

Cardiovascular biomarkers in patients with COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic has increased awareness that severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) may have profound effects on the cardiovascular system. COVID-19 often affects patients with pre-existing cardiac disease, and may trigger acute respiratory distress syndrome (ARDS), venous thromboembolism (VTE), acute myocardial infarction (AMI), and acute heart failure (AHF). However, as COVID-19 is primarily a respiratory infectious disease, there remain substantial uncertainty and controversy whether and how cardiovascular biomarkers should be used in patients with suspected COVID-19. To help clinicians understand the possible value as well as the most appropriate interpretation of cardiovascular biomarkers in COVID-19, it is important to highlight that recent findings regarding the prognostic role of cardiovascular biomarkers in patients hospitalized with COVID-19 are similar to those obtained in studies for pneumonia and ARDS in general. Cardiovascular biomarkers reflecting pathophysiological processes involved in COVID-19/pneumonia and its complications have a role evaluating disease severity, cardiac involvement, and risk of death in COVID-19 as well as in pneumonias caused by other pathogens. First, cardiomyocyte injury, as quantified by cardiac troponin concentrations, and haemodynamic cardiac stress, as quantified by natriuretic peptide concentrations, may occur in COVID-19 as in other pneumonias. The level of those biomarkers correlates with disease severity and mortality. Interpretation of cardiac troponin and natriuretic peptide concentrations as quantitative variables may aid in risk stratification in COVID-19/pneumonia and also will ensure that these biomarkers maintain high diagnostic accuracy for AMI and AHF. Second, activated coagulation as quantified by D-dimers seems more prominent in COVID-19 as in other pneumonias. Due to the central role of endothelitis and VTE in COVID-19, serial measurements of D-dimers may help physicians in the selection of patients for VTE imaging and the intensification of the level of anticoagulation from prophylactic to slightly higher or even therapeutic doses.

Keywords COVID-19 • Biomarkers • Cardiac troponin • Natriuretic peptides • D-dimer • Risk prediction

Introduction

The coronavirus disease 2019 (COVID-19) is an emerging respiratory infectious disease causing a pandemic affecting all countries

worldwide, with more than 54.3 million patients affected and more than 1 317 000 deaths as of 16 November 2020.¹ Although particularly young patients may have a mild or even asymptomatic course, many patients have a complicated course of COVID-19 as viral

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pneumonia that may result in severe systemic inflammation, the development of acute respiratory distress syndrome (ARDS), venous thromboembolism (VTE), stroke, acute myocardial infarction (AMI), acute heart failure (AHF), cardiac arrest, and tachyarrhythmias.^{1–17} As the heart may have a more prominent role in COVID-19 than previously appreciated, cardiovascular biomarkers have been suggested as possible aids to clinicians in COVID-19 by detecting and quantifying cardiomyocyte injury, haemodynamic cardiac stress, and intravascular coagulation.^{1–17,19,20} However, there remain substantial uncertainty and controversy whether and how cardiovascular biomarkers should be measured and used in patients with suspected COVID-19.

To help clinicians understand the possible value as well as the most appropriate interpretation of cardiovascular biomarkers in COVID-19, it is important to highlight that recent findings regarding the prognostic role of cardiovascular biomarkers in patients hospitalized with COVID-19 are remarkable similar to those obtained in studies for viral pneumonia due to influenza, as well as for pneumonia and ARDS in general.^{2–17} in addition to some of their unique characteristics.

We therefore initially summarize the evidence documenting the possible role of cardiovascular biomarkers in sepsis/pneumonia in general, and then put these findings into perspective with the evidence for cardiovascular biomarkers in COVID-19 obtained during recent months and add those unique characteristics at the end.

First, systemic infection such as pneumonia has a profound effect on the cardiovascular system, including increase in oxygen consumption and coronary plaque vulnerability.³ Already 15 years ago it was reported that in the 72 h following pneumonia patients were five times more likely to develop an AMI than at other times.³ Second, acute cardiomyocyte injury as quantified by increased systemic cardiac troponin (cTn) concentrations is rather common among patients hospitalized with bacterial or viral pneumonia and associated with the risk of death. For example, among patients hospitalized with influenza A (H7N9) in 2015–2017, cardiomyocyte injury was observed in about 10% and associated with increased mortality.⁵ Similarly, among patients hospitalized with pneumonia in 201 influenza A (H7N9), cardiomyocyte injury was observed in about 10% and associated with increased mortality.⁵ Third, among patients presenting to the emergency department with any kind of pneumonia multiple years prior to the COVID-19 pandemic, cardiac troponin, and N-terminal pro B-type natriuretic peptide (NT-proBNP) were higher in deceased patients compared to survivors, and strongly predicted mortality (Figure 1).⁷ Patients with cardiac troponin concentrations in the third tertile had about six times the all-cause mortality as well as cardiovascular mortality as compared to patients in the first tertile. Fourth, among patients admitted to an intensive care unit (ICU) with any kind of acute respiratory condition about 15 years ago, cardiac troponin was elevated in more than 40%. The higher the cardiac troponin concentration, the higher the risk of death within 30 days as well as 2 years (Figure 2).⁶

While clearly recognizing the need for further large prospective multicentre studies addressing remaining uncertainties, the aim of this review is to provide guidance for the clinical use of cardiovascular biomarkers in COVID-19.

Cardiac troponin

As a quantitative marker of cardiomyocyte injury, the concentrations of cardiac troponin in a patient with COVID-19 should be seen as the combination of the presence or extent of pre-existing cardiac disease and the acute myocardial injury related to COVID-19 and its complications.^{4,7–17} The potential mechanisms underlying myocardial injury in patients with COVID-19 infection are not fully understood, but are likely to be multifactorial (Figure 3).^{4–17} Myocardial involvement may occur due to a direct effect of the virus mediated through the angiotensin-converting enzyme-2 receptor on the vascular endothelial cells or cardiomyocytes. Alternatively, myocardial involvement may occur as an indirect response to COVID-19 mediated by a cytokine storm, or due to cardiomyocyte apoptosis triggered by excessive intracellular calcium in response to tissue hypoxia. Myocardial ischaemia may occur in the context of shock, prolonged tachycardia, or severe respiratory failure (type 2 AMI), or acute atherothrombosis (type 1 AMI). Finally, both myocarditis and takotsubo syndrome have been reported in patients with confirmed COVID-19 and in those without COVID-19 who had experienced severe anxiety due to the pandemic or with concomitant infections.¹⁰

Cohort studies from patients hospitalized with COVID-19 have shown that about 10–20% of patients had elevations in cardiac troponin, and that this was more common in patients admitted to the ICU (in general due to respiratory failure and ARDS) and among those who died.^{4,7–17} Concentrations remained in the normal range in the majority of survivors. The incidence of cardiomyocyte injury as quantified by elevated cardiac troponin concentration increases with greater severity of illness (Figure 4).¹⁶ In non-survivors, cardiac troponin concentrations progressively increased in parallel with the severity of COVID-19 and the development of ARDS (Figure 5).^{4,7–17} In 2736 patients hospitalized with COVID-19 in New York City with cardiac troponin measurements obtained within 24 h of admission, patients with elevated cardiac troponins more often had pre-existing cardiovascular disease including coronary artery disease, atrial fibrillation, and heart failure, as well as chronic kidney disease, hypertension, and diabetes mellitus.⁴ Inflammatory markers were higher among patients with more substantial cardiac troponin elevations. Patients who had lower haemoglobin, hypo- or hypertension, or tachycardia generally presented with higher cardiac troponin concentrations.⁴ Cardiac troponin elevations were classified as mild (one to three times the upper limit of normal, ULN) in the majority of those with increased levels. Sandoval et al.¹⁶ have proposed that there are three phases: first, where the cardiac troponin increases mostly reflect ongoing comorbidities—these are usually at admission; second, with critical illness like ARDS; third, the specific COVID-19 complications such as endothelitis, pulmonary embolism, stroke, and myocarditis.

Mild elevations in cardiac troponin concentrations, particularly in an older patient with pre-existing cardiac disease, are often explained by the combination of known or unknown pre-existing cardiac disease AND the acute myocardial injury related to COVID-19 or any pneumonia. These mild elevations in cardiac troponin concentrations do not necessarily require work-up for AMI, unless the clinical picture is suggestive with typical anginal chest pain and/or regional electrocardiogram (ECG) changes (Figure 6).

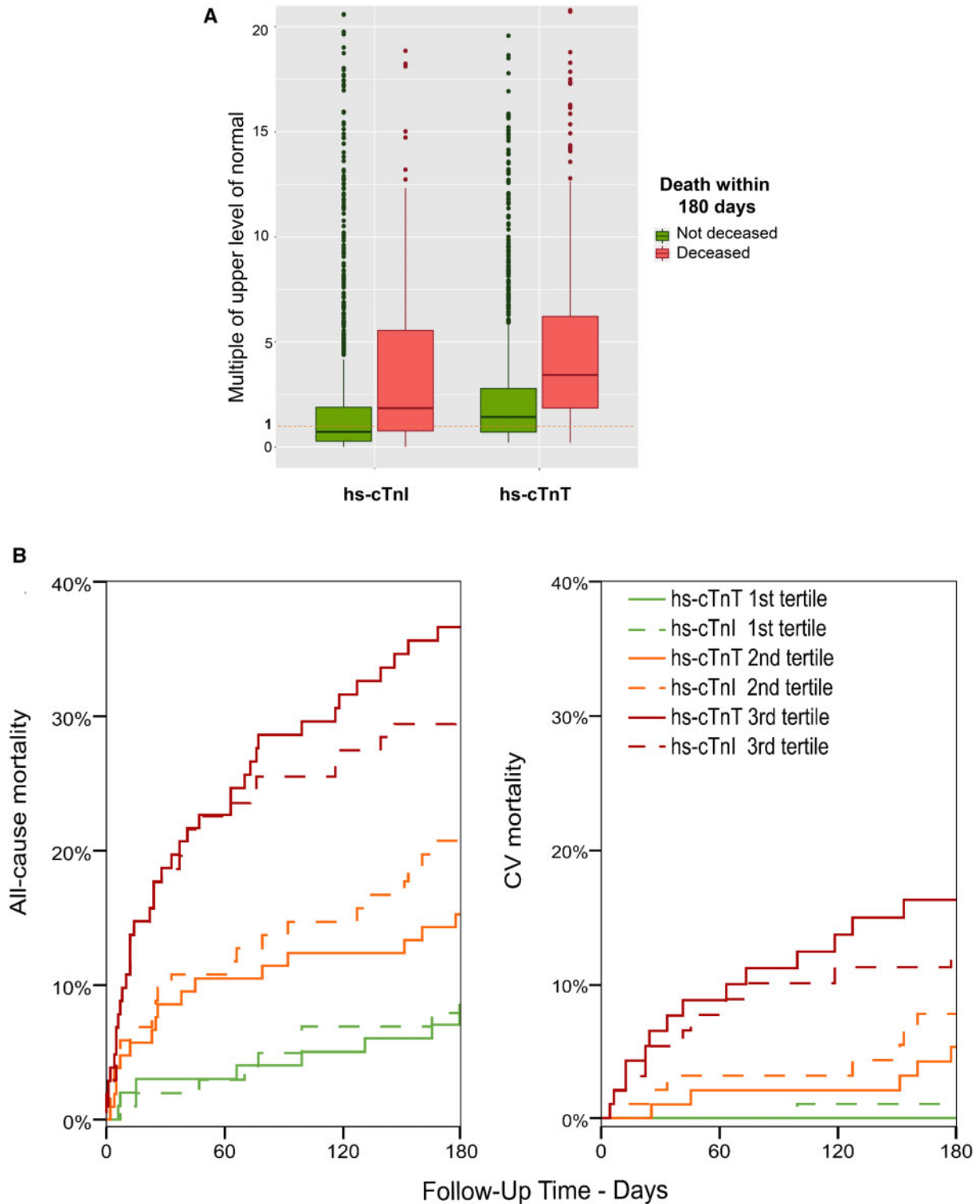


Figure 1 (A) High-sensitivity cardiac troponin (hs-cTn) concentrations were higher in deceased patients presenting with pneumonia to the emergency department compared to survivors. Comparison of multiples of the 99th percentile for hs-cTnI and hs-cTnT for 180-day all-cause mortality. HsTnI (Erenna, Singulex Inc. Alameda, USA) with a 99th percentile of 10.1 ng/L; hsTnT (Roche Elecsys 2010, Roche Diagnostics, Rotkreuz, Switzerland) with a 99th percentile of 14 ng/L. Boxers represent medians and interquartile ranges, while whiskers display the smallest and the largest non-outliers and dots display outliers. Red intercept represents 99th percentile (upper limit of normal) of each cardiac troponin assay. (B) Patients with hs-cTn concentrations in the third tertile had about 6-times the all-cause mortality (left) and cardiovascular (CV) mortality (right) as compared to patients in the first tertile.⁷

Marked elevations of cardiac troponin in patients who are not critically ill with e.g. ARDS, may indicate the presence of myocarditis, takotsubo syndrome or type 1 AMI triggered by COVID-19.⁴⁻¹⁸ In the absence of symptoms or ECG changes suggestive of type 1 AMI, echocardiography and/or cardiac magnetic resonance imaging should

be considered to detect left ventricular systolic dysfunction as a new and well-treatable condition. Patients with symptoms suggestive of type 1 AMI should be treated according to European Society of Cardiology (ESC) guidelines irrespective of COVID-19 and undergo rapid coronary angiography under specific protection of the catheter personnel.⁴⁻¹⁸ In patients with COVID-19 (or other pneumonias) who are critically-ill with septic shock and/or ARDS, even marked

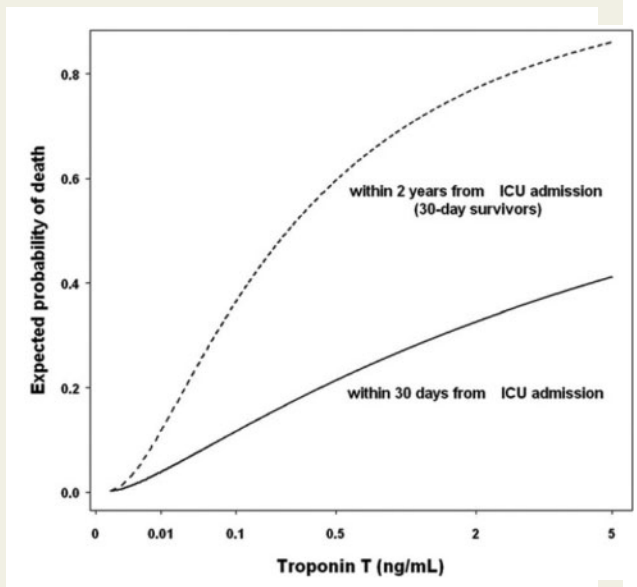


Figure 2 Probability of death according to cardiac troponin concentration in patients admitted with acute respiratory disease to the intensive care unit (with permission).⁶

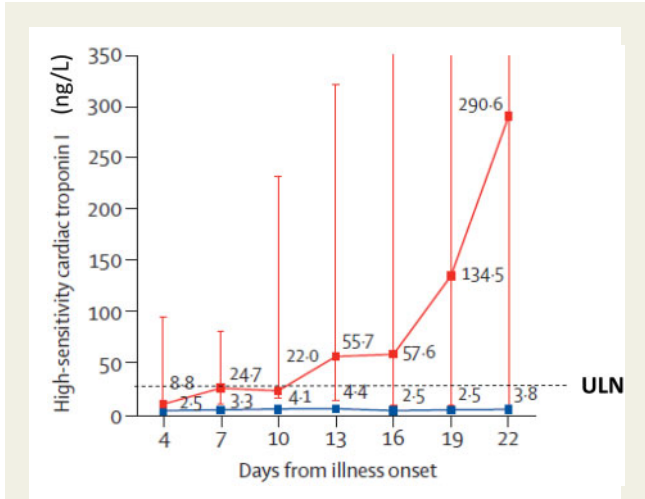


Figure 4 Temporal changes in high-sensitivity cardiac troponin I concentrations from illness onset in patients hospitalized with COVID-19. Differences between survivors and non-survivors were significant for all time points shown. ULN denotes upper limit of normal (adapted from ref.⁸).

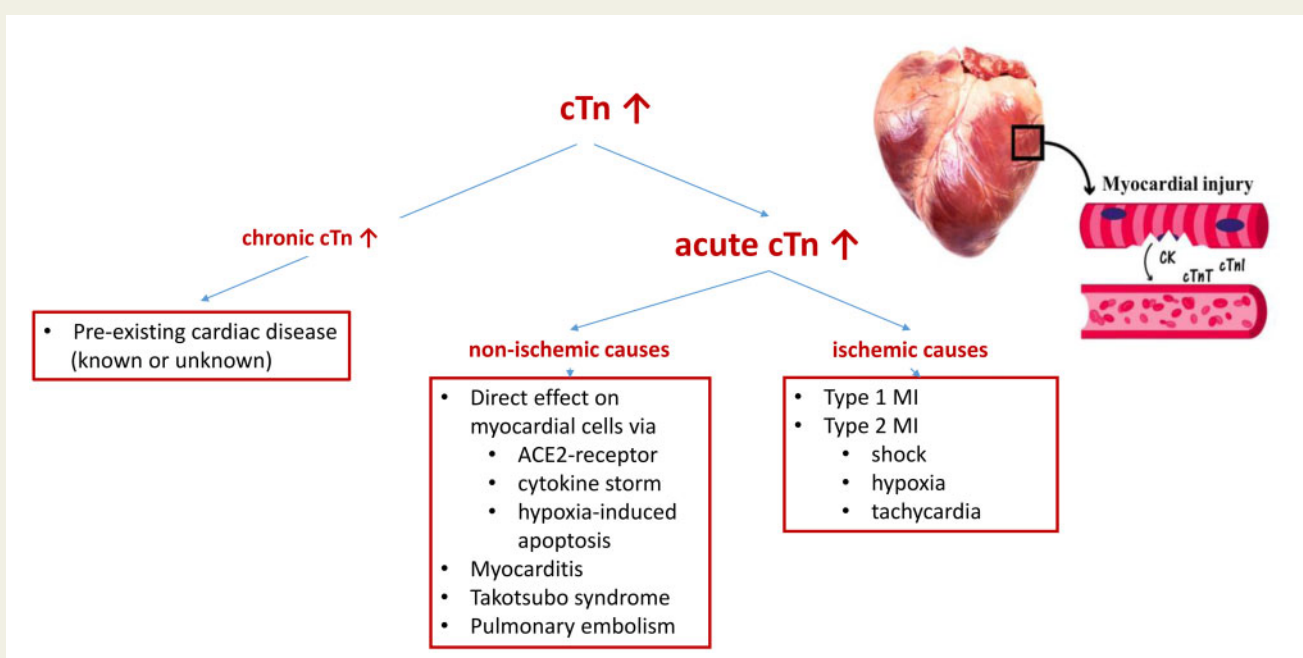


Figure 3 Potential mechanisms underlying elevations in cardiac troponin and therefore myocardial injury in patients with COVID-19.

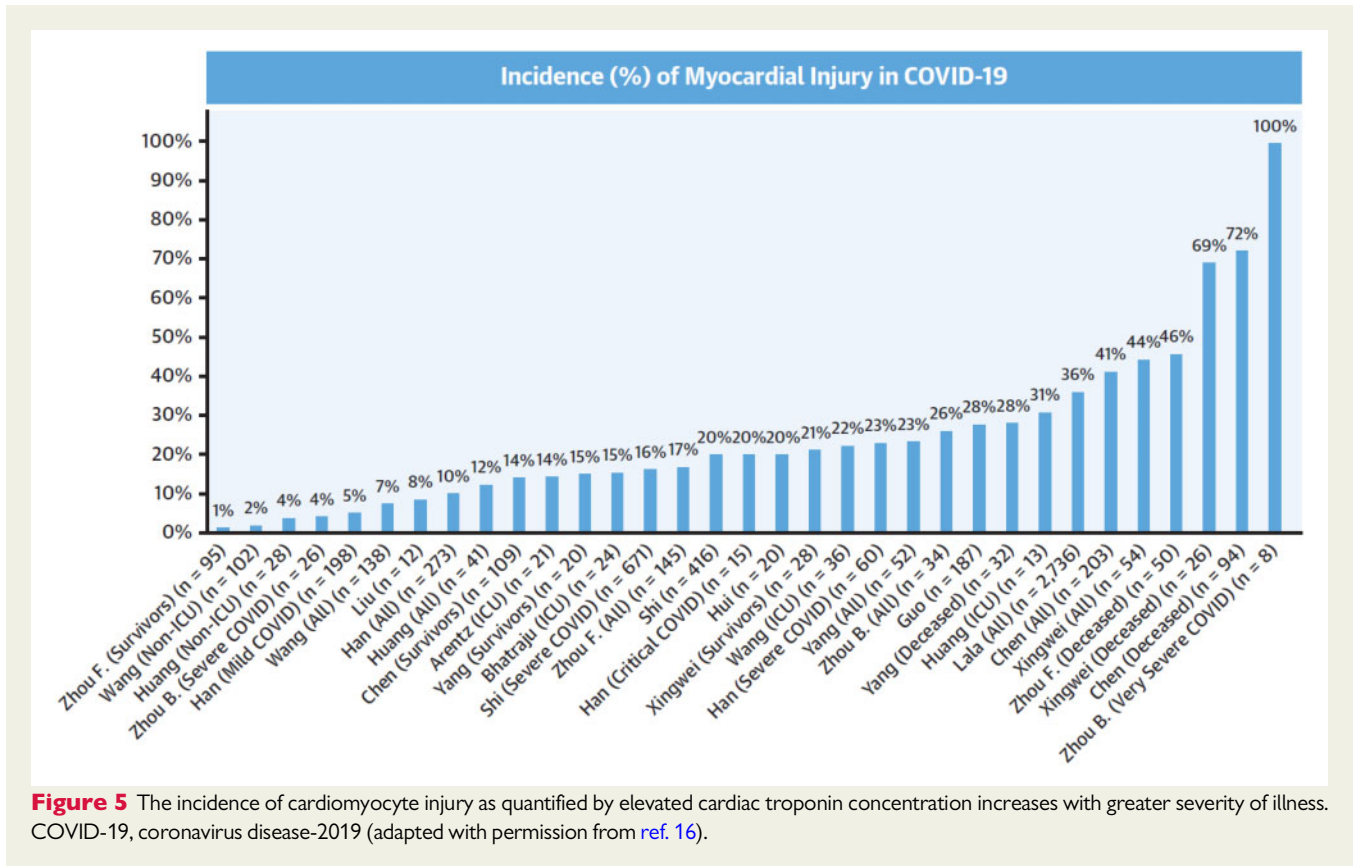


Figure 5 The incidence of cardiomyocyte injury as quantified by elevated cardiac troponin concentration increases with greater severity of illness. COVID-19, coronavirus disease-2019 (adapted with permission from [ref. 16](#)).

cardiac troponin elevations are much more likely the consequence of critical illness, be it myocardial injury or if ischaemia is present, type 2 myocardial infarction (MI), rather than a type 1 AMI.⁴⁻¹⁷

Clinical consequences

First, as in patients without pneumonia, cardiac troponin should be measured whenever type 1 AMI is suspected on clinical grounds.¹⁸ In patients with COVID-19, established diagnostic algorithms for rapid rule-out and/or rule-in of MI in patients with acute chest discomfort can be expected to provide comparable performance characteristics as in other challenging subgroups with higher baseline cardiac troponin concentrations such as the elderly: high safety for rule-out, but reduced efficacy.^{11,30-32} Detailed clinical assessment including chest pain characteristics, assessment of COVID-19 severity, hs-cTn measurement at 3 h, and cardiac imaging are key to the identification of AMI.^{11,21,30-32}

Second, it is a matter of ongoing debate whether 'hs-cTn can be an ally in the fight against COVID-19' and should be measured systematically as part of clinical routine in patients hospitalized with confirmed or suspected COVID-19.³³ The strong and consistent association with mortality, with evidence suggesting cardiac troponin is an independent predictor of mortality, is in favour of this approach.⁴⁻¹⁷ In addition, marked elevation in cardiac troponin may be an early indicator of AMI or AHF as treatable conditions that may arise as a consequence of COVID-19 or mimic its presentation.^{4-18,34} We are still learning about COVID-19; the cardiac consequences of this condition are currently poorly defined, and more information is needed to

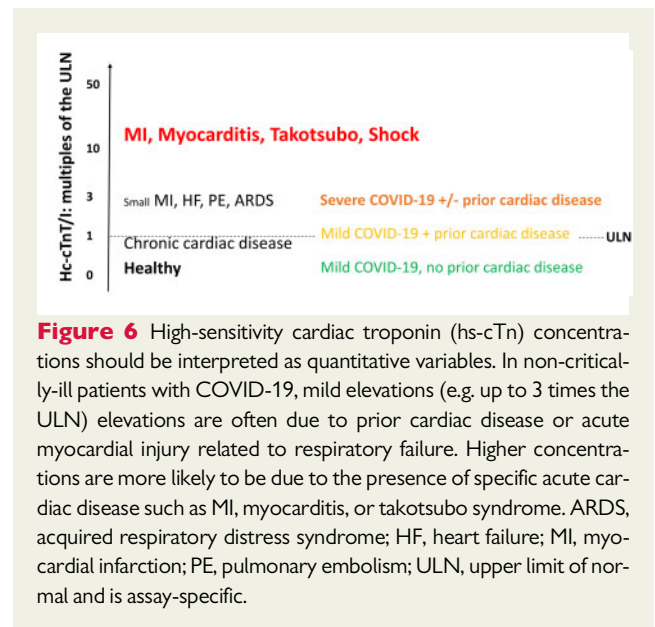


Figure 6 High-sensitivity cardiac troponin (hs-cTn) concentrations should be interpreted as quantitative variables. In non-critically-ill patients with COVID-19, mild elevations (e.g. up to 3 times the ULN) elevations are often due to prior cardiac disease or acute myocardial injury related to respiratory failure. Higher concentrations are more likely to be due to the presence of specific acute cardiac disease such as MI, myocarditis, or takotsubo syndrome. ARDS, acquired respiratory distress syndrome; HF, heart failure; MI, myocardial infarction; PE, pulmonary embolism; ULN, upper limit of normal and is assay-specific.

understand this, beyond highly selected case series or case reports. Widespread use cardiac troponin testing in clinical routine will substantially increase the datasets available worldwide for future analyses. Ultimately, large datasets with better clinical characterization, cardiac imaging, and follow-up will be necessary to define the pathophysiological mechanisms leading to cardiomyocyte injury in COVID-

19 and to inform therapeutic trials. Finally, as blood tests are performed routinely in these patients, no additional procedures are required, making cardiac biomarkers the easiest, cheapest and most accessible of cardiac investigations and appropriate gate-keeper for cardiac imaging, which is at times logistically difficult.

On the other hand, at this point in time, based on four arguments a more conservative approach can also be supported.^{4–17} First, beyond cardiac troponin other routinely available clinical and laboratory variables have also emerged as strong predictors of death in COVID-19 including older age, higher Sequential Organ Failure Assessment (SOFA) score, D-dimers, interleukin-6, and lymphocyte count. It is likely that cardiac troponin provides only incremental prognostic information in addition to other routinely available variables, particularly including vital signs and inflammatory markers. Second, there is a risk that inappropriate diagnostic and therapeutic interventions may be triggered by elevated cardiac troponin concentrations in patients with COVID-19 with the possibility of harm to patients, as well as to staff. Some clinicians may elect to move towards coronary angiography because of an isolated cardiac troponin elevation. In our opinion, this would be erroneous because the diagnosis of a possible type 1 event depends on having myocardial ischaemia in a situation where a spontaneous event not related to supply-demand imbalance is present. In addition, even non-invasive investigations may be associated with harm to e.g. critically ill patients due to the risk associated with transporting critically ill patients throughout the hospital. Obviously, all additional investigations may definitely be associated with harm to staff due to the risk of infection. However, with the appropriate use of personal protection equipment the risk is very small. It is for that reason that firm indications for such testing are advocated for. When these indications are present however, one should not withhold these essential evaluations. Third, there is concern that measuring cardiac troponin during the initial blood sampling in the emergency department may unnecessarily delay patient disposition, as elevated concentration may require additional investigation or consultation. Fourth, in patients with COVID-19 as well as with other pneumonias or patients with ARDS, there is currently no evidence that any intervention triggered by an elevation in cardiac troponin concentration will have an impact on patient outcomes.^{4–16}

Natriuretic peptides

Natriuretic peptides including B-type natriuretic peptide (BNP), NT-proBNP and midregional pro-atrial natriuretic peptide as quantitative biomarkers of hemodynamic myocardial stress and heart failure are frequently elevated among patients with severe inflammatory and/or respiratory illnesses.^{7,8,22–24} As for cardiac troponin, it is likely that some of the experience from other pneumonias can be extrapolated to COVID-19.^{7,8,22–24} As quantitative markers of haemodynamic stress and heart failure, intracardiac filling pressures and end-diastolic wall stress as well as hypoxaemia seem to be the predominant triggers of the release of BNP/NT-proBNP (Figure 7).^{7,8,22–24} Accordingly, the concentrations of BNP/NT-proBNP in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease AND the acute hemodynamic and hypoxaemic stress related to COVID-19.^{7,8,22–24} At least to some extent, the release of BNP/NT-proBNP seems to be associated

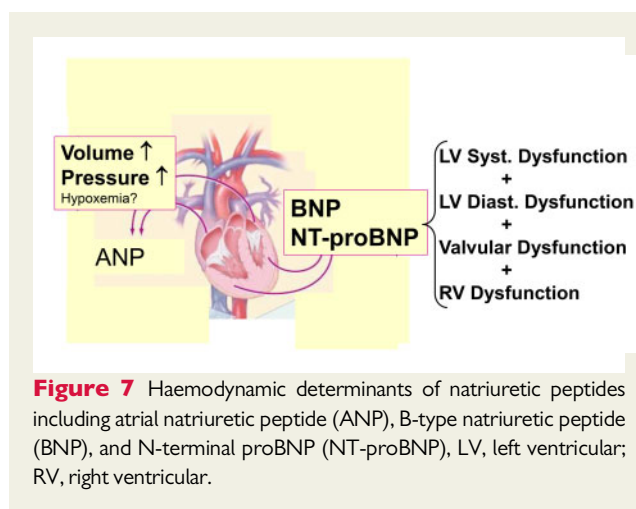


Figure 7 Haemodynamic determinants of natriuretic peptides including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and N-terminal proBNP (NT-proBNP), LV, left ventricular; RV, right ventricular.

with the extent of right ventricular haemodynamic stress due to increased afterload and hypoxaemia.

Clinical consequences

Natriuretic peptides should be measured whenever on clinical grounds heart failure is suspected.^{7,8,15–17} In patients who are not critically ill, rule-in cut-offs for heart failure maintain high positive predictive value even in patients with pneumonia.^{7,8,22–24} In contrast, currently recommended cut-offs should not be applied in critically-ill patients with ARDS or septic shock, as most critically-ill patients have substantial elevations in BNP/NT-proBNP, most likely due to the near-universal presence of hemodynamic stress and heart failure in these patients.^{7,8,22–24} As for cardiac troponin, there is an ongoing debate whether BNP/NT-proBNP should be part of the diagnostic panel in patients with COVID-19 or other pneumonias. Beyond the strong association with mortality in patients with pneumonias due to COVID-19 or other causes, marked elevation of natriuretic peptides could be an early indicator for the presence of left and right ventricular systolic dysfunction as a new and treatable condition.³⁴

D-dimers

D-dimers are generated by cleavage of fibrin monomers by plasmin, hence indicating both the presence of thrombus formation and subsequent fibrinolysis.¹⁸ The absence of elevated D-dimers beyond their assay specific cut-offs are therefore recommended as an aid to rule out VTE in low risk patients as negative D-dimers rule-out VTE with very high negative predictive values.^{18,25–29,35,36} In addition, D-dimers are used for the diagnosis and monitoring of disseminated intravascular coagulation associated with sepsis or shock. D-dimers can also be interpreted as quantitative variables with very high concentrations (e.g. >10-times the ULN) having a high positive predictive value for the diagnosis of VTE.³⁷

During the outbreak of COVID-19, a coagulopathy has been commonly observed in hospitalized patients that was characterized by mild prolongation of activated partial thromboplastin time and prothrombin time, increase of fibrin degradation products, as well as variable, mild to massive elevations of D-dimers.^{8,38,39} In one large series

Table 1 Potential mechanisms that account for coagulopathy in COVID-19^{8,38–50}

- Sepsis-induced disseminated intravascular coagulation (DIC)—consumptive coagulopathy
- Increased levels of fibrinogen and an excessive fibrin polymerization
- Cytokine-mediated DIC
- Activation of thrombin and suppression of fibrinolysis [local over-expression of tissue factor, and inhibition of urokinase plasminogen activator (uPA)] by plasminogen activators and PAI-1 inhibitors in ARDS
- Inhibition of plasmin by antiplasmins
- Plasmin-mediated increased binding of SARS-CoV-2 to angiotensin converting enzyme (ACE)-2 receptors
- Direct viral infection/endotheliitis

of 1099 patients with confirmed COVID-19, a D-dimer ≥ 0.5 mg/L was noted in 46.4% of patients, with a higher prevalence of 60% in cases with severe illness as compared to 43% in cases with non-severe disease.³⁹

In COVID-19, several putative mechanisms (Table 1) have been proposed to explain coagulopathy or disseminated intravascular coagulation (DIC). Severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) has a high affinity to endothelial cells and may induce endotheliitis, which could explain why the findings for D-dimer differ in patients with COVID-19 from other pneumonias.^{40–47} Similar to the findings reported for cardiac troponin, in patients with COVID-19 the D-dimer values increase progressively in non-survivors whereas values remain around the ULN in survivors (Figure 8).

Hence, monitoring of coagulation parameters may be useful as an aid to predict deterioration and potentially to guide therapeutic measures including the intensity of anticoagulation. Observational studies have shown that prophylactic and/or therapeutic anticoagulation is associated with better outcomes versus no anticoagulation.⁴⁶ Ongoing randomized controlled trials investigate whether increasing the intensity of anticoagulation from prophylactic doses to slightly higher than prophylactic doses or even therapeutic doses would prevent VTE and thereby improve outcomes.⁵³ As the coagulopathy associated with COVID-19 demonstrates a predominance for arterial or VTE^{41–47}, particularly obstructing the microvasculature, but cause less frequently haemorrhagic complications or overt bleedings, D-dimers may aid in the timing of imaging studies for the detection of VTE.^{8,38–46} Detection of VTE will have clear therapeutic consequence, i.e. increasing the level of anticoagulation from prophylactic doses, the current standard of care in patients hospitalized with COVID-19, to therapeutic doses.^{8,38–47}

Clinical consequences

Overall, D-dimers seem not only to reflect important pathophysiological aspects of COVID-19 disease but also to contribute to early risk assessment, provide guidance to select candidates for prophylactic or therapeutic anticoagulation. In addition, monitoring of D-

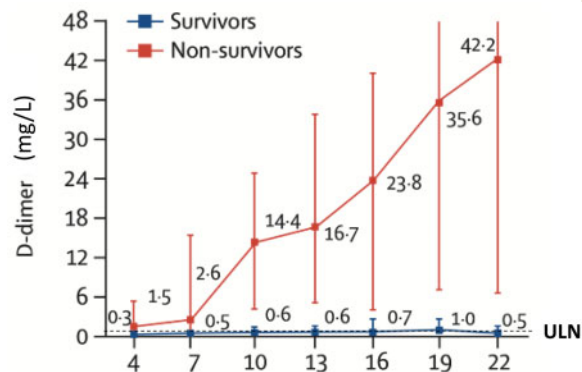


Figure 8 Temporal changes in D-dimer concentrations from illness onset in patients hospitalized with COVID-19. Differences between survivors and non-survivors were significant for all time points shown. ULN denotes upper limit of normal (adapted from ref.⁸).

Dimers may help to anticipate a potential unresponsiveness to therapies, progressive respiratory failure, and development of ARDS ultimately leading to death.^{8,38–47}

Remaining uncertainties

Current evidence regarding the possible role of cardiovascular biomarkers has been derived from COVID-19 studies performed during the first wave of the pandemic mainly in healthcare settings overwhelmed by the high number of severe cases. This has resulted in sometimes very high mortality in patients developing respiratory failure and ARDS, while with more ICU resources available mortality rates of about 20% have been reported. This introduces some uncertainties now for the applicability of these results for patients with severe COVID-19 hospitalized now during the second wave with better prepared healthcare systems.

Outlook

The clinical implications of the observation that biomarkers quantifying cardiovascular pathophysiology such as cardiomyocyte injury and hemodynamic cardiac stress are strongly associated with the risk of death in patients with primarily non-cardiac disorders, such as pneumonias due to SARS-CoV-2 or other causes, may be substantial. First, as hospital beds are a sparse and critical resource also during the second wave of the COVID-19 pandemic with many institutions required to temporarily closing their elective interventions and services, in patients with established or suspected COVID-19 normal hs-cTnT/II and BNP/NT-proBNP concentrations, of course always in conjunction with vital parameters including pulse oximetry, can reassure physicians that outpatient management is feasible. Second, it highlights the potential for cardiologists and cardiovascular therapy to possibly mitigate the detrimental effect of cardiomyocyte injury and hemodynamic cardiac stress in these primarily non-cardiac

disorders. Third, these insights might help to overcome limitations of the current classification of the cause of death. Apparently, the cardiovascular system seems to be a major contributor to a proportion of deaths classified as 'non-cardiovascular' by current classification schemes such as e.g. severe sepsis.^{48–52}

Multiple other cardiovascular biomarkers are examined in ongoing COVID-19 studies and also may be found to have value. For example, there is emerging data that growth differentiation factor 15 (GDF-15), a member of the transforming growth factor β superfamily that seems to be released by both hemodynamic and inflammatory stress, might provide even higher prognostic accuracy versus the more established biomarkers in patients with COVID-19. Among 123 patients hospitalized with COVID-19 in Norway, GDF-15 concentrations showed a C-statistic value of 0.78 for the prediction of ICU admission or in-hospital death.⁵⁴

In summary, based on the evidence available at the time of this writing, the following clinical concepts have emerged:

- (1) In patients with COVID-19 presenting with chest discomfort or dyspnoea to the ED, cardiac troponin, natriuretic peptide, and D-dimer may help physicians in the initial assessment.
- (2) Small increases in cardiac troponin concentrations are frequently seen and have multiple causes including myocardial oxygen supply demand mismatch, myocarditis, and a systemic inflammatory response syndrome.
- (3) Patients should be managed as acute coronary syndromes, if there is clear evidence of myocardial ischaemia considering all available clinical evidence.
- (4) Cardiac troponin, natriuretic peptide, and D-dimer testing is indicated in case of worsening of patients with COVID-19. In general, these cardiovascular biomarkers are easier to interpret in stable patients, than in critically ill patients due to confounding in the presence of ARDS, DIC, and shock.

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