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Cardiac biomarkers in COVID-19: a narrative review

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ABSTRACT

The diagnosis and risk stratification of coronavirus disease 2019 (COVID-19) is primarily based on discretionary use of laboratory resources. Several lines of evidence now attest that cardiovascular disease not only is a frequent complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but its pre-existence may increase the risk of morbidity, disability, and death in patients with COVID-19. To this end, routine assessment of biomarkers of cardiac injury (i.e., cardiac troponin I or T) and dysfunction (e.g., natriuretic peptides) has emerged as an almost essential practice in patients with moderate, severe, and critical COVID-19 illness. Therefore, this narrative review aims to provide an overview of cardiac involvement in patients with

SARS-CoV-2 infection as well as the clinical background for including cardiac biomarkers within specific panels of laboratory tests for managing COVID-19 patients.

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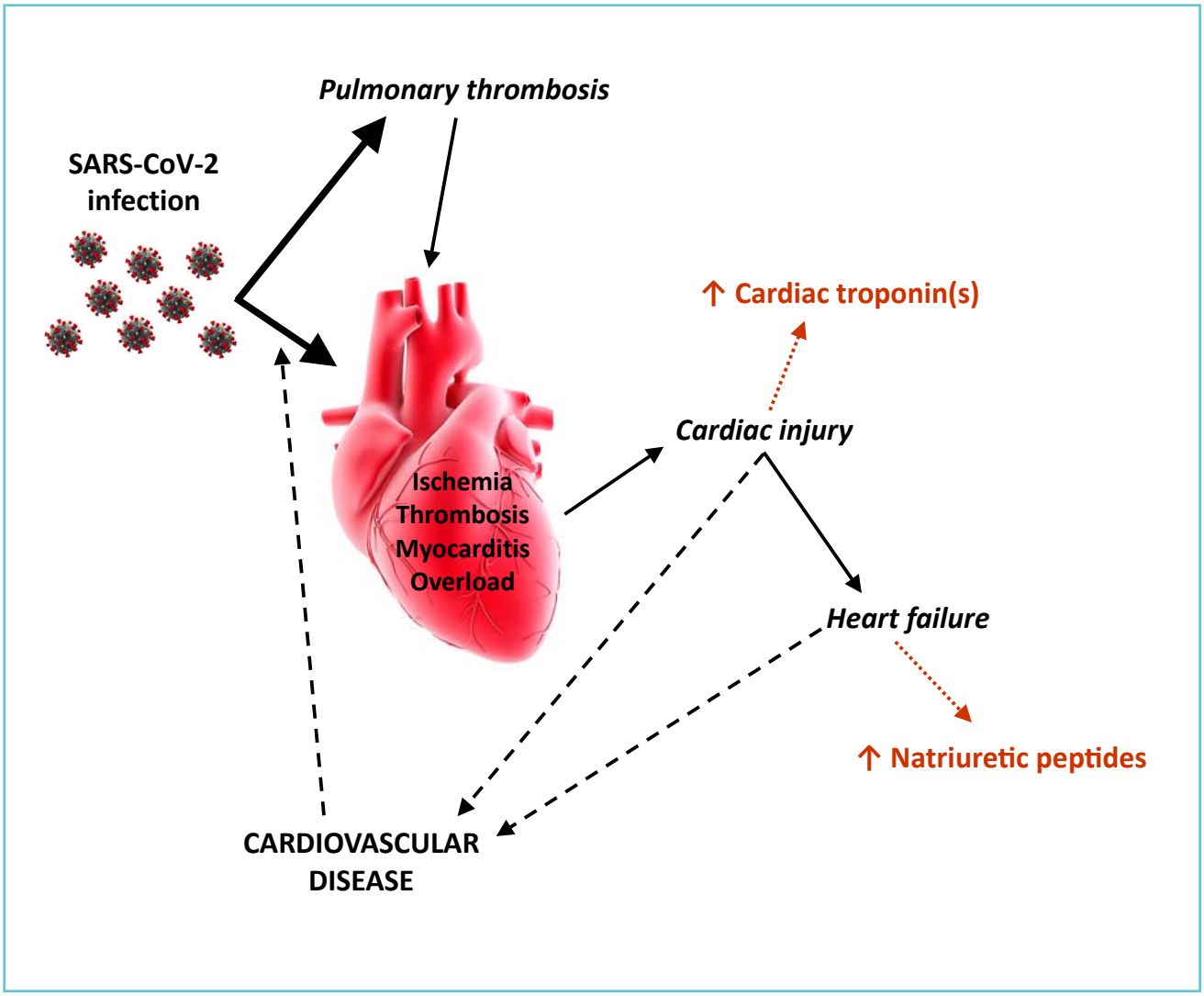
INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disorder caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first appeared at the end of 2019 in Wuhan (China) and has since then assumed a pandemic proportion, causing several million deaths around the world so far [1]. One essential aspect in the pathogenesis of COVID-19 is that SARS-CoV-2 infection seems to generate the worst damage in people with one or more co-morbidities. Along with older age and male sex, cumulative Italian data suggests that the death rate in people without a single co-morbidity is around 2.8%, but then increases exponentially in those with 1, 2, and up to 3 co-morbidities [2]. Notably, cardiac pathologies, thus encompassing ischemic heart disease (IHD), atrial fibrillation, heart failure (HF), and hypertension, are the most important predictors of unfavorable COVID-19 outcome [2]. Data published by the US Centers for Disease Control and Prevention (CDC) are virtually overlapping. Specifically, an analysis of patients who died of COVID-19 in 2020 in the US has revealed a considerably high prevalence of cardiovascular disease (CVD), nearly 61%, not differing substantially across different age groups [3]. Interestingly, another comprehensive report published by the CDC highlighted that the burden of CVD was as high as 22% in people younger than 21 years who died from COVID-19 in the US [4]. To specifically address the impact of CVD on the prognosis of COVID-19 patients, a recent meta-analysis found that this preexisting condition was associated with a 3-fold higher risk of developing severe COVID-19 disease, as well as with 11-fold and 1.7-fold enhanced risk of mortality in all COVID-19 patients and those with severe disease, respectively [5].

Irrespective of the dramatic impact that pre-existing CVD may have on the clinical progression of SARS-CoV-2 infection, it is undeniable that COVID-19 itself may have a substantial impact on cardiac integrity and function, thus paving the way to the establishment of a potentially devastating vicious circle (Figure 1). It has now become rather clear that COVID-19 is not a single-organ, clear-cut pulmonary disorder, but is instead a gradually evolving pathology, characterized by a series of stages sustained by different biological mechanisms, as reviewed comprehensively elsewhere [6]. Briefly, while remaining mostly asymptomatic, or only mildly symptomatic, in the vast majority of subjects, in a variable percentage between 15-30% of subjects with SARS-CoV-2 infection the illness progresses towards a respiratory phase, whose hallmark is the development of an (often bilateral) interstitial pneumonia. An abnormal, almost exaggerated, immune and inflammatory response in some COVID-19 patients then paves the way to progression towards a subsequent phase, characterized by development of lung and systemic hyper-inflammation and gradual evolution towards lung and multiple organ injury, thus including heart and blood vessels [7]. In a low but still clinically meaningful number of patients (i.e., between 2-5%), the disease progresses into a further - highly critical - phase, where hyper-inflammation triggers activation of both primary and secondary hemostasis, which then leads to generation of intravascular coagulopathies manifesting as in situ pulmonary thrombosis, venous thromboembolism with deep vein thrombosis and/or pulmonary embolism, secondary thrombotic microangiopathy, or even disseminated intravascular coagulation [8].

Figure 1 Pathways of cardiac involvement in patients with severe acute respiratory infection coronavirus disease 2019 (COVID-19)



COVID-19 AND THE HEART

The risk of cardiac tissue injury in SARS-CoV-2 infection is certainly not surprising if one considers that similar myocardial damage can also be observed in patients with many other viral infections. For example, elevations of cardiac troponins have been found in up to 33% of patients with influenza, especially in those infected by more virulent strains such as H1N1, which belongs to the same family which caused the dramatic Spanish flu outbreak nearly 100 years ago [9]. The mechanisms of influenza-related cardiac injury are likely similar to those causing myocardial injury in patients with SARS-CoV-2 infection and involve either direct or indirect cardiac injury. It is also interesting to compare the incidence of cardiac injury in COVID-19. For example, a recent study found that a certain degree of cardiac involvement can be present in 21% of patients hospitalized for COVID-19, increasing to 50% in those with critical illness [10]. Cardiac injury was found to be more frequent in patients with COVID-19,

though its burden was not so dissimilar from that found in those with H1N1 infection (i.e., 50% vs. 39%). A variable cardiac involvement seems hence relatively frequent in patients with COVID-19. Another recent meta-analysis has estimated an incidence as high as 42% in patients with severe illness and 26% in those with milder disease [11]. It is then noteworthy that the development of cardiac injury in patients with SARS-CoV-2 infection was found to be associated with an over 10-fold higher risk of death [11].

Although the pathophysiology of cardiac injury in patients with COVID-19 is virtually multifactorial, patients may develop ischemic heart disease (IHD), which can cause either worsening of pre-existent IHD or alternatively present as an ex-novo consequence of the paradigmatic thromboinflammatory condition which characterizes SARS-CoV-2 infection. This was demonstrated in a study of patients with acute myocardial infarction (AMI) with or without COVID-19, showing that the burden of coronary atherosclerosis was lower in those with SARS-CoV-2 infection. At the same time, the presence of neutrophil extracellular traps (NETs) was markedly enhanced in coronary thrombi of such patients, thus suggesting a de-novo pathology [12]. It is then noteworthy that COVID-19 patients who develop ischemic cardiac injury have a much worse outcome than those without SARS-CoV-2 infection. A prospective international registry of acute coronary syndromes, which compared the outcome of AMI in patients with or without COVID-19, revealed that the mortality was over 3-fold higher in patients with SARS-CoV-2 infection, and was also associated with significantly longer hospitalization [13].

Along with the thrombotic/ischemic injury, it cannot be discounted that some patients may also develop a localized SARS-CoV-2 myocardial infection. A comprehensive assessment of COVID-19 associated myocarditis has been recently carried out by Bailey et al. [14], who found that SARS-CoV-2 can infect cardiomyocytes through an angiotensin-converting enzyme 2 (ACE2) and endosomal, cysteine protease-dependent pathway, which is then followed by enhanced cytokine production, sarcomere disassembly, and irreversible injury, up to cell death. Importantly, infection of cardiomyocytes by SARS-CoV-2 seems to reduce contractility due to sarcomere breakdown and cardiomyocyte necrosis.

Post-mortem studies have convincingly confirmed the risk of developing severe involvement of cardiac tissue in patients with severe/critical COVID-19 illness. A cases series of post-mortem analyses of patients who died from COVID-19 revealed that heart microthrombosis was present in as many as 80% of cases, and was virtually commonplace in those who died after severe/critical illness [15]. The rate of fibrin microthrombi in the heart was also nearly 3-fold higher than that observed in patients who died from influenza. At the same time, the prevalence of myocarditis was relatively low in both circumstances, though remaining nearly twice as high in COVID-19 patients. This evidence has then been confirmed in another study involving 40 patients who died from COVID-19 [16]. Despite a relatively low prevalence of baseline coronary artery disease, present in less than one-fourth of all patients, myocardial infection could be detected in 7% of all subjects, while focal myocyte necrosis was widespread, found in 80% of patients with COVID-19-associated myocardial injury. Importantly, another study published by Marfella and colleagues evidenced that nearly 85% of all patients who died with SARS-CoV-2 infection had thrombus specimens in cardiac arteries that were positive for viral RNA, thus confirming the important role played by SARS-CoV-2 in triggering ischemic and non-ischemic cardiac injury [17].

In summary, the origin of myocardial injury seems multifactorial in patients with severe COVID-19, involving myocarditis directly caused by SARS-CoV-2 infection, myocardial damage caused by thrombo-inflammation, Takotsubo syndrome, cardiac overload due to pulmonary thrombosis, along with type 1 and 2 AMI, the former due to obstruction of blood flow within coronary arteries, the latter due to an imbalance between oxygen demand and supply, which is in turn due to pneumonia-causing lower blood oxygenation, combined with fever and/or tachycardia driving increased oxygen demand (Figure 1) [18].

One of the most obvious consequences of the onset of myocardial injury in COVID-19 patients, besides the enhanced risk of mortality, is the risk of developing HF in the medium- and long-term period. A recent meta-analysis showed that the prevalence of this condition was around 20% in patients who recovered from COVID-19, and its presence was associated with an over 9-fold higher risk of death [19]. Irrespective of the cause, the gradual impairment of cardiac function appears an important risk factor for unfavorable outcomes in COVID-19 patients, with both impaired left ventricular ejection fraction and right ventricular dysfunction found to be important predictors of mechanical ventilation and/or all-cause mortality [20].

CARDIAC BIOMARKERS IN COVID-19

Cardiac troponins

Before exploring the importance of measuring cardiac biomarkers in COVID-19, a brief introduction may be necessary. Cardiac troponins are no longer considered the sole and unique biomarkers of myocardial injury, with their assessment extending far beyond diagnosing myocardial damage, now encompassing risk stratification of medium and long-term adverse outcomes. As largely proven, the concentration of cardiac troponins may increase as a consequence of a kaleidoscope of biological pathophysiologic pathways affecting the cardiac tissue such as ischemic, traumatic, toxic, and, last but not least, infectious insults, as well as being associated with several secondary cardiac damages as a consequence of renal failure, sepsis, cancer, pulmonary embolism, rhabdomyolysis, traumas, and burns, among others [21]. All the above mechanisms will variably lead to increased serum or plasma cardiac troponin concentration, depending on type and severity of the primary or secondary cardiac injury. Patients with increased values of cardiac troponins have a magnified risk of long-term morbidity and mortality in the general population, as well as in patients with specific pathologies, as demonstrated by a vast array of published meta-analyses, that we have recently reviewed elsewhere [22].

Hence, it is not surprising that a strong association has also been found between increased values of cardiac biomarkers, especially cardiac troponins, and unfavourable outcome of COVID-19. In fact, we demonstrated this very early in the COVID-19 pandemic. A recent meta-analysis showed that the values of cardiac troponin I were significantly higher in patients with severe COVID-19 illness, as well as in those who died. Cumulatively, an increased value of cardiac troponin I was found to be associated with an over 5-fold higher risk of developing severe illness [23]. Another updated meta-analysis has more recently confirmed that increased values of cardiac troponin I were associated with a remarkable 25-fold higher risk of death in patients with COVID-19 [24]. This evidence has been reported in many other studies, like that published by Kinght et al. [25], who found that up to 71% of all COVID-19 patients present with abnormal levels of cardiac troponins, and the in-hospital mortality rate of those with pathological values is as high as 41%. In those with

apparently unknown causes of cardiac injury investigated with cardiac magnetic resonance imaging (MRI), the injury was non-ischemic in nearly 38% of cases, ischemic in 17% of cases, and both ischemic and non-ischemic in 14% of cases. Notably, in those with known causes of cardiac injury, acute coronary syndrome, and pulmonary embolism were identified in 27% and 54% of cases.

Another important aspect has been highlighted in the study of Tanboğa and colleagues [26], showing that not only are cardiac troponin levels significant predictors of worse outcomes in patients with SARS-CoV-2 infection, but also that the relative increase in the concentration of this biomarker was directly related to negative disease progression and mortality, with such risk increasing from 1.2 folds for values marginally exceeding the upper reference limit, up to over 2.4 folds when cardiac troponin levels were 50-fold increased over the upper limit of normal. In the study conducted by Cunningham et al. [27], the prognostic impact of cardiac troponin has been investigated in more than 12,000 patients hospitalized for COVID-19. Besides the fact that the risk of death increased steadily across classes of cardiac troponin values, it was also interestingly found that such risk increased nearly exponentially in parallel with aging within each type of cardiac troponin (I or T) values. This implies that cardiac troponin values in COVID-19 patients, as in most other pathologies, should be interpreted considering the patient's age. Another interesting perspective to approach the role of cardiac troponins in COVID-19 encompasses the stratification of COVID-19 patients according to the severity of myocardial injury, followed by analysis of the relationship between cardiac troponin and outcome.

In a study by Salbach et al. [28] this approach revealed that cardiac troponin values gradually increased across different stages of severity of myocardial injury, and the primary endpoints raised in parallel across classes of injury severity, cardiac troponin, and D-dimer values. It is also noteworthy that an increased cardiac troponin value is indeed associated with worse cumulative outcome, but also correlates with a variety of adverse secondary endpoints. The study published by Shah et al. clearly shows that not only does the risk of in hospital-mortality increase across the four quartiles of cardiac troponin I, but a similar trend can be seen in the need for dialysis, mechanical ventilation and intensive care [29].

The extent of cardiac troponins elevation seems to be a significant prognostic factor in patients with COVID-19, but also its kinetics during hospital stay appears to have an important influence on the outcome. As shown in the study of Nuzzi et al. [30], COVID-19 patients with normal cardiac troponin values at admission, but who then displayed increasing concentrations, were found to have a higher risk of in-hospital mortality than those admitted with baseline elevation and stable levels afterward.

The substantial role of cardiac troponins in the comprehensive management of COVID-19 patients has also been highlighted by studies showing that incorporation of their values within simple algorithms may be efficiently used for predicting a vast array of unfavorable outcomes [31,32].

Such an important role played by cardiac troponin in COVID-19 has hence persuaded us to elaborate an algorithm that would make sense of their testing in patients with SARS-CoV-2 infection, for allowing the identification of those at higher risk of developing cardiac injury, either directly triggered by SARS-CoV-2, or as an indirect consequence of thromboinflammation, ischemia and/or myocarditis, as available elsewhere [33]. According to this model, nonevolving cardiac troponin values, along with normal levels of other biomarkers of inflammation or

cardiac dysfunction, may safely limit the necessity to perform other diagnostic investigations such as transthoracic echocardiography or stress testing in patients with suggestive signs or symptoms of cardiac involvement.

Natriuretic peptides (NPs)

Besides cardiac troponins, the clinical usefulness of measuring NPs in COVID-19, mostly encompassing the assessment of B-type natriuretic peptide (BNP) and NT-pro-BNP, has been broadly supported by clinical evidence. Patients with HF often have elevations in NPs, and those with pre-COVID-19 HF, both with reduced and preserved ejection fraction (EF) have marked increases in mortality with COVID-19, whereas just EF does not correlate with outcomes. In a meta-analysis by Zinellu et al. [34], significantly increased values of NPs were found in COVID-19 patients with different degrees of clinical severity compared to those with milder illness, without evidence of substantial differences between measuring BNP or NT-proBNP. Interestingly, unlike the evidence reported by Zinellu et al [34], De Falco and colleagues concluded that the diagnostic performance for predicting unfavorable COVID-19 outcomes, specifically, mortality risk, appears to be higher using NT-proBNP (area under the curve (AUC), 0.943) than BNP (AUC, 0.736), with a prognostic accuracy that was similar to that found for cardiac troponin I (AUC, 0.939) [35]. In an ensuing study by [27], the authors explored the prognostic role of NPs in predicting the outcome of over 12,000 patients hospitalized for COVID-19. Two exciting findings emerged from this work. First, the risk of death was directly dependent upon admission values of NPs, and, even more importantly, such risk increased nearly exponentially in parallel with aging.

It is then noteworthy that the assessment of cardiac biomarkers would not only help predict clinical outcomes of COVID-19 in the adult population, since Güllü et al. found that NPs and cardiac troponins are efficient predictors of development of the multisystem inflammatory syndrome in children, perhaps the most severe manifestation of COVID-19 in childhood [36].

Additional cardiac biomarkers

Although it is now undeniable that laboratory assessment of cardiac injury and function shall be almost entirely limited to assessment of cardiac troponins (either I or T) [37] and natriuretic peptides (either BNP or NT-proBNP) [38], evidence has been provided that some additional biomarkers may have a supportive role in stratifying the risk of COVID-19 patients. For example, Growth Differentiation Factor-15 (GDF-15) is another cardiovascular biomarker that may provide useful prognostic information in COVID-19. In a preliminary study published by Myhre et al. [39], the concentration of this biomarker was significantly correlated with the viral load and also positively associated with higher risk of unfavourable disease progression. It is noteworthy that its predictive value (AUC, 0.78) was found to be even higher than that of D-dimer (AUC, 0.63), cardiac troponin T (AUC, 0.63), NT-proBNP (AUC, 0.61), either expressed as baseline level or variation from the admission value. In a recent meta-analysis, we found that mid regional proadrenomedullin (MR-proADM), whose increased levels are commonplace in patients with critical illness, were significantly enhanced by 74% in COVID-19 patients with severe or critical disease compared to those with milder illness [40]. This evidence was confirmed in an ensuing study, which also showed that assessment of MR-proADM has an accuracy as high as 95% for predicting mortality in patients with COVID-19 [41]. Emerging evidence suggests that the assessment of soluble suppressor of tumorigenicity 2 (sST2) may also provide valuable insight into the progression of COVID-19, though large prospective clinical

studies to confirm its usefulness are still needed [42]. Finally, among the various red blood cells (RBC) parameters that may be useful for monitoring COVID-19 or predicting the risk of developing serious illness, the RBC distribution width (RDW) deserves special attention. In an original investigation, we assessed the prognostic performance of RDW in 49 COVID-19 patients, 16 with severe illness, 12 with severe acute kidney injury, and 8 needing renal replacement therapy [43]. In this population, elevated RDW significantly predicted all the unfavorable clinical endpoints and, specifically, was found to be associated with an over 9- and 16-fold higher risk of developing severe illness and acute kidney injury.

CONCLUSIONS

Several lines of evidence now support the inclusion of cardiac troponins and NPs as essential parameters within specific panels of laboratory tests for managing COVID-19 patients. These tests would enable a more timely diagnosis of cardiac injury, either direct or indirect, overall disease progress, as well as may help predict the risk of developing post-COVID-19 cardiac dysfunction.

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