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Utility of Cardiac bioenzymes in predicting cardiovascular outcomes in SARS-CoV-2

Variation of cardiac bioenzymes with cardiovascular outcomes in COVID 19

Anjani Muthyala, Sandeep Sasidharan, Kevin John John, Amos Lal, Ajay K Mishra

Abstract

Cardiovascular complications have been increasingly recognized in the SARS-CoV-2 associated coronavirus disease 2019 (COVID-19). Cardiac biomarkers are released because of this ongoing cardiovascular injury and can act as surrogate markers to assess the disease severity. We reviewed the variation and utility of these biomarkers in COVID-19 to ascertain their role in diagnosis, prognosis and clinical outcomes of the disease. We performed a literature search in PubMed using the search terms "COVID-19" and "cardiac bioenzymes" or "cardiac biomarkers". Cardiac troponin has been consistently elevated in patients with COVID-19 associated myocarditis, and strongly correlated with adverse prognosis. Natriuretic peptides including brain natriuretic peptide (BNP) and pro-BNP is elevated in patients with COVID-19 associated cardiac injury, irrespective of their prior heart failure (HF) status, and independently correlated with worst outcomes. Alongside these traditional biomarkers, novel cardiac bioenzymes including presepsin, soluble ST2 and copeptin, are also increasingly recognized as markers of cardiovascular injury in COVID-19 and can be associated with poor outcomes. Assessment of cardiac bioenzymes at admission and their serial monitoring can help assess the severity of disease and predict mortality in patients with SARS-CoV-2 infection. Future studies are needed to elude the critical importance of novel biomarkers.

Key Words: SARS-CoV-2; Troponin; Brain natriuretic peptide; Prognosis; Outcomes; Heart failure

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Core Tip: Cardiac bioenzymes act as surrogate markers for various cardiovascular complications associated with coronavirus disease 2019 (COVID-19). Cardiac bioenzymes at admission and their serial monitoring can help assess the disease

severity and predict mortality in patients with COVID-19. This review summarizes the role of these bioenzymes in diagnosis, prognosis and clinical implications on outcomes of various cardiovascular complications associated with COVID-19.

INTRODUCTION

Abbreviation

COVID-19

Coronavirus disease 2019

SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus-2

HF

Heart failure

cTn

Cardiac troponin

cTnT

Cardiac troponin T

cTnI

Cardiac troponin I

cTnC

Cardiac troponin C

NP

Natriuretic peptide

NT-proBNP

N terminal pro brain natriuretic peptide

BNP

Brain natriuretic peptide

sST2

Soluble ST2

Gal-3

Galectin-3

ACE

Angiotensin-converting enzyme

AngII

Angiotensin II

ARDS

Acute respiratory distress syndrome

PA

Pulmonary artery

TTE

Transthoracic echocardiography

10

HFpEF

Heart failure with preserved ejection fraction

HFA-PEFF

Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology

CKMB

Creatine kinase MB

IL-6

Interleukin 6

INR

International normalized ratio

MYO

Myoglobin

LDH

Lactate dehydrogenase

ACE/ARB

Angiotensin-converting enzyme/Angiotensin receptor blocker

Glossary:

The Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has since infected nearly 500 million people across 200 different countries and killed more than six million people worldwide. Lung injury is the most common presentation seen; however, cardiac injury is another dreaded consequence of this viral disease. Multiple mechanisms of injury have been hypothesized that culminate in widespread inflammation and cytokine storm causing significant cardiovascular dysfunction. A few authors have hypothesized that the inciting events for this injury include microvascular damage in the heart, causing perfusion defects, vessel hyperpermeability, and vasospasm (1–5). Cardiac biomarkers are released because of this ongoing cardiovascular injury and can act as surrogate markers to assess the disease severity. These biomarkers can be elevated in many cardiac conditions, including acute Myocardial infarction (AMI), heart failure (HF), arrhythmias and cardiomyopathies. Among the available biomarkers, cardiac troponin (cTn) and natriuretic peptides including brain natriuretic peptide (BNP) and N terminal pro-BNP (NT-proBNP), have been extensively studied. Numerous reports from China have noted elevated cTn in COVID-19 patients (6,7). A major review on cardiac biomarkers in HF emphasized the importance of negative NPs in ruling out HF (8). In addition, novel biomarkers including soluble ST2 (sST2), Galectin-3 (Gal-3), and copeptin have also been studied. In this review, we aimed to study in detail the various cardiac biomarkers that have been reported in the literature in patients with COVID-19. We also aimed to identify the role of these cardiac biomarkers in diagnosing the impact of cardiac injury and their role in prognostication of morbidity and mortality among patients with COVID-19.

Methods:

We conducted an extensive review of the literature of all the studies on patients with COVID-19 associated cardiac injury and cardiac bioenzymes. We screened for articles on cardiac biomarkers in patients with COVID-19 in the MEDLINE/PubMed database. Published articles between November 2019 and March 2022 were reviewed. Keywords for the search criteria included "Coronavirus disease 2019", OR "COVID-19", OR "Severe Acute Respiratory Syndrome Coronavirus-2", OR "cardiac bioenzymes", OR 'biomarkers", OR "prognosis", OR "heart failure", OR "myocarditis" OR "outcome", OR "morbidity", and "mortality". We also used the related article search feature and manual search of references to identify further articles. Additionally, we used the latest reference citation analysis tool to screen for more articles. Two independent trained physician reviewers were involved in screening and reviewing relevant articles. As of March 2022, a total of 560 papers were identified. Among them, only 61 papers were eligible to be included (Figure 1). All articles with details on COVID-19 patients with cardiac injury and measured cardiac biomarkers were eligible to be included in this review. We included all articles published in English from all over the world. Independent reviews, editorials, letters, abstracts, preprints, and opinions were excluded. Most studies reporting cardiac biomarkers in patients with COVID-19 were from China, North America, and Europe. The reporting of study design, methodology, data collection, biomarker levels, and measured outcomes were not consistent across all the studies. To simplify the role of each cardiac biomarker with regard to COVID-19 disease diagnosis, prognosis, and mortality, we subdivided this review into three principal sections. The three sections were 1) Studies on the role of cardiac troponin in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality; 2) Studies on the role of natriuretic peptides in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality; 3) Studies on the role of other biomarkers and novel cardiac biomarkers in diagnosing and prognosticating COVID-19 associated myocardial injury and mortality.

Cardiac troponin:

Pathophysiology:

Cardiac troponins (cTn) include troponin T (cTnT) and troponin I (cTnI), which are universally accepted markers of cardiac injury (9). Cardiac troponin, a regulatory protein complex with three units, is located at the sarcomere thin filament. The inhibitory unit cTnI and a tropomyosin binding unit cTnT are responsible for maintaining a relaxed state when intracellular Ca2+ concentrations are low in diastole. In systole, the rise in intracellular Ca2+ leads to Ca2+ binding to cardiac troponin C (cTnC), releasing inhibition and promoting contraction and ejection (10).

Troponin as a diagnostic marker of cardiovascular injury in COVID-19:

In the early phases of the pandemic caused by SARS-CoV-2, the emphasis was on lung damage and treatment of the same. Guidelines from AHA had recommended against the determination of cTnT and cTnI. However, this notion changed in 2020, when Chapman *et al*. published a statement strongly supporting the determination of serum cTnI and cTnT, emphasizing their role as biomarkers for cardiac injury in COVID-19 infected patients (11). Initially, the exact mechanism leading to serum elevations of these biomarkers was unclear, with several theories being proposed. Recent evidence showed direct infection of cardiac myocytes by SARS-CoV-2 (12), leading to a decrease in Angiotensin-converting enzyme 2 (ACE2) and an increase in Angiotensin II (AngII). The dysfunctional signaling leads to necrosis or membrane instability, causing the leak of the bioenzymes (13). Multiple additional studies (14–16) have reiterated the importance of cardiac troponin as a diagnostic tool and have been summarized in Table 1. The evidence of cardiac troponin as a diagnostic marker for cardiovascular injury in COVID-19 is robust and has been shown on thousands (n = 11,290) of patients worldwide, in both prospective and retrospective studies (Table 1). Cardiac troponins have been reported to be elevated irrespective of the pattern of cardiac injury and clinical presentation. Levels have been reported to be higher among patients with an ischemic pattern of injury than in non-ischemic injury. A consistently elevated level of cTn has been reported in COVID-19 patients with mild myocarditis to severe

cardiogenic shock. The release of cTn has been seen in COVID-19 patients with acute coronary syndrome, tachyarrhythmias, cardiomyopathy, and myocarditis. In COVID-19, patients' cTn has been used as a marker of inflammation and myocardial injury. A large observational study from New York on patients hospitalized with SARS-CoV-2 showed a positive correlation between elevated cTnT and inflammatory markers (14)

Role of troponin as a prognostic indicator of cardiovascular outcomes in COVID-19:

Sandoval *et al*. found higher levels of cTn in severe SARS-CoV-2 infection and opined that their serial measurement can aid in the risk stratification of COVID-19 patients. Based on the progression of the disease, they grouped COVID-19 patients in three phases; first – during admission where cTn elevation reflected the comorbidities; second – further rise in cTn with critical ARDS and; third – peak cTn with COVID-19 associated complications, including myocarditis and pulmonary embolism (17). Studies have shown that a high level of cTn and serial up-trending of cTn have been predictive of worse prognosis (18–20). Troponin levels between 0.03 and 0.09ng/mL were considered to be predictive of cardiac damage, with levels above 0.09ng/mL conferring an even higher risk. Multiple studies have shown that troponin levels above the 99th percentile of upper limit of normal, to be associated with worse prognosis. A few studies utilising high sensitivity troponin have shown that troponin levels above 4ng/L, 13ng/L and 37ng/L to be predictive of mild, severe and critical illness respectively (19). Similarly, lower levels of cTn at presentation and a downward trend have been consistently reported among the survivors. Importantly COVID-19 patients with prior cardiovascular comorbidities have been at risk of further cardiovascular injury. Among these patients with cardiovascular comorbidities, cTn has been associated with further adverse prognosis.

Role of troponin on outcomes and mortality in COVID-19:

Among patients with COVID-19, cTn was higher in deceased patients compared to survivors. Multiple studies have shown a significant correlation between cTn and in-

hospital adverse events and mortality even in patients without comorbidities (14,21–28) (Table 1). Multiple studies show that cTnT and cTnI are independent predictors of mortality even after adjusting for confounding factors (29,30). Scart *et al.* reported that, in hospitalized patients with pre-existing comorbidities and SARS-CoV-2, there was a significant correlation between serum cTnI level and mortality (21). Elevated cTn has been shown to correlate with severe disease, higher oxygen requirement, acute respiratory distress syndrome (ARDS), the need for respiratory support including noninvasive and invasive mechanical ventilation, the requirement of intensive care unit admission, acute kidney injury, multiorgan failure, sepsis, pulmonary embolism, major bleeding and in-hospital mortality. Troponin levels elevated five times the upper limit of normal have shown a 2.5% increase in in-hospital mortality. Salvatici *et al.* in their study utilising high sensitivity troponin, showed that in hospital survival rates was about 90% when cTnI was normal. The survival rate decreased to 87% when cTnI was above normal but less than 40ng/L, and further reduced to 59% with cTnI above 40ng/L (27). These studies have shown that cTn drawn at admission had a high positive predictive value for serious illness and a high negative predictive value for death. An up-trending cTn among COVID-19 patients is shown to correlate with a twofold increase in complications including sepsis, pulmonary embolism, and acute kidney injury and a threefold increase in mortality. The level of cTn has been shown to correlate with the outcome within 24 h of hospital admission. A study from Florida showed that COVID-19 patients with elevated cTnI levels in the first 24 h of admission had a significantly higher in-hospital mortality as compared to those with a normal cTnI level (28). Patients with a normal cTnI level at admission had a low risk of worse outcome demonstrating an 89.7% negative predictive value. Similar results were reported by two other studies showing an increased need for invasive mechanical ventilation and risk of death among patients with elevated cTn levels within the first 24 h of admission (18,19). Therefore, measurement of cTnI after hospitalization for COVID-19, followed by longitudinal monitoring, can help clinicians intercept dynamic changes in the levels of cTnI as a surrogate marker of myocardial injury.

Troponin as a surrogate marker of cardiovascular dysfunction post-discharge in COVID-19:

Elevated cTn has been associated with impaired left ventricular relaxation and decline in right ventricular function resulting in long-term sequelae. As a component of Long COVID-19, the persistence of cardiac injury has been reported in young patients following an acute COVID-19 episode until six months. A cross-sectional study of 144 patients who were followed up for 85 days after their recovery from SARS-CoV-2 showed that patients with baseline elevations in cTn had a higher incidence of dyspnea after discharge. These patients also had impaired diastolic dysfunction and elevated pulmonary artery (PA) pressures, as noted by echocardiography. They also had persistence of cTn until mid-follow-up (31). A rise in the incidence of HF has also been seen in COVID-19 patients with elevated cTn in two large multicenter studies (15,26). These studies signify that cTn can be used as diagnostic and prognostic tools for long-term cardiac outcomes related to SARS-CoV2 infection in select subgroup of patients. Despite these observations, clinical judgment should be used to avoid any unnecessary diagnostic and therapeutic interventions triggered by the isolated cTn elevation.

Natriuretic peptides:

Pathophysiology:

Natriuretic peptides (NPs), including BNP and NT-proBNP, are quantitative biomarkers of hemodynamic myocardial stress and heart failure (32). Brain natriuretic peptide is a preprohormone which is split into a single peptide and a propeptide (pro-BNP). Natriuretic peptides mediate their biological effects through guanylyl cyclase receptors (natriuretic peptide receptor [NPR]) A, B, and C. Stress of the ventricular wall due to volume or pressure overload is the primary inducer of BNP synthesis, which acts on the kidney to induce natriuresis and diuresis (33). Natriuretic peptides are considered one of the initial diagnostic tools in acute HF patients. Historically, studies like TOPCAT (34) have supported its value, and over the past years, NT-proBNP has had a growing role in the standardization of the definition of HF.

Natriuretic peptides as a diagnostic marker of cardiovascular injury in COVID-19:

Prior to the advent of SARS-CoV-2, multiple viral infections have been reported to induce HF due to direct viral invasion and pro-inflammatory cytokines leading to sympathetic activation. In SARS-CoV-2, elevation in NPs is a result of inflammatory overdrive, specifically interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1), which can lead to fulminant myocarditis. The rise in NPs is believed to be secondary to hypoxia and cardiac injury. In addition, widespread inflammation and decreased nitric oxide levels result in endothelial dysfunction, which causes heart failure symptoms. This can be a combination of pre-existing cardiac disease and the acute hemodynamic and hypoxemic stress related to COVID-19 (32,35). The use of vasopressor therapy, hypoxia-induced pulmonary vasoconstriction, inflammatory involvement of the myocardium, oxidative stress, and fibrin microthrombi in the vasculature contributes to the release of NPs (36–38). NPs are the second most studied cardiac biomarker in studies reporting cardiac injury in patients with COVID 19. Across multiple studies, NPs level were high among COVID 19 patients with and without HF. Higher levels of NPs have not been consistently shown to correlate with severe COVID 19 disease. Still, they have been shown to correlate with developing or worsening of heart failure in these patients (Table 2).

Role of natriuretic peptides as a prognostic indicator of cardiovascular complications in HF and COVID-19:

In patients with COVID-19 and myocardial injury, the elevation of NPs has been reported consistently (7,36) . Mehra *et al*. suggested that in patients with COVID-19 and cardiac comorbidities, the earliest manifestation of cardiac decompensation is due to diastolic dysfunction. This is secondary to hemodynamic instability and pulmonary complications in the early course of the disease. Subsequently, because of cytokine storm, systolic dysfunction ensues (39). Multiple studies have echoed a significant positive correlation between the rise in natriuretic peptides and disease severity in

SARS-CoV-2 (20,40–43) (summary in table 2). Many of these studies have utilised the cutoff points for NT-proBNP based off the triple cut point strategy from European society guidelines (32). A large multicenter study from Italy showed a positive correlation between the rise in NPs and associated SARS-CoV-2 severity (20). Half of the patients in this study had their NP level above the upper limit of normal. Similar results were reported from a large meta-analysis of 13 observational studies, including 2,248 patients. The average NT-proBNP among COVID-19 patients with severe disease was 791pg/mL, *vs* 160pg/mL in non severe patients (42). In patients with pre-existing HF and COVID-19, an elevation of NT-proBNP above the cut-off for normal (32) suggested an acute decompensation of HF, leading to a prolonged hospital stay (40). Interestingly, in a different study from New York that included 679 patients without a history of HF, elevations in NT-proBNP correlated with longer ICU stay, hospital stay, and the increased need for mechanical ventilation (43). Negative results were also seen in a few studies which did not identify any difference in the NP levels and COVID-19 severity (44–46). These were however small studies, and given the lack of a diverse population, the results cannot be generalized.

Role of natriuretic peptide on outcomes and mortality in COVID-19:

Heart failure per se is a significant risk factor for developing severe COVID-19 (1,2,12). In a series of 113 patients who died from SARS-CoV-2, HF was the most frequent cause of death after ARDS and sepsis (47). In patients with pre-existing HF, natriuretic peptides have been independently associated with increased odds of the need for mechanical ventilation and death across studies (40,48–55) as summarized in Table 2. In a large population study from Spain that enrolled patients with HF, elevation in NT-proBNP above the cut-off for normal was independently associated with mortality, even after adjusting for confounders (40). Gao *et al.* reported an increased mortality in COVID-19 patients who had an elevated BNP above 88.64pg/mL, with a 100% sensitivity and a 66.7% specificity (48). The significance of NPs in predicting mortality among SARS-CoV-2 patients is independent of their HF status. A single-center study

with 137 patients without a prior diagnosis of HF showed that elevation of NPs is an independent predictor of mortality (50). This study used a cut-off value of 260pg/mL, predicting in-hospital mortality with 82% sensitivity and 93% specificity. It must be noted that the threshold used for NT-proBNP in this study is lower than the cut-off used in the clinic and clinical trials for the diagnosis of HF. This implies that elevated NT-proBNP levels even within the upper limit of the normal reference range could indicate an occult cardiac injury in COVID-19 patients. In patients with chronic HF, an elevated pro-BNP above suggested cut off of 2598pg/mL was associated with an increased odds of 30 day mortality (52). An extensive systematic review from India, including 5,967 patients, found that non-survivors and patients with fulminant SARS-CoV-2 with elevated NPs, had an 8-fold increased risk of acute cardiac injury and death compared to their counterparts (53). The average NT-proBNP across patients with severe COVID-19 was 1142pg/mL. Two large center studies from Italy studied the combined role of troponins and NPs in COVID-19 associated disease progression and mortality. They found that patients with dual biomarker elevation had increased mortality, irrespective of their prior HF status (51,55).

Natriuretic peptides as a surrogate marker for new-onset heart failure post-discharge:

Elevated NT-proBNP in COVID-19 patients without cardiac comorbidities indicates SARS-CoV-2 mediated cardiac complications. New-onset HF was seen in 23% of hospitalized patients with COVID-19 and was the most frequent cause of death after sepsis and ARDS (47). A large prospective study in COVID-19 patients (56) used HFA-PEFF score (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology) with a specificity of 93% and a positive predictive value of 98% to rule in HFpEF. These patients had higher NT-proBNP levels when compared to their counterparts. Cardiac biomarkers are known to decline after the resolution of acute infection, as seen in ECHOVID-19 study (57). On the contrary, persistent biomarker elevation despite infection resolution has been noted in two different studies (58,59). They also had echocardiographic parameters of ventricular

dysfunction. The exact cause of reduced ventricular myocardial function is unknown; however, it is presumed to be secondary to systemic inflammation and ventricular remodeling (60–62). If the recovery is good, the prognosis is better, else, it predisposes them to the development of HF (63).

Additional biomarkers:

Other biomarkers have also been implicated in determining prognosis and predicting mortality in patients with SARS-CoV-2. Significant elevations in creatine kinase MB (CK-MB) and NT-proBNP above the upper limit of normal are seen in critically ill patients with COVID-19, helping in risk stratification (64,65). An increase in the level of myoglobin (MYO), NT-proBNP, and cTnI correlated with disease severity in patients with SARS-CoV-2 (66). Similar results were seen in two other studies identifying the prognostic significance of myoglobin, procalcitonin, and d-dimer in COVID-19 (67,68). Alongside troponin and natriuretic peptides, elevations in CK-MB and LDH (lactate dehydrogenase) have been shown to predict in-hospital mortality in patients with COVID-19 (69). Similarly, a rise in IL-6 and INR predicted an increased odds of 7-day mortality in patients admitted with SARS-CoV-2 (64). In addition, there is now data on novel emerging biomarkers and their role in predicting the disease severity in COVID-19. Among them, presepsin, growth differentiation factor 15 (GDF-15), soluble ST2, galectin 3, and copeptin have been studied.

Presepsin:

Presepsin is a CD14 biomarker released into circulation by pro-inflammatory signals during infection. Through its interaction with T and B cells, it acts as an immunomodulator and has diagnostic and prognostic significance in sepsis (70). Its role has been implicated alongside natriuretic peptides in the diagnosis of HF. A single-center study with 506 patients showed that presepsin was elevated in patients with acute HF decompensation and correlated with their 6-month mortality (71). Similar

results were seen in another study, with higher presepsin levels correlating with longer ICU stay and increased mortality (72).

Role of presepsin in prognosis and outcomes in COVID-19:

Presepsin elevation has been noted in patients with COVID-19, thus serving as a reliable biomarker (73). Studies have shown a four-to-five-fold increase in serum presepsin, which correlates with disease severity when compared to their counterparts (74–76). Fukada *et al.*, in a small series of patients with COVID-19-related respiratory failure, found that presepsin is more expressed in severe cases than in mild cases (77). Similar results have been seen in other studies identifying the prognostic importance of presepsin with COVID-19 related disease severity (73,78). Patients with presepsin values higher than 250ng/L had a longer ICU stay when compared to the patients with lower values (78). Park *et al.* suggested that an elevated presepsin level at 717pg/mL is a significant predictor of 30-day mortality (74). A threefold rise in presepsin has been identified as a very specific indicator of 30-day mortality (75,79). Thus, routine assessment of presepsin in COVID-19 may provide valuable clinical information for predicting adverse outcomes, as well as for guiding the clinical and therapeutic decision-making.

Soluble ST2:

Soluble ST2 (sST2) is among the most important novel biomarkers for prognosis in HF. Upregulated in states of mechanical strain, it plays an essential role in myocardial hypertrophy and fibrosis. Studies have shown an increase in sST2 gene expression in the presence of cardiac injury. High circulating levels of sST2 are involved in the aberrant inflammatory process of ARDS and have also been linked to acute and chronic HF, myocardial infarction, sepsis, and fibrosis (80). Among patients with ARDS, sST2 elevations up to ten times the normal expected for HF has been seen, and this correlated with an increase in their mortality (81,82). As evident in PRIDE study, among the 593 patients admitted with acute dyspnea, sST2 concentrations were higher among those with acute HF (79). NT-proBNP however outperformed sST2 for acute HF diagnosis (AUC = 0.94 *vs* 0.80; $P < .001$). In patients with HFpEF, Manzano–Fernández *et al*

showed sST2 to be superior to NT–proBNP for prognosis (83). In addition, it also strongly correlated to the 30-day, one-year, and four-year mortality. Rehman *et al.* found that values of sST2 correlated with the severity of HF, making it a powerful predictor of mortality (84). Lassus *et al.* showed that in patients with pre-existing HF, sST2, relative to other biomarkers, is a powerful variable for one-year mortality (85). Similarly, Breidthardt *et al.* reported that a dynamic change in sST2 value from admission to discharge was a stronger predictor of mortality than baseline values alone (86).

Role of sST2 in prognosis and outcomes in COVID-19:

Soluble ST2 is linked to SARS-CoV-2 viremia and indicators of inflammation, cardiovascular disease, and thrombosis. Omland *et al.*found an association between sST2 and disease severity among patients hospitalized for COVID-19 and was independent of established risk factors (87). Elevated ST2 concentrations above 37.9 ng/mL correlated with severe disease, with non-survivors having concentration as high as 107ng/mL. Similar results were seen by Huang *et al*. and Ragusa *et al.,* who concluded that sST2 is an important COVID-19 prognostic marker and correlated with disease severity (88,89). This association was deemed secondary to pulmonary fibrosis, seen as a complication in COVID-19. Elevations in sST2 Levels strongly correlated with mortality in ICU patients with sepsis secondary to COVID-19 (87,90). Omland *et al*. also noted that elevations in sST2 correlated with poor outcomes on days 3 and 9 of hospitalization among patients with COVID-19 (87).

Galectin-3 (Gal-3):

Galectin-3 is a mineralocorticoid receptor-regulated pro-inflammatory molecule. It exhibits a pleiotropic role in mediating infection and inflammation. Gal-3 is a biomarker of fibrosis and inflammation and has been implicated in the development and progression of HF (91). ARDS is chiefly mediated by releasing IL-1, IL-6, and TNF-α from macrophages, monocytes, and dendritic cells (92). Gal-3 inhibition has been shown to reduce the release of these cytokines from immune cells (93). The PRIDE study showed that higher galectin–3 concentration was a strong independent predictor of 60–

day mortality and recurrent HF admissions (94). Shah *et al.* showed that galectin–3 above a median value of 15.0 had a strong prognostic significance in HF and was a significant predictor of 4-year mortality (95).

Role of galectin-3 in prognosis and outcomes in COVID-19:

Multiple studies have shown Gal-3 to be upregulated in patients suffering from severe COVID-19. Among patients with COVID-19, Gal-3 was shown to be considerably higher in bronchoalveolar immune cells in patients with severe disease when compared to those with mild disease (96). Higher galectin–3 Levels were found to be a major predictor of 60–day mortality and recurrent HF hospitalizations. In a study of SARS-CoV-2 associated ARDS patients, high Gal-3 above 35.3ng/mL was linked to worse outcomes and shorter survival (97).

Copeptin:

Copeptin is a surrogate marker for vasopressin release. Copeptin is an arginine- vasopressin (AVP) glycopeptide composed of 39 amino acids. It is released from the neurohypophysis by osmotic or hemodynamic stimulation with AVP, and its plasma levels correlate well. AVP is an antidiuretic and vasoconstrictive hormone. It shows the endogenous stress response and is released by stimuli including hypotension, hypoxia, and infections. However, its circadian rhythm, short half- life, and unstable molecule make it impossible to use it as a biomarker (98). Copeptin is a more stable peptide, and its level in the blood can be easily detected. The role of copeptin has been implicated in chronic HF. Elevated copeptin levels, especially in HF patients with hyponatremia, has been linked to poor outcomes. Maisel *et al.* noted that patients with elevated copeptin levels had a greater risk of 90-day mortality and HF readmission (99).

Role of copeptin in prognosis and outcomes in COVID-19:

The importance of copeptin as a biomarker in COVID-19 patients has not been very well studied. Gregoriano *et al.* found that the rise in copeptin levels correlated with the disease severity in COVID-19 patients (100). Copeptin level of 20pmol/L had an 88.2% sensitivity and a 64.9% specificity for identifying severe disease. Similar results were

seen by Hammad *et al*. by using a cut off level of 18.5pmol/L, yielding a sensitivity of 93.3% and a specificity of 100% for severe COVID-19 disease (101). In these studies, patients with severe COVID-19 disease were also noted to have increased mortality.

Growth differentiation factor 15 (GDF-15)

Growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine (MIC-1), is a member of the transforming growth factor-beta (TGF-β) superfamily that helps tissues survive inflammatory stress. GDF-15 expression outside the reproductive organs is low to absent; it is upregulated in pathological conditions that involve inflammation or oxidative stress, including cancer, cardiovascular, pulmonary, and renal disease (102)

Role of GDF-15 in prognosis and outcomes in COVID-19:

In a study of 84 patients with COVID-19, Alserawan *et al.* determined that higher circulating levels of GDF-15 correlated with the disease severity (103). Patients with COVID-19 had an average GDF-15 Level of 2051pg/mL when compared to 582pg/mL in non COVID patients. GDF-15 Levels were higher in patients requiring mechanical ventilation and correlated with increasing oxygen requirements. In a different study by Verhamme *et al*., higher GDF-15 Levels were associated with increased mortality risk (102).

Figure 2 illustrates the variation of different cardiac bioenzymes across different etiologies for cardiovascular dysfunction.

Discussion:

SARS-CoV-2 associated COVID-19 infection is a global disease with multiple clinical manifestations. Cardiovascular complications are a dreaded outcome, and assessment of cardiac bio enzymes is crucial in gauging the disease severity. Our review aims at highlighting the variation in these bio enzymes through the disease process and their role in predicting outcomes.

Troponin has been seen as a robust indicator of cardiovascular injury across aetiologies including myocarditis, coronary syndromes, and cardiomyopathy. Serum cTn above 0.09ng/mL have been shown to confer a higher risk of cardiovascular injury. Generally, studies have shown that troponin levels above the 99th percentile of upper limit of normal are associated with a worse prognosis. Elevated levels on admission, and serial up-trending carry a high positive predictive value for worse prognosis. Furthermore, long term sequelae with impaired ventricular function and subsequent development of heart failure is seen in a select subset of patients with cTn elevation.(103) Alongside cTn, natriuretic peptides help in prognostication mainly in patients with HF. Elevations in levels above cut off for normal (32) have been associated with worse outcomes. Multiple different studies citing the utility of NPs have been included in this review, and each of them had a unique cut off for HF. Irrespective of the cut-off used, elevated NT-proBNP was independently associated with poor outcomes regardless of the HF status. (104) This finding was common across studies.

The role of a few of these cardiac biomarkers has been studied before. However our review is unique in its discussion about the role of novel biomarkers including presepsin, soluble ST2, galectin-3 which have not been studied extensively yet. Prior studies have highlighted their importance in HF, but not so much in COVID-19. Our review has consolidated these studies, to mention that these biomarkers, similar to troponin and NPs are elevated in patients with severe COVID-19 and can aid in prognosis. (105,106)

Our study has a few limitations too. Majority of the studies that have been included are from China and European countries. This is partly because many studies were originally from Wuhan China, where the pandemic began, opening a possibility that many patients would have been repeated across studies. Another limitation is the nature of these studies, majority were retrospective or observational in nature. The

trend of these bio enzymes could not be followed in patients who recovered from the illness. Small sample size of a few of these studies also precludes the generalisability. Hence future large prospective studies with follow up will be beneficial, especially for novel biomarkers.

CONCLUSION

SARS-CoV-2 associated COVID-19 infection undeniably has respiratory complications, however, extensive cardiovascular implications are also seen. Multiple cardiac biomarkers can help predict the severity of the disease and serve as prognostic indicators for outcomes and mortality. Assessment of cardiac bioenzymes at admission and their serial monitoring can help assess the severity of disease and predict mortality in patients with SARS-CoV-2 infection. A more liberal determination of cardiac biomarkers may improve early diagnosis and management of AHF, and other cardiovascular complications. COVID-19 associated myocarditis and HF have sequential effects even after the resolution of primary illness, and hence long-term correlation needs to be studied. In addition, there is emerging data on novel biomarkers, including growth differentiation factor 15 (GDF-15), soluble ST2, galectin 3, presepsin, and copeptin, which can aid in evaluation alongside natriuretic peptides and troponins. Further studies are needed to elude the critical importance of these novel markers.

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