A Marker of Systemic Inflammation or Direct Cardiac Injury: Should Cardiac Troponin Levels be Monitored in COVID-19 Patients?

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As the medical and scientific community grapples with the rise of coronavirus disease 2019 (COVID-19), the continuous critical reflection and subsequent modification of the current protocols in place has been, and will continue to be, tantamount to an optimised outcome. The most recent enigma concerning COVID-19 has involved it's two-way relationship with cardiac disease; as both an established risk-factor, and a possible complication in its pathogenesis.

The first and perhaps most significant overlap between COVID-19 and cardiac disease lies in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)'s pathogenicity and virulence. SARS-Cov-2, like other coronaviruses, was found to utilise its characteristic spike glycoprotein to hijack cells by binding to their angiotensin-converting enzyme 2 (ACE2) receptors on the cell's outer surface—An enzyme that is highly expressed in the lungs, as well as myocytes and vascular endothelial cells.[1,2] As such, despite the evidently manifesting impact of this on the host's respiratory system, it is unclear to what extent of severity and breadth the cardiovascular system is involved.

In a prospective cohort study in Wuhan, China, laboratory findings from 416 hospitalized patients diagnosed with COVID-19 were analysed (median age 64 [21-95] years, 50.7% female). Of this cohort, 19.7% of patients had cardiac injury, accompanied by more comorbidities, and higher levels of C-reactive protein (CRP), procalcitonin, creatine kinase-myocardial band (MB fraction), myoglobin, high-sensitivity troponin I (hs-cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), aspartate aminotransferase (AST) and creatinine. A greater proportion of patients with cardiac injury required both invasive and non-invasive mechanical ventilation compared to patients without cardiac injury. Complications were also more common, in addition to a higher mortality (42 of 82 [51.2%] vs 15 of 334 [4.5%]; P<.001). The study emphasises the significant role of the cardiac system in the pathophysiology of COVID-19. However, since many of the patients included in the

analysis are still being observed and have not reached clinical end points, and since electrocardiography and echocardiography data as well as cytokine level measurements were not collected, the exact contribution of COVID-19 towards the elevated lab values and poor prognosis cannot be identified with certainity.[3]

In another retrospective cohort study of 191 adult patients (median age 56 [18-87] years; 62% male) in Wuhan, China, cardiac involvement was likewise evident. Of the non-survivors (54 patients), 59% had acute cardiac injury, 50% had coagulopathy, and 52% heart failure. Interestingly, the median time from illness onset to acute cardiac injury among non-survivors was 14.5 days, compared to only one incidence of acute cardiac injury in survivors, which took place 21 days post-illness onset. Non-survivors had higher levels of d-dimer, hs-cTnI, lactate dehydrogenase (LDH), and interleukin 6 (IL6), with increasing levels as illness deteriorated. Hs-cTnI levels increased rapidly from day 16 after disease onset, whereas LDH increased for both survivors and non-survivors in the early stages of progression, but decreased from day 13 for survivors. Elevated blood levels of IL-6, hs-cTnI, and LDH, as well as lymphopenia were more commonly seen in cases of severe COVID-19.[2]

Most recently, a retrospective case-series of 187 COVID-19 patients in Wuhan, China (mean age 58.5 years) found that around 35% of patients had underlying cardiovascular disease (CVD), including hypertension, coronary heart disease, and cardiomyopathy. 28% of patients exhibited myocardial injury. Mortality during hospitalization was around 8% (8 of 105) for patients without underlying CVD and normal TnT levels, and around 69% (25 of 36) for those with underlying CVD and elevated TnT levels. Another interesting finding in this study is that patients without underlying CVD but elevated TnT level had a mortality rate of 37.5% which was significantly higher than in those with underlying CVD, but normal TnT (13.3%). Unlike the other studies that reported TnI only, this study found that the plasma TnT and NT-proBNP levels during hospitalization on one hand, and impending death on the

other, increased significantly compared with admission values in patients who died, while no significant dynamic changes of TnT and NT-proBNP were observed in survivors. Additionally, patients with elevated TnT levels had more frequent malignant arrhythmias, and need for mechanical ventilation. Only around 9% of patients with normal TnT levels (with or without underlying CVD) had died during hospitalization as compared to around 60% with elevated TnT. Of important notice, the elevation of TnT levels was significantly associated with elevation of other cardiac biomarkers such as NT-proBNP, myoglobin, and creatine kinase-MB fraction, as well as inflammatory biomarkers such as CRP, CVD related comorbidities, and coagulopathy.[4] Table 1 Summarises the results of the relevant cardiac-implicated studies up to date.

Of particular interest concerning the studies above is the elevated levels of cardiac troponin I and T (cTnI and cTnT)—A muscle-associated protein often released into the blood upon cell injury. cTnI has been used as an essential biomarker for non-specific cardiac disease (e.g. infarction, acute coronary syndrome) for several decades. In order to improve its utility as a marker in detecting true positives, the high sensitivity cTnI assay was developed, allowing for wider screening and consequent detection and reversal of cardiac injury at the very early stages (albeit with a higher false positive rate for acute myocardial infarction [MI]).[5] With relation to COVID-19, a meta-analyses of four studies that included a total of 341 patients in China found the values of cTnI to be significantly increased in cases of severe disease (SMD, 25.6 ng/L; 95% CI, 6.8–44.5 ng/L) compared to milder forms.[6] However, given that the troponin measurements did not seem to precede the disease's progression, it cannot be determined for certain that troponin is a "predictive" marker for severe forms of COVID-19.[7] However, it is important to remember that although cTnI is cardiac-specific, it is not disease-specific. These findings thus lead to questioning of the mechanisms behind the

elevated troponin levels that have evidently been associated with not only disease severity, but mortality.

In order to further assess the prognostic potential of troponin levels (both cTnT and hs-cTnI) in predicting mortality, we input the raw data on mortality counts by normal vs elevated troponin levels from Shi et al's (2020)[3] and Guo et al's (2020)[4] studies, and modelled mortality as a function of the full factorial model [died = intercept + high/normal + cTnT/hs-cTnI + interaction (high/normal, cTnT/hs-cTnI)]. No significant difference was found between the predictive abilities of hs-cTnI (used by Shi et al) and cTnT (used by Guo et al). Patients with elevated hs-cTnI had a 51.2% probability of death (CI: 40.5%-61.8%) compared to 4.5% (CI: 2.7%-7.3%) in patients with normal values. Likewise, patients with elevated TnT (more specific), had a 59.6% (CI: 45.9%-72.0%) mortality estimate compared to 8.9% (CI: 5.1%-15.0%) in patients with normal TnT values.

As shown from the previous three cohort studies, troponin levels were increased with a myriad of biomarkers, including those associated more generally with inflammation (e.g. IL6).[2,3] Contributory mechanisms can hence include a systemic pro-inflammatory cytokine storm as mediated by the immune system's direct response to the virus, or as related to the exacerbated inflammatory activity within coronary atherosclerotic plaques rupturing in response to local inflammation. On the other hand, the elevated levels of d-dimers and incidence of coagulopathy amongst COVID-19 patients points towards a procoagulant state and general hemodynamic changes which may predispose to ischaemia and thrombosis,[2,3] leading to cardiac injury. The elevated d-dimers were additionally accompanied by elevated fibrinogen levels in some cases, which is atypical of the pathogenomic of acute disseminated intravascular coagulopathy (DIC) seen in critically ill individuals. It is possible that this may be triggered by lipoprotein(a), a low-density lipoprotein associated with both CVD and thrombosis, in response to the elevation in IL-6

levels as part of the cytokine storm observed in COVID-19 patients. Findings from an autopsy indicated an MI,[2] while electrocardiographs performed during the period of elevated cardiac biomarkers all showed abnormal findings compatible with myocardial ischemia (T-wave depression and inversion, ST-segment depression, and Q-waves).[3] Additionally, the observed large number of cardiovascular events (e.g. arrhythmia and heart failure) in non-surviving patients can be interpreted in-line with findings of stress cardiomyopathy. The observed cardiac injury may also be a result of type two MI, secondary to ischemia triggered by an increase in demand and decrease in supply caused by the severe respiratory illness. On the other hand, considering the ACE2-related pathogenesis of SARS-CoV-2, and the receptors expression in myocytes,[2] it is possible, theoretically, that the virus's direct impact on the cells can lead to infectious myocarditis and apoptosis-induced cellular damage.[3] Nonetheless, since interstitial mononuclear inflammatory infiltrates were documented in heart tissue of fatal COVID-19 cases, while viral detection has not yet been reported,[8] indirect inflammatory mechanisms are more likely related to the cardiac complications associated with COVID-19. Ongoing registries to collect cardiovascular data in COVID-19 patients, such as CAPACITY-COVID, will help better our understanding of the disease's implications. The primary focus of this registry in the short term will be to develop prognostic models with the collected data. The incidence and pattern of cardiovascular complications as well as vulnerability and clinical course of COVID-19 in patients with an underlying CVD will also be collected.[9] Another registry includes COVID-ACS which focus particularly on acute coronary syndrome patients.

It is evident that cardiac injury in relation to COVID-19 plays a significant role in the diseases' progression. Thus, it is only reasonable that indicators of cardiac injury are involved in patient diagnosis, monitoring, and prognosis, while recognizing that their abnormality may not be related to a direct coronary process. In fact, patients with markers of cardiac injury

were at a higher risk of death both during the time from symptom onset and from admission to end point,[3] suggesting that related biomarkers such as hs-cTnI can provide prognostic information early on and throughout disease progression. Levels of troponin reported in the studies were also significantly associated with other inflammatory markers and morbidities, and were dynamically changing with worsening outcomes, which was not the case in survivors.[4] It is important to mention that unrelated to COVID-19, it has been shown in large cohort studies (n=250,000) that a positive troponin result, even if slightly above normal, is associated with a clinically important increased mortality, regardless of age or acute coronary syndrome diagnosis. In other words, troponin levels have always been a marker of worse prognosis in critically ill patients.[10]

In summary, there are several mechanisms that could be at play to explain myocardial injury in relation to COVID-19 infection, that include but are not limited to: Myocarditis, sepsis and associated systemic inflammatory response, pro-coagulant condition, destabilization of coronary plaque, and hypoxia.

Hence, we recommend several measures to be considered:

1. Cardiologists as well as multidisciplinary teams involved in the care of COVID-19 patients are encouraged to participate in cardiac registries such as CAPACITY-COVID to better our collective understanding of the disease's implications.
2. Cardiologists should be prepared to attend to CVD related morbidities associated with COVID-19 infections.
3. Consider screening COVID-19 positive patients using high sensitivity troponin in order to triage them into high and low risk groups.
4. In admitted symptomatic patients, consider monitoring troponin daily when elevated. If not elevated, levels can be monitored longitudinally at different

intervals, to predict potential worsening in disease course. Since the studies referenced above reported minimal elevation of troponin levels in surviving patients, use of hs-cTnI assays can provide a highly sensitive test to potentially rule out severe complications and a poor prognosis early on, and may prove useful in last-resort and limited-resource situations that demand triaging of COVID-19 patients.

5. Similar to non-pandemic situations, troponin levels should not be used in isolation as an indicator of MI or for activation of systems of care, as such elevation can be related to non-coronary mechanisms. Troponin values should be used in the context of clinical signs and symptoms, ECGs, chest x-rays, echocardiogram and other clinical and laboratory investigations.
6. The reported prevalence of coagulopathy in COVID-19, that seems to differ from other coagulopathies (such as DIC) present in critically ill patients, invites consideration for the use of anticoagulants in the management of patients with elevated biomarkers indicative of thromboembolic processes, though prospective trials are needed.
7. Since d-dimer levels greater than 1 μg/mL at admission were associated with increased odds of death, and since several different pathogeneses may be involved, monitoring of a range of cardiac and coagulation biomarkers that includes d-dimers, troponins T and I, NT-pro-BNP, CRP, Lipoprotein (a), fibrinogen and LDH may allow for a more proactive rather than reactive approach to the management of COVID-19 patients.

Conflicts of Interest

None.

Table 1. Summarising the results of the relevant cardiac-implicated studies up to date.

Study	Population	Cardiovascular Outcomes	Cardiac Biomarkers
Lippi et al., March 10th, 2020 Meta-analysis	341 patients; China	Not Applicable	- Values of cTnI significantly ↑ in COVID-19 patients with severe disease vs milder forms (standardized mean difference, 25.6 ng/L; 95% CI 6.8–44.5 ng/L). - Heterogeneity was considerably high (i.e., I^2, 98%; $p < 0.001$)
Zhou et al., March 11th, 2020 Retrospective Cohort Study	191 patients; China	- Of non-survivors (54 patients), 59% had acute cardiac injury, 50% coagulopathy, and 52% heart failure - Odds of in-hospital death ↑ in patients with diabetes or coronary heart disease	- Non-survivors had ↑ levels of d-dimer, hs-cTnI, LDH, and IL6, with increasing levels as illness deteriorated - ↑ odds of in-hospital death associated with d-dimer greater than 1 μg/mL on admission. - ↑ blood levels of IL-6, hs-cTnI, LDH more commonly seen in cases of severe COVID-19
Shi et al., March 25th, 2020 Prospective Cohort Study	416 patients; China	Patients with cardiac injury (19.7%) had: - ↑ comorbidities. - A ↑ proportion required both invasive and non-invasive mechanical ventilation. - ↑ complications - ↑ mortality (51.2% vs 4.5%; P < .001) - ↑ risk of death, both during the time from symptom onset (hazard ratio, 4.26 [95%CI, 1.92-9.49]) and from admission to end point (hazard ratio, 3.41 [95%CI, 1.62-7.16]).	Patients with cardiac injury had ↑: - Hs-cTnI - Leukocyte count - Levels of C-reactive protein - Procalcitonin - Creatine kinase-myocardial band - Myohemoglobin - NT-proBNP - Aspartate aminotransferase - Creatinine
Guo et al., March 27th, 2020	187 patients; China	- 66 (35.3%) had underlying CVD - 52 (27.8%) exhibited myocardial injury	- ↑ TnT levels significantly associated with higher levels of other biomarkers of cardiac injury.

Retrospective Case Series	- 42 (34.1%) exhibited coagulopathy complications	- 37.50% (6 of 16) with ↑ TnT levels without underlying CVD, and 69.44% (25 of 36) with ↑ TnT levels with underlying CVD died during hospitalization. - Around 9% of patients with normal TnT levels (with or without underlying CVD) died during hospitalization, vs around 60%. - ↑ TnT correlated with frequent malignant arrhythmias and mechanical ventilation use (59.6% vs 10.4% in non-elevated)

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