

High-Sensitivity Cardiac Troponin Can Be An Ally in the Fight Against COVID-19

Running Title: *Chapman et al.; Troponin in the Fight Against COVID-19*

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel pathogen responsible for the now widely recognised disease, COVID-19. To date, there are no evidence-based treatments, and the mainstay of management is supportive care. Mortality estimates for the condition vary, with an overall case fatality rate between 1.4% and 2.3%. [1,2] Despite only a minority of patients having a severe illness, the observed exponential spread of COVID-19 across many countries indicates the critical care capacity in every region and country may become overwhelmed. As such, it is imperative that we effectively risk stratify patients to determine those at highest risk who may require more intensive surveillance and support. Similarly, in patients most vulnerable for adverse outcomes, early recognition of a clinical state that is incompatible with survival may inform clinical decision making to prioritize palliative care and influence resource allocation, in a manner similar to triage after a major incident.

The American College of Cardiology recently published a short review of the role of biomarker testing in patients with COVID-19. It states *'clinicians are advised to only measure troponin if the diagnosis of acute myocardial infarction is being considered on clinical grounds'*. [3] This approach was recommended on the basis that troponin elevation in patients with COVID-19 is likely to be multifactorial, and less likely to be due to atherothrombotic coronary occlusion.

Circulating cardiac troponin is a marker of myocardial injury, including but not limited to myocardial infarction or myocarditis and the clinical relevance of this distinction has never been so clear. Clinicians who have used troponin measurement as a binary test for myocardial infarction independent of clinical context and those who consider an elevated cardiac troponin concentration to be a mandate for invasive coronary angiography must recalibrate. Rather than encouraging avoidance of troponin testing, we must harness the unheralded engagement from the

cardiovascular community due to COVID-19 to better understand the utility of this essential biomarker and to educate clinicians on its interpretation and implications for prognosis and clinical decision making.

Whereas the interpretation of high-sensitivity cardiac troponin (hs-cTn) concentrations can undoubtedly cause frustration to those who long for a disease-specific biomarker for myocardial infarction, there is an opportunity here. With COVID-19 infection, mortality rates are highest in those who are older (14.8% in those over 80 years) and in those with a history of underlying cardiovascular disease.[1] In a cohort of 191 patients with confirmed COVID-19 based on SARS-CoV-2 RNA detection, the univariable odds ratio for death when hs-cTnI concentrations were above the 99th percentile upper reference limit was 80.1 (95% confidence interval [CI] 10.3 to 620.4, $P < 0.0001$).[4] This was higher than the odds ratios observed for all other biomarkers tested, including D-Dimer and lymphocyte count. A further study of 416 hospitalized patients with COVID-19 reported that cardiac troponin concentrations were elevated in 1 in 5 patients on presentation. These patients were more likely to require invasive or non-invasive ventilation (22% versus 4%, and 46% versus 4%), and to develop acute respiratory distress syndrome (59% versus 15%) or acute kidney injury (9% versus 0%, $P < 0.001$ for all). The observed rate of mortality was 10-fold higher in those with myocardial injury on presentation (51% versus 5%, adjusted hazard ratio 3.41 (95% CI 1.62-7.16)).[5]

If clinicians are reluctant to measure cardiac troponin in these patients, the consequence may be to ignore the plethora of ischemic and non-ischemic causes of myocardial injury related to COVID-19 (*Figure*), which may be directly or indirectly associated with poor outcomes. Early recognition could facilitate appropriate triage to a high intensity or critical care area, improve our understanding of the systemic consequences of COVID-19, and inform the use of

inotropes, vasopressors, and diuretics in those with significant cardiac dysfunction. Furthermore, testing may identify patients with a clearly defined cardiac phenotype with therapeutic implications. For example, it has been suggested that patients with COVID-19 associated myocarditis may benefit from other therapies such as a combination of immunoglobulin and corticosteroid therapy.

Elevated cardiac troponin concentrations are common in hospitalized patients and are as likely to be due to non-ischemic causes of myocardial injury or type 2 myocardial infarction (myocardial oxygen supply-demand imbalance), than as a consequence of an acute coronary syndrome. While these patients are at increased risk of future cardiovascular events and may have underlying coronary artery disease, they do not have acute atherothrombosis, and there is no established role for dual anti-platelet therapy, anti-coagulants, or early coronary angiography. In a situation in which the majority of hospitalized patients may be affected by COVID-19 and have significant respiratory compromise, the prevalence of non-ischemic myocardial injury and type 2 myocardial infarction is likely to increase.

In critically unwell patients, oxygen supply-demand imbalance does not exclusively affect the myocardium, and is likely to be occurring at a cellular level in the majority of organ systems. However, it is the sensitivity of cardiac troponin testing that ensures it is one of the earliest and most precise indicators of end organ dysfunction. Here, cardiac troponin testing could prompt early initiation of measures to improve tissue oxygenation and perfusion.

We acknowledge that cardiac troponin testing in patients with COVID-19 could increase the need for cardiology consultation and downstream testing, including bedside echocardiography and angiography. However, the recognition of a normal or modestly elevated troponin could conversely reduce the need for cardiac imaging and minimize the risk of exposure

to cardiac physiology staff. The role of further investigation must be carefully considered and based on risk to the individual performing the test and the likelihood of informing clinical management. Whereas the decision to undertake coronary angiography with appropriate personal protective equipment may be straightforward in a patient with regional ST-segment elevation and symptoms of myocardial ischemia, distinguishing pulmonary edema from acute respiratory distress syndrome (ARDS) may be more challenging. In this setting, cardiac biomarkers, such as hs-cTn and NT-pro BNP may be informative, and certainly require further evaluation.

Although it is prudent to act with caution, it is likely that the studies published to date have over-estimated the prevalence of myocardial injury. Troponin testing was available in 145/191 (75%) patients included in a report drawn from 813 consecutive adults admitted to Jinyintan Hospital or Wuhan Pulmonary Hospital [4], and in 416/645 (64%) consecutive patients admitted to the Renmin Hospital of Wuhan University [5]. It is likely that cardiac troponin measurements were requested in those who were more unwell or where there was reasonable suspicion of myocardial ischemia or myocardial dysfunction. Only systematic testing of both symptomatic and asymptomatic patients infected with SARS-CoV-2 will provide an accurate estimate of the prevalence of myocardial injury in this condition.

Clinicians must recognize that troponin is *not* a test for myocardial infarction, and it never was. No biomarker has ever had the ability to detect acute atherothrombotic occlusion in a coronary artery. This myth has been perpetuated in clinical practice and it is limiting our ability to evaluate and triage care in critically unwell patients. We need, more rather than less, information to guide the international response to the COVID-19 pandemic. Taken together with clinical assessment and the electrocardiogram, elevations of cardiac troponin can inform the diagnosis of a number of cardiac conditions related to COVID-19. We must take advantage of all

available prognostic markers to identify patients with important systemic consequences of COVID-19 and determine those at highest risk of adverse outcomes as early as possible.

Troponin should be considered an ally and a crucial diagnostic and prognostic aid in what will become even more challenging times for healthcare provision worldwide.

Acknowledgments

ARC receives support from a Starter Grant for Clinical Lecturers by the Academy of Medical Sciences (SGL021/1075). AB and NLM are funded by a Scholarship (CH/09/002) and the Butler Senior Clinical Research Fellowship (FS/16/14/32023) from the British Heart Foundation.

Disclosures

ARC and AB have no declarations of interest. NLM has received honoraria from Abbott Diagnostics, Roche Diagnostics, Siemens Healthineers, and LumiraDx, and the University of Edinburgh has received research grants from Abbott Diagnostics and Siemens Healthineers.



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Figure Legend

Figure. Potential mechanisms of acute myocardial injury in COVID-19 and related cardiac phenotypes

Potential mechanisms of myocardial injury in COVID-19 and related cardiac phenotypes include viral myocarditis, coronary microvascular ischemia mediated by SARS-CoV-2 binding of the endothelial ACE-2 receptor, or stress cardiomyopathy and tachyarrhythmia due to endogenous or exogenous adrenergic stimulation. Type 1 myocardial infarction due to atherothrombosis may be triggered by the proinflammatory and prothrombotic state. Type 2 myocardial infarction is more likely in those with prolonged myocardial oxygen supply or demand imbalance with hypoxia, hypotension or tachycardia.

