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REVIEW ARTICLE

The use of cardiac troponins and B-type natriuretic peptide in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is still challenging health care systems worldwide. Over time, it has become clear that respiratory disease is not the only important entity as critically ill patients are also more prone to develop complications, such as acute cardiac injury. Despite extensive research, the mainstay of treatment still relies on supportive care and targeted therapy of these complications. The development of a prognostic model which helps clinicians to diverge patients to an appropriate level of care is thus crucial. As a result, several prognostic markers have been studied in the past few months. Among them are the cardiac biomarkers, especially cardiac troponins T/I and brain natriuretic peptide, which seem to have important prognostic values as several reports have confirmed their strong association with adverse clinical outcomes and death. The use of these biomarkers as part of a prognostic tool could potentially result in more precise risk stratification of COVID-19 patients and divergence to an adequate level of care. However, several caveats persist causing international guidelines to still recommend in favour of a more conservative approach to cardiac biomarker testing for prognostic purposes.

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Background

COVID-19 is still dominating human society. As of 21 February 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 110 million people worldwide, resulting in over 2.4 million deaths [1]. Although the main focus remains on pulmonary disease, cardiac involvement in patients with severe COVID-19 is also of concern as these patients are more likely to develop adverse clinical outcomes, such as acute cardiac injury and ultimately, death [2]. As there is no targeted therapy yet, a prognostic model for early triage to appropriate care, further investigations and prevention of complications could be useful. Cardiac troponins (cTn) and B-type natriuretic peptide (BNP) are frequently increased in severe COVID-19 cases and might be associated with adverse outcomes and mortality. The aim of this paper is to provide an overview of the prognostic role of these biomarkers in COVID-19.

Cardiac injury and the role of cardiac troponin in COVID-19

Cardiac troponin I and T (resp. cTnI, and cTnT) are regulatory proteins that control the calcium-mediated interaction between actin and myosin, and are exclusively found in cardiac myocytes [3]. When the myocardial injury occurs, they leak into the bloodstream and can be detected by various assays. Therefore, the assessment of cardiac troponins is the preferred serologic test for the evaluation of patients with suspected myocardial injury [4]. The value varies depending upon which assay is used, although values above the 99th percentile of the upper reference limit (URL) are considered abnormal [5].

Myocardial injury in COVID-19 can be subdivided between non-ischaemic and ischaemic causes. Non-ischaemic myocardial injury may be the result of a variety of mechanisms, such as myocarditis, Takotsubo syndrome, tachycardia, pulmonary embolism, and septic shock [6–10]. Equally important, SARS-CoV-2 is known to use the angiotensin-converting enzyme 2 (ACE-2) receptor, which is abundant in the human heart and vasculature, for ligand binding and entering the cell, resulting in viral replication and non-ischaemic cell damage [11]. Ischaemic cardiac damage, on the other hand, can be both caused by type 1 and type 2 ischaemia [5]. The underlying pathophysiology of type 1 ischaemia (T1I) in COVID-19 is not fully

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understood. On one hand, the inflammatory response due to a COVID-19 infection may lead to plaque instability by activating inflammatory cells in the plaques and release of inflammatory mediators, causing oxidative stress. On the other hand, COVID-19 infection is associated with endothelialitis and a prothrombotic state [12–16]. Type 2 ischaemia (T2I) can be attributed to hypoxaemia, sometimes combined with a hypovolemic state, which causes a demand-supply inequity of oxygen [14].

Myocardial injury is both common and important in critically ill patients but often goes unnoticed on the surface ECG [17]. The prevalence of elevated cTn in COVID-19 patients varies widely, ranging from 20% in cohorts of hospitalised patients to more than 40% in critically ill patients [2,18,19]. Despite the high prevalence of elevated cTn, several reports in different countries have reported a substantial decrease in hospital admissions for acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI) procedures during the COVID-19 era [20–23]. A recent, large retrospective study in England compared hospital admission for ACS between January and May 2020 with the weekly average in 2019 and confirmed this reduction in admission (23% reduction in admission for ST-elevation myocardial infarction (STEMI) and 42% reduction in admissions for non-STEMI) [24]. However, this reduction may be due to an under-detection of ACS, rather than a true decline in incidence, as the time between symptom onset and first medical contact is clearly increased, mainly because people fear infection in the hospital environment [24,25]. On the other hand, it may be possible that elevated cTn in the largest portion of COVID-19 patients do not represent ischaemic cardiac injury, but are due to non-ischaemic causes. The true incidence of T1I in COVID-19 is not known and it is suggested that it may be even decreased due to reduced air pollution, less work-related stress, and less physical activity during the multiple lockdowns in different countries [25]. However, there is currently no clear evidence to support this statement.

In the past, myocardial injury has proven to be an independent predictor of mortality in patients with acute respiratory failure [26]. Early in the pandemic, two Chinese retrospective cohort studies showed similar findings in acute respiratory failure due to COVID-19 [2,19]. In the first report, Shi et al. retrospectively studied 416 hospitalised COVID-19 patients in which they reported that compared to those without cTn elevation, patients with an elevated cTn needed more mechanical ventilation (22.0% vs. 4.2%: $p < 0.001$), experienced more ARDS (58.5% vs. 14.7%: $p < 0.001$) and had a 10 fold higher mortality rate (51.2% vs. 4.5%: $p < 0.001$, adjusted HR 3.41, 95% CI 1.62–7.16) [2]. In the second report, Guo et al. examined a cohort of 187 hospitalised COVID-19 patients and confirmed that elevated cTn levels have a significant association with fatal outcomes. Additionally, dynamic changes in cTn levels during admission were also associated with mortality, as an increase in these parameters was only seen in those who ultimately died [19]. Following these initial observations, a myriad of studies has investigated the role of circulating cardiac biomarkers. Zhou et al. showed that a cTn over the 99th URL was retrospectively associated with an odds ratio for death of 80.1 [27]. A retrospective cohort study of Al Abbasi et al. of 257 patients showed that, in addition to being associated with mortality, a low cTn on admission had a high negative predictive value (89.7%) for all-cause in-hospital mortality [28]. Prospectively, Saleh et al. reported that, in a cohort of 386 hospitalised patients with COVID-19, the presence of cardiac injury was significantly associated with a higher in-hospital mortality rate compared to those with normal troponin levels [29]. Finally, several meta-analyses of observational, retrospective studies confirmed that the association between cardiac injury and adverse clinical outcomes is consistent, as summarised in Table 1. Nevertheless, retrospective studies are inherently prone to bias. Therefore, more prospective studies are needed to further validate these observational data.

Hemodynamic stress and the role of brain natriuretic peptide in COVID-19

Brain natriuretic peptide (BNP) is a natriuretic hormone that was first identified in the brain, though is primarily released in the cardiac ventricles in response to high ventricle filling pressures and ventricular wall stress [30]. BNP and its N-terminal portion (NT-proBNP) are usual markers for congestive heart failure (CHF), though maybe elevated in several other (non-)cardiovascular conditions, with age and renal impairment being the most important ones. On the other hand, values may be disproportionately low in obese patients [31]. Therefore, the diagnosis of CHF cannot be made solely upon the measurement of (NT-pro)BNP and remains mainly clinical, based upon typical symptoms and signs (e.g. fatigue, dyspnoea, peripheral oedema, elevated jugular pressure), mostly added with cardiac imaging [31]. These symptoms may however be subtle and/or evoked by other cardiopulmonary comorbidities, such as COVID-19, which makes a definitive diagnosis often hard to

Table 1. Non-exhaustive list of meta-analyses comparing outcomes between COVID-19 patients with and without evidence of cardiac injury or wall stress.

First author, journal	Publication date	Study size	Outcome	Result
Cardiac injury				
Santoso A, et al., Am J Emerg Med [46]	April 2020	13 studies 2389 patients	• Mortality • ARDS • ICU admission • Severe disease	• Mortality RR 7.95 (95% CI 5.12-12.34, I^2 65%) • ARDS RR 2.57 (95% CI 0.96–6.85: I^2 84%) • ICU admission RR 7.94 (95% CI 1.51–41.78, I^2 79%) • Severe disease RR 13.81 (95% CI 5.52–34.52: I^2 0%)
Li X, et al., Heart [47]	April 2020	8 studies 1429 patients	• Mortality	• Mortality OR 21.15 (95% CI 10.19–43.94: I^2 71%)
Shao M, et al. J Geriatr Cardiol [48]	April 2020	9 studies 1470 patients	• Mortality	• Mortality OR 13.68 (95% CI 9.81–19.08 I^2 52%)
Dawson D, et al. Res Sq [49]	June 2020	12 studies 2197 patients	• Mortality	• Mortality OR 6.641 (95% CI 1.26–35.1)
Aikawa T, et al, J Med Virol [50]	June 2020	6 studies 1231 patients	• Mortality	• Mortality OR 22.7 (95% CI 13.6–38.1: I^2 28%)
Li X, et al., Crit Care [51]	July 2020	23 studies 4631 patients	• Mortality • Severe disease • ICU admission	• Mortality RR 5.64 (95% CI 2.69–11.83: I^2 89.1%) • Severe disease RR 5.57 (95% CI 3.04–10.22: I^2 78.6%) • ICU admission RR 6.20 (95% CI 2.52–15.29: I^2 89.3%)
Li J, et al., Prog Cardiovasc Dis [52]	July 2020	28 studies 4189 patients	• Mortality	• Mortality RR 3.85 (95% CI 2.13–6–96: I^2 89.6%)
Sanz-Sánchez J, et al., Hellenic J Cardiol [53]	August 2020	14 studies 6462 patients	• Mortality	• Mortality OR 9.16 (95% CI 5.30–15.83: I^2 88.8%)
Zhou F, et al., CJC Open [54]	September 2020	16 studies 2224 patients	• Mortality • Composite of death, ICU admission, respiratory failure in need of mechanical ventilation, or shock	• Mortality OR 17.32 (95% CI 9.21–32.57: I^2 66%) • Composite 17.83 (95% CI 10.89–29.21: I^2 52%)
Huang Z, et al. Nutr Metab Cardiovasc Dis [55]	September 2020	43 studies 9475 patients	• Mortality • Severe disease • ICU admission	• Mortality ES 4.99 (95% CI 3.38–7.37: I^2 91.4%) • Severe disease ES 3.54 (95% CI 2.25–5.58: I^2 80.3%) • ICU admission ES 5.03 (95% CI 2.69–9.39: I^2 87.2%)
Zeng L, et al. Epidemiol Infect [56]	October 2020	17 studies 5726 patients	• Mortality • AKI • ARDS • ICU admission	• Mortality RR 4.89 (95% CI 3.84–6.22: I^2 60%) • AKI RR 10.09 (95% CI 3.06–33.29: I^2 71.2%) • ARDS RR 5.89 (95% CI 3.30–10.53: I^2 64.4%) • ICU admission RR 2.99 (95% CI 1.85–4.83: I^2 92.8%)
Zuin M, et al. J Cardiovasc Med [57]	October 2020	8 studies 1686 patients	• Mortality	• Mortality OR 21.6 (95% CI 8.6–54.4: I^2 82%)
Hessami A, et al. Am J Emerg Med [58]	October 2020	56 studies 29056 patients	• Mortality • ICU admission	• Mortality OR 13.29 (95% CI 7.35–24.03: I^2 74.3%) • ICU admission OR 15.58 (95% CI 5.15–47.12: I^2 61.7%)
Bansal A, et al., Am J Cardiol [14]	November 2020	14 studies 3175 patients	• Mortality • ICU admission • Mechanical ventilation • Coagulopathy • ARDS • AKI	• Mortality RR 7.79 (95% CI: 4.69–13.01: I^2 58%) • ICU admission RR 4.06 (95% CI: 1.50–10.97: I^2 61%) • Mechanical ventilation RR 5.53 (95% CI: 3.09–9.91: I^2 0%) • Coagulopathy RR 3.86 (95% CI: 2.81–5.32: I^2 0%) • *ARDS RR 3.22 (95% CI: 0.72–14.47: I^2 73%) • * AKI RR 11.52 (95% CI: 0.03–4159.80: I^2 0%)
Zhao B, et al. J Intensive Care [59]	November 2020	11 studies 13 889 patients	• Mortality	• Mortality RR 2.68 (95% CI 2.08–3.46: I^2 76.2%)
Malik P, et al. Infez Med [60]	December 2020	10 studies 3982 patients	• Mortality	• Mortality OR 7.92 (95% CI 3.70–16.97: I^2 70%)
Wall stress				
Pranata R, et al. Postgrad Med J [33]	April 2020	6 studies 967 patients	• Mortality	• Mortality RR 3.63 (95% CI 2.21–5.95: I^2 60%)

Most of the included studies defined cardiac injury as cTn elevation above the 99th percentile of the URL. RR: relative risk; OR: odds ratio; ES: effect size. *Non-statistically significant result.

establish. Therefore, (NT-pro)BNP does play a growing role in defining and standardising CHF [32]. The typical cut-off values are subdivided between acute and chronic CHF. The URL in the non-acute setting for BNP is 35 pg/mL and for NT-proBNP 125 pg/mL, whereas higher values should be used in the acute setting (BNP $>$ 100 pg/mL and NT-proBNP $>$ 300 pg/mL) [31].

The presence of circulating (NT-pro)BNP in patients with COVID-19 can be attributed to several factors. First and foremost, the cardiac injury may lead to cardiac dysfunction and increased ventricular wall stress. Additionally, the use of mechanical ventilation and vasopressor agents in critically ill patients may increase myocardial wall stress [33]. Hypoxia-induced pulmonary hypertension may further aggravate myocardial wall stress by increasing right ventricular afterload [34,35]. Furthermore, acute kidney injury, which has been reported in up to 25% of critically ill patients with COVID-19, may reduce the clearance of natriuretic peptides (and cTn) and therefore also increasing its plasma level [34,36].

CHF is one of the leading causes of morbidity and mortality worldwide and infectious agents, such as influenza, have proven to be a known trigger for acute decompensation [37]. Moreover, the presence of (NT-pro)BNP is associated with an unfavourable course among patients with inflammatory and/or respiratory problems, e.g. pneumonia and ARDS [38–42]. However, data about the prognostic implication of circulating (NT-pro)BNP in COVID-19 is scarce, although existing data suggest that it may be an indicator of clinical severity and adverse outcome as well.

In early COVID-19 reports, Guo et al. and Shi et al. noted a significant positive correlation between NT-proBNP levels and cTn levels. Moreover, they found that both increased significantly in those who did not survive [2,19]. However, these reports did not show an independent association between elevated NT-proBNP and mortality. Gao et al. were the first to state that elevated admission levels of NT-proBNP might be an independent predictor of mortality, though the sample size in this retrospective observational study was low (55 patients) [43]. A meta-analysis of Pranata et al., including 967 patients in 6 retrospective studies, confirmed that elevated NT-proBNP was significantly associated with increased mortality (RR 3.63 (95% CI 2.21–5.95) [33]. As previously stated, more good-quality evidence is needed in order to further validate these findings.

Clinical use in COVID-19

Although both cardiac biomarkers have proven their prognostic value before the COVID-era, their clinical use in COVID-19 patients remains unclear. Nevertheless, published data have underscored the association between elevated cardiac biomarkers and adverse outcomes. Therefore, these markers could be integrated into prognostic models which might help in clinical decision making and the triage of high-risk patients to a higher level of monitoring. Based upon serial measurement of cardiac biomarkers, one could identify two distinct groups of patients. On one hand, there are patients with no or only mildly elevated cTn (typically below the 99th percentile of the URL) and no significant rise during the subsequent days. This is the most frequent pattern of cTn elevation in patients with COVID-19 and seems to be associated with overall survival. On the other hand, there are patients with a cTn on admission above the 99th percentile of the URL and/or clinical deterioration over the subsequent days with a progressive increase of these (cardiac) biomarkers. This pattern seems to be associated with non-survivors.

Although easy to use, the discussion will remain whether or not to use cardiac biomarkers routinely in every COVID-19 patient. As Sandoval et al. recently stated, a big caveat is a fact that a liberal biomarker measurement should always be accompanied by education about implications and responses to testing results, as it should not lead to unnecessary diagnostic investigations and medical overuse [44]. Furthermore, until now, treatment of a COVID-19 patient is mainly supportive and no specific therapeutic intervention has proven benefit following elevated cTn and/or BNP [10]. Last, several other (bio)-markers (e.g. lymphocyte count, IL-6, SOFA-score, D dimers) are also readily available and of prognostic value. Whether cTn and/or BNP are of incremental value to these markers is not yet known, although Manocha et al. recently published data that suggest that cTn is the most potent predictor of mortality and that the utility of tracking a wide range of biomarkers other than cTn for prognostic purposes may be limited [45].

Due to the poverty of good quality, prospectively designed, large-scale studies, current observations may be severely biased. While awaiting good quality evidence, international organisations, such as the European Society of Cardiology, currently do not recommend routine measurement of cTn and BNP in the context of COVID-19 prognostication [10].

Conclusion

Cardiac troponins and brain natriuretic peptide are important cardiac biomarkers and extensively proved their usefulness before the COVID-19 era. In COVID-19, these markers have been shown to be associated with

unfavourable outcomes. When used appropriately, they could help in prognostication and must not necessarily lead to medical overuse. However, current data are almost solely based upon small observational series, prone to several forms of bias. Until more high-quality evidence is available, the discussion will remain whether or not these biomarkers should be routinely measured to optimise risk stratification and triage in COVID-19 patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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