Cardiac biomarkers alterations in patients with SARS-CoV-2 infection

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Reliable biomarkers are necessary for the risk stratification of patients infected with SARS-CoV-2. This novel coronavirus is now established to affect several organs in addition to the lungs, most prominently the heart. This is achieved through direct damage to the myocardium and indirect immune-associated effects during the cytokine storm. We performed a literature review aiming to identify the prognostic value of alterations of cardiac biomarkers in SARS-CoV-2 infection. Cardiac biomarkers are significantly elevated in patients with severe COVID-19 and are independent predictors of mortality. High-sensitivity troponin I and T are correlated with multiple inflammatory indexes and poor outcomes. Although cut-off values have been established for most of cardiac biomarkers, lower limits for troponins may have better prognostic values and longitudinal monitoring of cardiac biomarkers can help the clinician assess the patient's course. Additional measurements of NT-proBNP, can detect the subgroup of patients with poor prognosis.

Key words: SARS-CoV-2, biomarkers, troponins, natriuretic peptides, prognosis.

What is new? What is important?

- Troponin elevation during SARS-CoV-2 infection is mainly attributed to direct viral damage and indirect myocardial injury, due to cytokine storm.
- Cardiac troponins have sufficient prognostic value for adverse outcomes in patients infected with SARS-CoV-2.
- Lower cut-off values for troponins should be used in these patients.
- Measurement of NT-proBNP can provide the clinician with additional prognostic information.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a worldwide public health emergency evoked by SARS-CoV-2 which primarily targets the respiratory system. However, cardiovascular involvement is present and occasionally profound, including disorders such as myocardial injury, myocarditis, pericarditis, cardiomyopathy, heart failure, cardiogenic shock, arrhythmia and cardiac arrest. Abnormal plasma levels of cardiac biomarkers were described by early reports from patients in Wuhan, and since then, a plethora of studies have focused on their clinical significance. In this report, we summarize the findings of current literature concerning cardiac biomarkers in COVID-19 with emphasis on cardiac troponins.

Pathophysiology

Several putative mechanisms of the underlying cardiac injury during the process of

SARS-CoV-2 infection have been reported in accumulating studies, which conclude that myocardial damage – defined by increased troponins – can be caused either by direct viral infection, or secondary to systemic events [1].

Direct myocardial damage

Angiotensin-Converting Enzyme receptor 2 (ACE2) is a monocarboxylate and component of the Renin–Angiotensin–Aldosterone System (RAAS). Briefly, the role of ACE2 is to metabolize angiotensin II to angiotensin (1–7) and secondary convert Ang I to Ang-(1–9), which is further converted by ACE into Ang-(1–7). The effect of this sequence is the reduction of blood pressure in the systemic circulation [2]. ACE2 is identified as a cellular receptor of SARS-CoV-2, predominantly expressed by epithelial cells of several human organs including the lungs, heart, kidney, blood vessels, brain, and small intestine. [3–6]. On this basis, viral penetration into these

organs, clinically apparent or not, is a possible scenario during SARS-CoV-2 infection [4]. In regards to the cardiac tissue, the high expression of ACE2 in the myocardium, provides an entry point for the coronavirus to insert into the target host cells and replicate rapidly, resulting in acute myocarditis. In this setting, ACE2 is down-regulated through binding of the viral surface spike glycoprotein to ACE2, while ACE functions normally, converting Ang I to Ang II. As ACE2 normally antagonizes ACE, the decreased ACE2 level, upon viral infection, de-regulates the balance of RAAS, inhibiting the cardio-protective role of Ang-(1–7) [7]. Underlying consequences are accumulation of Ang II and pro-inflammatory cytokines, vasoconstriction, pro-oxidative effects, and subsequent cardiovascular injury [6,8]. Thus, a potential mechanism of acute myocardial cells' damage and viral myocarditis, during SARS-CoV-2 infection, could occur by way of ACE-2 signaling.

Indirect myocardial injury

In addition to the direct virus-induced myocardial damage, de-regulation of cardiac function can be caused by hyper-inflammation and underlying increased cytokine secretion. This key pathogenetic mechanism, named “cytokine storm”, is characterized by high immune cell proliferation, resulting in profound and uncontrolled immune response, with continued activation of monocytes, macrophages, granulocytes, and natural killer cells [8]. These inflammatory mediators contribute to the overproduction of abundant pro-inflammatory cytokines including interleukin (IL)-1 β , IL-6, granulocyte colony stimulating factor (GCSF) and tumor necrosis factor- α (TNF- α), IFN- γ , monocyte chemo-attractant protein 1 (MCP-1) and macrophage inflammatory protein 1A (MIP1A) [5,8,9]. Consequences of these are the creation of a positive feedback cycle which maintains the robust and dysfunctional immune response, causing damage to the myocardium and impeding mechanical cardiac function, among patients with COVID-19 [3,8,10].

Another plausible mechanism of indirect myocardial injury is the Acute Respiratory Distress Syndrome (ARDS)-induced hypoxia, which leads to poor oxygen supply to the cardiac muscle, and an increase of the right ventricular pressure and volume overload, creating supply-demand mismatch and ischemic cardiac damage. Endothelial injury, micro-thrombi caused by

hypercoagulability and arrhythmias further burden the cardiac and pulmonary function [1].

Cardiac troponins

Cardiac troponin T and I are cytoplasmic proteins found in the cardiac myocytes and regulate muscle contraction by binding to the actin-tropomyosin complex. As a response to myocardial damage, these proteins are released in the bloodstream, but hypertroponinemia can be present in a variety of non-cardiac diseases. In clinical practice, they are used to identify potential myocardial injury and most importantly myocardial infarction and can provide prognostic information in cardiomyopathies and stroke. Apart from acute coronary syndromes, increased troponin levels can be found in patients with tachyarrhythmias, heart failure, pulmonary hypertension, ARDS and systemic diseases such as sepsis. The lack of standardization in the immunoassays used to determine cardiac troponin values, can lead to difficulties in the comparison of results from different studies, when only absolute troponin values are reported. Thus, current literature suggests the use the 99th percentile of upper range limit instead.

During the first period of the pandemic, increased troponin values described in patients in Wuhan were attributed to virus-related cardiac injury and were associated with poor prognosis [11]. Since then, elevated troponins have been associated with multiple adverse outcomes by a plethora of studies. Increased mortality has been reported for both patients with increased TnI and TnT [12,13]. Patients with severe disease or admitted in the ICU more often have elevated troponins and their values are significantly higher than those of patients with mild disease [14]. Abnormal hs-TnI levels were more common in older, male patients with higher rates of comorbidities [12,15–18]. According to a meta-analysis, patients with elevated TnI had increased risk of poor outcomes and were more likely to be admitted to the ICU [12]. In an observational retrospective study, Mu *et al.* [19] found positive correlations between cTnI and SOFA and APACHE score, but not CURB-65 score. It is noteworthy that higher mortality rates are associated with further increase in troponin values [20].

Multiple inflammatory indexes, including CRP, d-dimers and ferritin have been positively correlated with troponin elevation [19,21,22], thus

it is speculated that myocardial damage is of inflammatory origin. The results of a multicenter observational study, indicated a positive correlation of cTnI, d-dimers and PO₂/FiO₂ (P/F) ratio, raising the question, whether TnI elevation indicates a subset of patients with higher inflammatory responses [23], while they consider elevated proBNP indicative of prior cardiovascular disease as the main aggravating factor. On this matter, other researchers describe troponins and BNP as biomarkers of myocardial injury and cardiac stress, respectively [24].

Prognostic value

Original studies analyzing the prognostic value of cardiac troponins have shown promising results. Since myocardial damage in SARS-CoV-2 infection is mostly attributed to systemic inflammation rather than myocardial infarction, the standard cut-off values have been challenged, as they significantly underestimated cardiac injury in these patients [25]. Mild troponin elevation is common in SARS-CoV-2 infection and thus lower cut-off values have been proposed. For hs-TnI, the lowest cut-off values proposed are 6 ng/L and 7.8 ng/L with sensitivity 95%, specificity 52% and sensitivity 78%, specificity 86% respectively, for prediction of death [21, 26]. A cut-off value of 20 ng/L may have greater prognostic value than 40ng/L, with a sensitivity and specificity of 85% for predicting 30-day mortality [27]. A similar value is proposed by Peiro *et al.*, yields lower results (Sensitivity 81%, Specificity 70%), when measured on admission [16]. Lastly, a cut-off value of 40 ng/L provides great specificity (94%) but low sensitivity (47%) [26].

According to these data, it may be useful to use multiple cut-off points for making clinical decisions. Salvatici *et al.* suggest that due to its high specificity a cut-off point of 40 ng/L, could help identify high-risk patients in need of aggressive therapeutic plans [26]. Clinicians should keep in mind that patients with supposedly normal values, still have increased risk for mortality and that absolute risk of death rises significantly when troponin is elevated more than two-folds [28]. It should be noted that, a retrospective study with over 1000 patients, found that patients with non-detectable hs-TnI levels on admission had 15% risk for ICU admission or death [29].

In comparison to inflammatory markers, hs-TnI has better predictive value [16,26]. Its ability

to predict poor outcomes may be increased when combined with old age or elevated AST [30]. Moreover, the risk of death is increased when NT-proBNP is also elevated [23,24,31].

Although most studies agree that troponins can be used as prognostic biomarkers in SARS-CoV-2 infection, the literature results are not equivocal. A study from Yao *et al.* argues that when adjusting for all comorbidities, hs-TnI loses its predictive value, and considers NT-proBNP superior instead [32]. Additionally, a retrospective observational study, report that hs-cTnT cannot be used to predict ICU admission [33].

The discrepancy between the findings of the studies could potentially be due to the use of different immunoassays. As experts suggest, percentile values of upper range limits should be used in studies instead of absolute values. More prospective multicenter studies on the prognostic value of troponins could help identify algorithms that will lead to evidence-based clinical decisions.

Troponin trends

Cardiac troponins are dynamic markers of myocardial injury and their values on different time points is indicative of the ongoing myocardial injury. Evidence shows that if hs-TnT values peak during the first day of admission, mortality and ICU stay decrease [34]. This applies to both patients with low and high hs-TnT levels on admission. Additionally, Li *et al.* reported that in survivors with severe disease hs-cTnI levels increased from admission to day three but then declined, while in non-survivors they abruptly increased before the patient's death [35]. Another study showed relatively unchanged values and a similar abrupt increase near death in non-survivors, and a steady downwards trend in survivors [26]. In addition, peak values of both hs-TnT and hs-TnI are associated with adverse outcomes, with peak cTnI values predicting the need for invasive ventilation [36,37]. Lastly, an elevated troponin level (above 99th percentile of Upper Range Limit), was found in 6.2% of survivors 1–4 weeks after hospital discharge, but without clinical or cardiovascular MRI evidence of heart dysfunction [38].

This evidence supports that besides measurement of troponins on admission, longitudinal monitoring, can help clinicians to assess better the patient's course. Also, close monitoring of troponin values during the first day of admission, provides prognostic information.

Comorbidities

Cardiovascular comorbidities are common in severe COVID-19 disease, as these patients are often of old age. While the effect of cardiovascular disease on the course of SARS-CoV-2 infection is outside of the scope of this report, it should be noted that in contrary to elevated hs-TnI levels, cardiovascular comorbidities were not an independent risk factor for in-hospital mortality at multivariable analysis in an Italian study [39]. However, another retrospective study from Li *et al.* reported different results [40].

Tornero *et al.* published a study focusing on chronic heart failure (CHF) and SARS-CoV-2 with interesting results [41]. They reported a significant increase in mortality in patients with CHF (n=43) and in this population, the mortality was associated with hs-TnT, but not NT-proBNP. Additionally, they suggest that hs-TnT values above 14 ng/L, indicate high risk patients. Elevated hs-TnT was found in most CHF patients, but surprisingly none of those with normal troponin levels died. Lastly, in this subset, a cutoff of 38 ng/L can be used to predict 30-day mortality (sensitivity 79%, specificity 67%).

While hypertension is the most frequent comorbidity in SARS-CoV-2 patients [40], people with hypertension are not over-represented amongst those with severe SARS-CoV-2 infection, according to the International Society of Hypertension. Regarding cardiac biomarkers, in mild and moderate cases but not in severe infections, elevated hs-TnI (>26 ng/L) is more common in patients with hypertension than in those without [32]. In this subset of patients, dynamic changes of troponin levels were associated with increased risk of death. Smoother trends of median hs-TnI were also reported in patients without hypertension than those with.

Systemic inflammation and sympathetic activation during SARS-CoV-2 infection may induce cardiac arrhythmias, and their presence may promote a more pronounced troponin elevation [36,42]. Indeed, there is evidence that patients with elevated TnI have increased prevalence of ventricular and atrial tachyarrhythmias [14,43] and that hs-TnT levels are significantly higher in patients with arrhythmia, than in those without [42]. The presence of elevated troponin levels and atrial tachyarrhythmias identifies a group of patients in high risk of death [36].

Paraclinical findings

The literature regarding echocardiographic findings and alterations in cardiac biomarkers is inconclusive and prone to selection bias. A retrospective study reported that although right ventricular (RV) dysfunction is common in patients with elevated hs-TnI, there was no significant correlation between the two [44]. In contrary, the left ventricle was only seldomly impaired. In another multicenter study, TAPSE (Tricuspid Annular Plane Systolic Excursion) – an index for RV dysfunction – was significantly reduced in patients with abnormal hs-TnI and NT-proBNP [23]. Additional studies report results in favor of statistically significant correlation between cardiac biomarkers and ventricular dysfunction [13,45], as well as against it [23,46,47]. Prospective multicenter studies must be performed before any conclusions on this matter can be made.

The data on ECG and elevated troponins, in the current literature, are clearer. hs-TnT is significantly higher in patients with ECG abnormalities [36]. Additionally, elevated hs-TnI levels are associated with the presence of longer QTc interval, conduction disturbances and other ECG abnormalities, but not atrial fibrillation [48]. Wide QRS complex and abnormal lateral ST-T segment are more common in patients with elevated cardiac biomarkers [49]. Giustino *et al.* suggest that Transthoracic Echocardiography (TTE) may be considered in COVID-19 positive patients with elevated troponins and ST-segment changes, to identify patients with acute coronary syndromes that would benefit from invasive treatment [15]. In patients with troponin elevation attributed to Acute Coronary Syndromes (ACS), inflammatory biomarkers were lower, ECG changes were more pronounced, and all had regional-wall abnormalities in TTE. The latter was present only in 20% of patients with troponin elevation unrelated to ACS [15]. To our knowledge, the role of cardiac MRI in SARS-CoV-2 patients with troponin elevation, has not been systemically studied, but it could provide an alternative to TTE for non-invasive assessment of cardiac injury [50]. Myocarditis-like features were reported in the cardiac MRI of patients with unexplained troponin elevation [51].

Natriuretic peptides

NT-proBNP and BNP are cardiac biomarkers commonly used to diagnose heart failure and cardiac dysfunction. Increased

intracardial pressure and mechanical stress induce the synthesis and secretion of natriuretic peptides. In the past, abnormal BNP and NT-proBNP values have been associated with worse clinical outcomes among patients with ARDS [52].

The literature on NT-proBNP in SARS-CoV-2 infection is more scarce compared to troponin literature. A strong positive correlation between the two cardiac biomarkers has been described [22]. NT-proBNP is also correlated with inflammatory biomarkers and T-cell markers [53]. In parallel with troponins, NT-proBNP is more commonly elevated in non-survivors and meta-analyses have reported a significant association between NT-proBNP and mortality [54,55]. NT-proBNP is an independent risk factor for negative outcomes and in clinical practice it could be used in conjunction with troponins, to detect patients with poor prognosis [31]. The proposed cut-off values for NT-proBNP in current literature are 88.64 pg/mL with a sensitivity 100% and specificity 67% for predicting in-hospital death and in the CHF subgroup 2598 pg/ml (sensitivity 91.7%, specificity 80%) [41,56]. In order to achieve more reliable prognosis in SARS-CoV-2 infection, further research should establish different cut-off values according to the patients' age, as is the norm for NT-proBNP. Contrariwise, studies reported that BNP is not a valid prognostic factor in COVID-19 patients [57,58].

Miscellaneous biomarkers

CK-MB and myoglobin are closely related to myocardial damage and as expected they are significantly elevated in severe SARS-CoV2

infection [54]. Their prognostic value in these patients is similar, but according to some studies, inferior to troponins'. As current literature is more focused on troponins than CK-MB and myoglobin, the use of troponins in clinical practice seems more appropriate.

GDF-15 belongs to the TGF- β superfamily and is a novel biomarker associated with inflammation, cardiac damage, and cancer. Its prognostic value in COVID-19 was reported to be greater than that of troponin and NT-proBNP, but more studies are needed to prove its potency [59].

CONCLUSION

The unprecedented and significant burden of the COVID-19 pandemic on the health system, has created an urgent need for practical and reliable prognostic tools, in order to facilitate stratification and management of patients. Our study highlights the role of cardiac biomarkers, and especially cardiac troponins, in modern emergency medicine in the context of SARS-CoV-2 infection. As their predictive value is now supported by many studies, future research should focus on how troponins can assist in evidence-based clinical decision making. Concerning hs-TnI, it is necessary to establish the use of percentile values, so that the results of different troponin studies can be compared reliably. Therefore, measurement of cardiac biomarkers on admission, combined with monitoring of their values during hospitalization, can provide the clinician with important information about the clinical course of COVID-19 patients.

Este nevoie de biomarkeri pentru stratificarea riscului la pacienții infectați cu SARS-CoV-2. Pe lângă plămâni, și inima este afectată de acest virus, fie direct, fie prin furtuna citokinică. A fost realizat un studiu extensiv al literaturii privind biomarkerii prognostici pentru afectarea miocardică în cadrul infecției cu virusul SARS-CoV-2. Biomarkerii cardiaci sunt modificați la pacienții cu infecție severă și sunt predictorii independenți pentru mortalitate. Troponina I și T high sensitivity se corelează cu un efect prognostic prost. Analizând în plus nivelurile NT-proBNP se poate detecta subgrupul de pacienți cu prognostic prost.

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Conflict of interest disclosure: The authors have no conflicts of interest to declare.

Funding sources: This research did not receive any financial support or sponsorship.

Author contributions: EO and TP did literature search and wrote the manuscript. EO and TP contributed equally in the manuscript. DV wrote the manuscript and supervised the study.

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Received 2nd June 2021