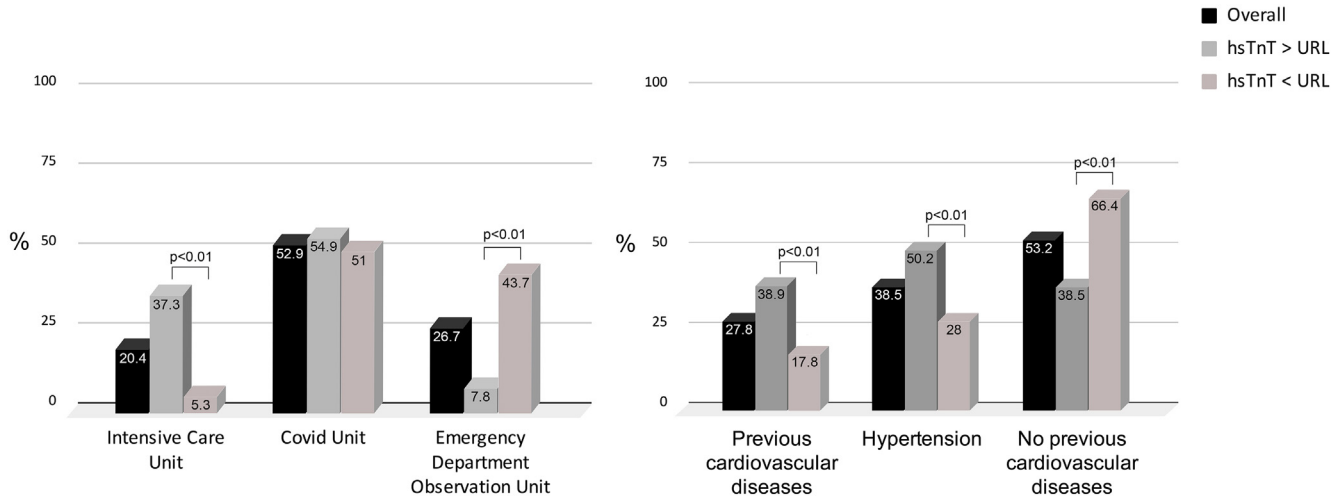

Fig. 2. (A) distribution of patients based on the presence/absence of previous cardiovascular diseases and hypertension with hs-cTnT values. (B) Different distribution in the hospitalization units of patients based on hs-cTnT values.

Table 1
The table shows the cardiovascular complications in the patients studied.

Cardiovascular complications	Number of patients (257) (%)
Myocarditis and pericarditis	18 (7%)
Acute coronary sindromes	4 (1,6%)
Arrhythmias	47 (18,3%)
Heart failure/cardiogenic shock	36 (14%)
Pulmonary thromboembolism	9 (3,5%)
Stroke	1 (0,3%)
Myocardial injury	142 (55,3%)

state of increased thrombophilia, also responsible for pulmonary thromboembolism [16–18].

While the first published studies have shown an increased vulnerability of patients with previous cardiovascular diseases [14,15], more recent studies have shown cardiac complications even in patients who did not have cardiovascular disease before viral infection [19,20]. In particular in our study we found that among the 231 patients studied without previous cardiovascular disease, 81 (31.5%) showed hs-cTnT values above URL.

Also in these patients troponin elevation in the setting of COVID-19 can be explained by different causes:

- ischemic myocardial injury (less frequently) with also different potential mechanisms (e.g, plaque rupture, coronary spasm, microthrombi, or direct endothelial or vascular injury) [21,22].
- non-ischemic myocardial injury (more commonly) related to different possible mechanisms (eg, severe hypoxia, sepsis, systemic inflammation, pulmonary thromboembolism, cytokine storm, stress cardiomyopathy) [21,22] or to direct damage with episodes of myocarditis [23,34].

Indeed, several authors have shown that in patients with COVID-19, in the absence of previous cardiovascular diseases, an increase in cardiac troponin was due to episodes of myocarditis, associated with the typical pattern of interstitial pneumonia [24–

Table 2
The table summarises the current available evidence on reported cardiovascular complications of COVID-19.

Cardiovascular complications	References
Myocarditis and pericarditis	Ruan et al. [31]; Sala et al. [32]
Acute coronary syndromes	Kwong et al. [33]; Yang et al. [34]
Arrhythmias	Guo et al. [35]; Zheng et al. [36]
Myocardial injury	Driggin et al. [37]; Yang et al. [34]
Heart failure/cardiogenic shock	Zhou et al. [38]; Chen et al. [39]
Pulmonary thromboembolism	Klok et al. [40]; Poissy et al. [41]
Stroke	Mao et al. [42]; Beyrouti et al. [42]

26]. Some authors have shown that COVID-19 patients could have myocarditis, confirmed with cardiac magnetic resonance, also in the absence of pneumonia [19,20]. The definitive evidence of tropism for cardiac cells by the new coronavirus has been demonstrated by the recent study by Pesaresi et al. where the authors showed the SARS-CoV-2 identification in heart specimens by transmission and scanning electron microscopy [27]. At the same time, concomitant heart failure was present in 23% to 49% of patients infected with COVID-19 [21]. Notably, it was associated with worse prognosis as it was almost 5 times more common in patients who did not survive the hospitalization (51.9% vs 11.7%) [21,22,28]. In the setting of COVID-19, heart failure could be attributable to either the exacerbation of underlying cardiovascular disease (ischemic heart disease) or the new onset of cardiomyopathy (particularly myocarditis or stress cardiomyopathy) [22,29].

Table 2 summarises the current available evidence on reported cardiovascular complications of COVID-19

However, several studies have shown that cardiovascular involvement and elevated cardiac troponin levels were present in patients with severe COVID-19 related symptoms compared to those with non-severe presentation [21,22,30]. Furthermore, the same studies showed that myocardial damage was associated with higher levels of inflammatory biomarkers; more severe lung involvement; increased need for non-invasive and invasive ventilation; and increased rates of ARDS, acute kidney injury and bleeding disorders. Therefore patients with myocardial damage were at increased risk of death [21,22,30]. It is therefore reasonable, in accordance with our data, to perform an initial cardiac troponin measurement even upon admission for SARS-CoV-2 infection. This could identify high-risk patients who could be the target of advanced therapies and timely treatments

6. Conclusions

Our multicenter study showed that almost half of the patients studied with COVID-19 had high hs-cTnT values with more severe symptoms and clinical course of the disease. We strongly recommend measuring high sensitivity cardiac troponin in patients diagnosed with COVID-19 for early diagnosis of cardiac complications and therefore timely treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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