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Use and Prognostic Implications of Cardiac Troponin in COVID-19



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KEYWORDS

- COVID-19 • Cardiac troponin • High sensitivity cardiac troponin • Myocardial injury
- Risk stratification • Prognosis

KEY POINTS

- For patients with COVID-19 infection, myocardial injury is diagnosed when cardiac troponin (cTn) concentrations exceed the 99th percentile upper-reference limit.
- Although myocardial injury is common, cTn increases are usually modest and criteria for myocardial infarction (MI) are infrequently met.
- While both direct and indirect mechanisms of myocardial damage play a role in acute myocardial injury during COVID-19, chronic myocardial injury related to comorbidities is frequently present.
- Myocardial injury has adverse short-term prognostic implications, with more data needed on long-term outcomes. The magnitude of cTn increases is also prognostic.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 infection continues to have a severe global impact. Since the earliest reports from China,¹⁻³ it has been clear that cardiac involvement is frequent in patients with COVID-19, especially in those with concomitant cardiovascular comorbidities. The early studies had limitations due in part to arbitrary definitions for cardiac involvement.⁴ Numerous studies have documented the value of cardiac troponin (cTn) to detect myocardial injury and for risk stratification. This review will discuss the latest information about cardiac involvement with an emphasis on the use of cTn.

DEFINITION OF MYOCARDIAL INJURY

Per the Fourth Universal Definition of Myocardial Infarction (4UDMI),⁵ cTn is the biomarker of choice for the detection of myocardial injury and, in the

proper clinical situation, the diagnosis of myocardial infarction (MI). If available, high-sensitivity (hs-cTn) cTn assays are preferred.⁶ An assay is defined as high sensitivity if (a) the 99th percentile can be measured with analytical imprecision $\leq 10\%$ and (b) the assay measures cTn concentrations above the limit of detection (LOD) in $\geq 50\%$ of both healthy men and women.⁷

Myocardial injury is defined as any cTn increase above the assay-specific 99th percentile upper reference limit (URL) of a healthy population. When acute myocardial injury occurs, defined as a dynamic rising and/or falling pattern of cTn concentrations with at least one cTn concentration above the 99th percentile, and there are signs and/or symptoms of acute myocardial ischemia, a diagnosis of MI is made. Due to the increased sensitivity of hs-cTn assays, myocardial injury is detected far more frequently in a variety of clinical situations not related to myocardial ischemia than in those with MI.⁵ It is often challenging for

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clinicians to identify the specific reason for hs-cTn elevations, as it can often occur in the critically ill. COVID-19 infections can induce alterations in myocardial oxygen consumption and contribute to ischemia but are also associated with pulmonary embolism (PE), critical illness, myocarditis, as well as the direct effects of SARS-CoV-2 on the myocardium and perhaps the microvasculature, making it challenging for clinicians to determine a discrete etiology.

ETIOLOGIES MYOCARDIAL INJURY IN COVID-19

There are multiple mechanisms that link COVID-19 disease to myocardial injury but also with other forms of cardiac involvement like heart failure (HF) with reduced ejection fraction and arrhythmias.⁸ While clinicians often associate cTn increases in COVID-19 to direct effects, many patients often have clear antecedent causes for chronic injury like chronic cardiovascular disease that explain such elevations. In this section, we will analyze potential mechanisms of cardiac involvement that can lead to myocardial injury in this setting.

Direct Damage of SARS-CoV-2 in the Cardiovascular System

One possible mechanism for direct damage is the cytotoxic effect of SARS-CoV-2 on the endothelium which can cause diffuse microthrombosis.^{9,10} At postmortem evaluation, nonocclusive fibrin microthrombi (without ischemic injury) are common (12/15 patients with COVID-19).¹¹

Another potential mechanism is direct virus-induced myocardial injury and the potential for myocarditis. SARS-CoV-2 has been detected in the myocardium¹² and, in a multicenter autopsy study,¹³ increased interstitial myocardial macrophages were identified in most of the cases but lymphocytic myocarditis in only a small fraction. Clinical studies suggest that myocarditis caused by SARS-CoV-2 is uncommon.¹⁴

Other hypotheses for direct damage include the possibility of infection and replication of virus within noncontractile cells in the heart such as endothelial cells, fibroblasts, and pericytes with matrix inflammation and fibrosis. There also are other speculative hypotheses.⁹

Nondirect Effects of SARS-CoV-2 in the Cardiovascular System

Nondirect effects of SARS-CoV-2 could be related to angiotensin-converting enzyme 2 (ACE2) downregulation/shedding with a subsequent hyperactive

renin-angiotensin-aldosterone system (RAAS). Moreover, SARS-CoV-2 infection induces the activation of the innate immune system, leading to elevated levels of proinflammatory cytokines, including interleukin-6 (IL-6), interleukin-1, interleukin-2, tumor necrosis factor alpha, and interferon- γ .⁹

Furthermore, SARS-CoV-2 can activate a cascade of thrombotic mechanisms through hyperactivated monocytes, platelets, and neutrophils generating neutrophil extracellular traps (NETs).⁹ Indeed, hypercoagulation with diffuse microthrombi is considered the main cause of organ failure in severe cases.^{11,13}

Viral Load and Myocardial Injury

There may be a relationship between viral load and myocardial injury. In one study,¹⁵ all patients with detectable SARS-CoV-2 viral load had quantifiable (≥ 6 ng/L) hs-cTnT concentrations, and 76% of them had concentrations above the assay-specific 99th percentile indicative of myocardial injury. While those without viremia also had quantifiable hs-cTnT concentrations (59% of cases) and myocardial injury (38%),¹⁵ these abnormalities were significantly more common in those with viremia. Another report¹⁶ evaluating both groups, however, concluded that there was no significant difference in the incidence of myocardial injury in patients with low compared with elevated viral load. Nonetheless, both myocardial injury and an elevated viral load were independent predictors of in-hospital mortality.¹⁶ Finally, a study of symptomatic hospitalized patients suggest that patients with COVID-19 and viremia have higher concentrations of inflammatory markers (such as IL-6, C-reactive protein, procalcitonin, and ferritin), but similar levels of cTnT and NT-proBNP to patients without viremia.¹⁷

CLASSIFICATION OF MYOCARDIAL INJURY IN COVID-19

As suggested previously,⁴ each cTn increase greater than the 99th percentile URL should be classified as chronic myocardial injury, acute non-ischemic myocardial injury, or acute MI. **Fig. 1** summarizes this classification and some of the possible mechanisms of myocardial injury in patients with COVID-19.

Chronic Myocardial Injury

Chronic myocardial injury is defined as stable increases ($<20\%$ variation) above the 99th percentile of cTn concentrations.⁵ Patients with COVID-19 are frequently affected by chronic

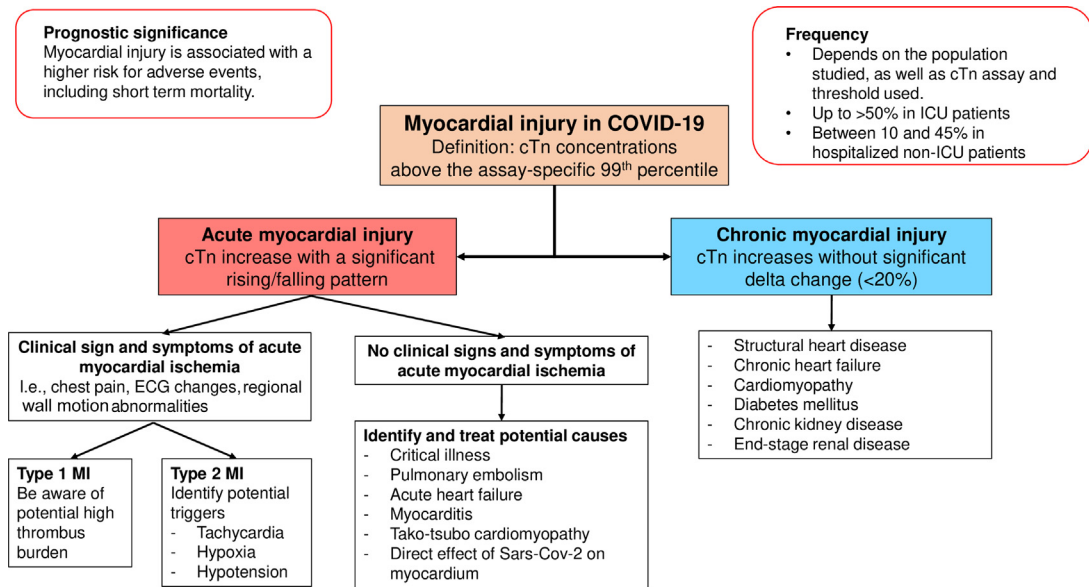


Fig. 1. Classification of myocardial injury and its possible pathogenetic mechanisms in patients with COVID-19.

cardiovascular comorbidities, such as hypertension, diabetes, coronary artery disease, HF, and chronic kidney disease (CKD),^{1,3,18} all of which can be associated with cTn increases above the 99th percentile. Structural heart disease and HF are often associated with chronic cTn increases which portend an adverse prognosis.^{5,19–21} Similarly, an elevated cTn in patients with diabetes and CKD identifies patients at higher risk of cardiovascular events.^{22,23}

Studies in patients with COVID-19 with serial cTn measurements indicate that from 13% to 26% have stable and thus chronic increases in cTn.^{24–26} In our multicenter Mayo Clinic health system study,²⁷ we adjudicated every hs-cTnT increase above the sex-specific 99th percentile among patients with COVID-19. Most hs-cTnT elevations were modest, with a median value of 12 ng/L, and significantly higher in men than in women (15 vs 9 ng/L). About half of the increases were associated with conditions such as HF, cardiomyopathy, or CKD. These data support the hypothesis that, in significant proportions of patients with COVID-19, myocardial injury is chronic and not due to effects directly related to COVID-19.

Acute Nonischemic Myocardial Injury

Acute nonischemic myocardial injury is defined as a significant rise and/or fall in cTn concentrations with at least one cTn concentration above the 99th percentile without clinical signs and symptoms of acute myocardial ischemia.⁵ These occur

often in critically ill patients^{4,8} and are not specific to COVID-19. A recent study²⁸ comparing COVID-19 with influenza patients showed that, despite a higher absolute risk of death in patients with COVID-19, myocardial injury was frequent and increased the risk of death in both diseases. Moreover, acute myocardial injury is common in critically ill patients,²⁹ in those with acute respiratory distress,³⁰ and sepsis.³¹ In our COVID-19 study,²⁷ we found that critical illness and sepsis could be identified as drivers of cTn increases in about 40% of patients. Metkus and colleagues³² compared the frequency of myocardial injury in intubated patients with COVID-19 with patients with other causes of acute respiratory distress syndrome (ARDS) and reported that the rate of myocardial injury was similar (51% in COVID-19 compared with 49.6% in ARDS). They concluded that myocardial injury in severe COVID-19 is related to baseline comorbidities, advanced age, and multisystem organ dysfunction, like what happens in traditional ARDS. In addition to the multiorgan dysfunction and hemodynamic impairment that can lead to cTn increases, patients with severe sepsis and septic shock may manifest abnormal systolic function and impaired myocardial relaxation.³³ An echocardiography study in patients with COVID-19 reported that those with myocardial injury more frequently manifested left ventricular (LV) dysfunction detected by global longitudinal strain (GLS) and right ventricular (RV) dysfunction, which only partially resolved during follow-up.³⁴ Similarly, another study reported that patients with myocardial injury more frequently

manifest global LV dysfunction, regional wall motion abnormalities, diastolic dysfunction, RV dysfunction, and pericardial effusions.³⁵

Other causes of acute nonischemic myocardial injury include RV pressure overload related to PE^{36,37} and/or microthrombi in the pulmonary circulation.¹³ In a retrospective study³⁷ of 1240 patients with COVID-19, PE was identified in 8.3% by computed tomography. Male gender, higher C-reactive protein levels, and longer hospitalization were associated with higher risk of PE while anticoagulation (both at prophylactic and therapeutic dose) were protective. A meta-analysis³⁶ of 7178 patients with COVID-19 reported a pooled incidence of acute PE in 15% of patients hospitalized in general wards and in 23% of ICU patients.

Data on endomyocardial biopsy (EMB)/autopsy tissue characterization in suspected COVID-19 are scarce³⁸ but myocardial inflammation (without necrosis) caused by macrophages and T cells is common in noninfectious and in COVID-19 related deaths but usually without histologic criteria for myocarditis.³⁹ There are, however, a few cases of EMB/autopsy-proven histologic and immunohistological active myocarditis but only 3 tested positive for SARS-CoV-2 by polymerase chain reaction on heart tissue suggesting the hypothesis that a virus-negative form, possibly triggered by the infection, might be etiologic.³⁸ In our report,²⁷ myocarditis was rare. There was clinical suspicion in 3 patients, but none had confirmatory testing performed.

Finally, features compatible with Takotsubo cardiomyopathy have been identified in 2% to 4%^{40,41} of patients with COVID-19 undergoing transthoracic echocardiogram. It could develop from catecholamine-induced microvascular dysfunction or secondary to the metabolic, inflammatory, and emotional impairment associated with COVID-19.⁴¹

Type 1 and type 2 Myocardial Infarction

When reports demonstrated a high incidence of myocardial injury in patients with COVID-19, there were concerns about a possible high incidence of type 1 MI related to the prothrombotic state or, in those critically ill, type 2 MI. In our study²⁷ which used systematic adjudication⁵ of all hs-cTnT increases, only a minority (5%) met MI criteria. Among those with type 2 MI, the most frequent triggers were hypoxia, hypotension, and/or tachyarrhythmias. Salbach and colleagues²⁶ reported a similarly low incidence. Differences in the frequency of type 2 MI in nonadjudicated studies are likely related to patient selection and less rigor in applying criteria establishing the presence of

acute myocardial ischemia. One potential difference is that⁴² in patients with COVID-19, oxygen demand-supply imbalance is often secondary to hypoxemia, increased heart rate, inflammatory status, and/or decompensated HF, whereas in most type 2 MIs, tachyarrhythmias and anemia are often prevalent mechanisms. Conventional treatment strategies seem appropriate but individualized care is warranted given the heterogeneous presentations and mechanisms. It is worth noting that in those with STEMI,⁴³ there seems to be a higher thrombus burden, and these patients can have worse outcomes.

FREQUENCY OF MYOCARDIAL INJURY IN PATIENTS WITH COVID-19

Many studies in this area have used arbitrary definitions and cutoffs to define myocardial injury^{2,44} and others have been based on non-high sensitivity cTn assays.⁴⁵ **Table 1** tabulates the frequency of myocardial injury based on hs-cTn concentrations above the 99th percentile URL or above specified thresholds. As shown in **Fig. 2**, the frequency of myocardial injury varies widely probably in relation to patient selection. In studies of patients admitted to intensive care units (ICU), the frequency of myocardial injury is as high as or greater than 50%.^{32,46,47} Studies that include a broader spectrum of patients suggest a frequency that ranges from 10%^{48,49} to more than 45%.^{26,27,50–52} This variation is likely related to the specific assay and/or threshold used, patient selection, and the population baseline characteristics. Only a small number of studies (see **Table 1**) applied sex-specific 99th percentiles as recommended.⁵

THE USE OF CARDIAC TROPONIN IN PATIENTS WITH COVID-19

Using high-sensitivity cTn assays, following guideline recommendations, sex-specific 99th percentile URLs should be used to define myocardial injury.⁵ The use of uniform criteria will allow reporting in a comparable way between studies. Moreover, the prognostic significance of myocardial injury as defined by cTn concentrations greater than 99th percentile URL has been demonstrated repeatedly in the COVID-19 population. Irrespective of etiology, myocardial injury is associated with adverse events and increased mortality in patients with COVID-19.^{2,45,51}

Single Sample Versus Serial Samples

Most studies only report values at baseline. Limited data exist addressing serial samples.

Table 1
Frequency of myocardial injury based on hs-cTn concentrations above the 99th percentile URL or above specified thresholds

Study	Location	Population	Cardiac Troponin Assay	Cutoffs Used	Frequency of Myocardial Injury
Cao et al, ⁶³ 2020	Wuhan, China	244 COVID-19 admitted patients w/o CV disease or CKD	ADVIA Centaur XP, Siemens Healthcare Diagnostics, Erlangen, Germany).	>40 ng/L	11%
Li et al, ⁴⁸ 2020	Wuhan, China	2068 COVID-19 admitted patients	Hs-cTnI, other details NR	>34.2 pg/mL	8.8% total, 2.3% in non-critically ill 30% in critically ill
Lorente-Ros et al, ⁶⁴ 2020	Spain	707 COVID-19 admitted patients	Abbott hs-cTnI	> 14 ng/L	20.9%
Huang et al, ⁴⁴ 2020	Wuhan, China.	41 COVID-19 admitted patients	Hs-cTnI, other details NR.	>28 ng/L	All: 12% ICU: 31% Non-ICU: 4%
Zhou F. et al, ³ 2020	Wuhan, China.	191 COVID-19 admitted patients	Hs-cTnI, other details NR	>28 pg/mL	All: 17% Non-survivor: 46% Survivor: 1%
Inciardi et al, ⁵⁰ 2020	Brescia, Italy	99 COVID-19 admitted patients	Hs-TnT	>14 ng/L	71% of patients with cardiac disease, 47% without cardiac disease
Cecconi et al, ⁶⁵ 2020	Milano, Italy	239 COVID-19 admitted patients	Troponin I, other details NR	>19.8 ng/L	27.7% overall
Nie et al, ⁶⁶ 2020	Huazhong, China	311 COVID-19 admitted patients	hs-cTnI, ARCHITECT STAT, Abbott	>99th URL	33.1%
Wei et al, ⁶⁷ 2020	China	101 COVID-19 admitted patients	hs-TnT	>14 ng/L	15.8%
Wang et al, ⁶⁸ 2020	Wuhan, China	22 COVID-19 admitted patients with severe pneumonia	hs-TnI, other details NR	>34.2 pg/mL	13%
Heberto et al, ⁶⁹ 2020	Mexico	254 COVID-19 admitted patients	hs-cTnI Beckman Coulter	>17.5 ng/L	28.7%
Raad et al, ⁷⁰ 2020	Southeast Michigan, USA	1020 COVID-19 admitted patients	hs-cTnI Beckman-Coulter	>18 ng/L	38%

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Table 1
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Study	Location	Population	Cardiac Troponin Assay	Cutoffs Used	Frequency of Myocardial Injury
Stefanini et al, ⁷¹ 2020	Milan, Italy	397 COVID-19 admitted patients	hs-TnI Beckman Coulter	≥19.6 ng/L	25%
Schiavone et al, ⁷² 2020	Italy	674 COVID-19 admitted patients	Hs-cTn, other details NR	>99th URL	43.8% in CCS 14.4% without CCS
Arcari et al, ⁷³ 2020	Rome, Italy	111 COVID-19 admitted patients	Hs-Troponin T Hs-Troponin I (other details NR)	< 14 pg/mL < 35 pg/mL	38%
Ghio et al, ⁷⁴ 2020	Pavia, Italy	405 COVID-19 admitted patients	Hs-cTnI (other details NR)	99th URL	74/340 (22%)
Karbalai Saleh et al, ⁷⁵ 2020	Tehran, Iran	386 COVID-19 admitted patients	hs-cTnI, other details NR	>26 ng/mL for men >11 ng/L for women	29.8%
Lombardi et al, ⁵¹ 2020	Italy, multicentric	614 COVID-19 patients admitted to Cardiology Units	Hs-cTnI or hs-cTnT, other details NR	>99th URL	45%
Salvatici et al, ⁷⁶ 2020	Milan, Italy	523 COVID-19 admitted patients	hs-TnI Beckman Coulter	11.6 ng/L for women 19.8 ng/L for men	37.3%
Singh et al, ⁵² 2020	Chicago USA	276 COVID-19 admitted patients	Hs-TnT	17 ng/L (median in their population)	48%
Fan et al, ⁷⁷ 2020	Wuhan china	353 COVID-19 admitted patients	Hs-cTnI STAT High Sensitive Troponin-I Abbott	>34.2 pg/mL for men >15.6 pg/mL for women	22.4%
He et al, ⁷⁸ 2020	Wuhan china	1031 COVID-19 admitted patients	Hs-cTnI, other details NR	>99th URL	20.7%
Zaninotto et al, ²⁴ 2020	Padova, Italy	113 COVID-19 admitted patients	Hs-cTnI Architect i2000, Abbott Diagnostics	16 ng/L for women 34 ng/L for men	45%
Ferrante et al, ⁷⁹ 2020	Milano, Italy	332 COVID-19 admitted patients with chest CT	Hs-cTnI, other details NR	>20 ng/L	37%
Chen et al, ⁸⁰ 2020	Wuhan china	726 COVID-19 admitted patients severe or critically ill	Hs-cTnI Architect i2000, Abbott Diagnostics	>28 ng/L	37.4% in critical patients 10.4% in severe patients
Poterucha et al, ⁸¹ 2021	New York, USA	887 COVID-19 admitted patients with ECG	Hs-cTnT	≥20 ng/L	43%

Perrone et al, ⁸² 2021	Italy, multicentric	543 COVID-19 admitted patients	hs-cTnT	>14 ng/L	47%
Metkus et al, ³² 2021	Baltimore, USA	243 COVID-19 admitted patients intubated.	Hs-cTnI and hs-cTnT	>99th URL	51%
Peirò et al, ⁸³ 2021	Tarragona, Spain	196 COVID-19 patients ED/hospital	Hs-cTn I Assay, Advia Centaur, Siemens	>21 ng/L	39.3%
Efros et al, ⁸⁴ 2021	Tel-Aviv, Israel	559 COVID-19 admitted patients	hs-TnT	>99th URL	28.4%
Cipriani et al, ⁸⁵ 2021	Padova, Italy	109 COVID-19 admitted patients	Hs-cTnI Architect i2000, Abbott Diagnostics	16 ng/L for women 34 ng/L for men	38%
Qian et al, ⁸⁶ 2021	Wuhan china	77 ICU COVID-19 patients	Hs-cTnI, other details NR	>28 ng/L	53%
De Michieli et al, ⁵⁴ 2021	Padova, Italy	426 ED COVID-19 patients	Hs-cTnI Architect i2000, Abbott Diagnostics	16 ng/L for women 34 ng/L for men	27.2%
Siddiqi et al, ¹⁵ 2021	Boston, USA	70 COVID-19 admitted patients	Hs-cTnT	>14 ng/L	16/21 (76%) Pts with viremia 18/49 (38%) w/o viremia
Larcher et al, ⁴⁷ 2021	France	111 ICU COVID-19 patients	Hs-cTnT	>14 ng/L	55%
Demir et al, ⁴⁶ 2021	London, UK	176 ICU COVID-19 pts with cTn	Hs-cTnT	>14 ng/L	56%
Myhre et al, ¹⁷ 2021	Akershus University Hospital Norway	123 COVID-19 admitted patients	Hs-cTnT	>10 ng/L for women >15 ng/L for men	42% in pts with viremia 33% in pts w/o
Bieber et al, ³⁴ 2021	Munich, Germany	32 COVID-19 admitted patients with 3D echo	Hs-cTnT	>14 ng/L	56%
Garcia de Guadiana-Romualdo et al, ⁸⁷ 2021	Spain, multicenter	1280 ED COVID-19 patients	Hs-cTnT cTnI Siemens Atellica cTnI Siemens Advia Centaur cTnI Siemens Dimension EXL cTnI Abbott Architect cTn I Beckman Dxl 800/Access	>99th URL	26.9% w/o sex-specific cutoffs 30% with sex-specific cutoffs
de Falco et al, ⁴⁹ 2021	Naples, Italy	174 COVID-19 admitted patients	Hs-cTnI Architect i2000, Abbott Diagnostics	16 ng/L for women 34 ng/L for men	11.5%
Barman et al, ⁵⁸ 2021	Turkey	607 COVID-19 admitted patients	Hs-cTnI, other details NR	>14 pg/mL	24.7%
De Michieli et al, ²⁷ 2021	USA, multicenter	367 COVID-19 admitted patients with cTn measured	Hs-cTnT	>10 ng/L for women, >15 ng/L for men	46%

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Table 1
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Study	Location	Population	Cardiac Troponin Assay	Cutoffs Used	Frequency of Myocardial Injury
Ozer et al, ⁸⁸ 2021	Turkey	73 COVID-19 admitted patients with Chest CT	Abbott, ARCHITECT STAT High Sensitive Troponin-I	>11.5 ng/L	39.7%
Caro-Codón et al, ⁸⁹ 2021	Madrid, Spain	918 patients with COVID-19 ED with cTn measured	Atellica Solution IM1600, Siemens Healthineers hs-cTnI	> 34.1 ng/L > 53.5 ng/L	20.7%
Maino et al, ⁹⁰ 2021	Rome, Italy	189 COVID-19 admitted patients	hs-TnI Advia Centaur Siemens	57 ng/L For men 37 ng/L for women	16% overall 9.7% in mild 29.0% in severe 61.3% in critical
Chehab et al, ¹⁶ 2021	Detroit, USA	270 COVID-19 admitted patients with cTn	Hs-cTnI Beckman Coulter	100 ng/L (not URL)	32.6%
Arcari et al, ⁹¹ 2021	Italy, multicenter	252 COVID-19 admitted patients, 229 with cTn	Hs-Troponin T hs-Troponin I, other details NR	14 pg/mL 35 pg/mL	36%
Salbach et al, ²⁶ 2021	Heildeberg, Germany	104 COVID-19 admitted patients	Hs-cTnT	>14 ng/L	44.2%

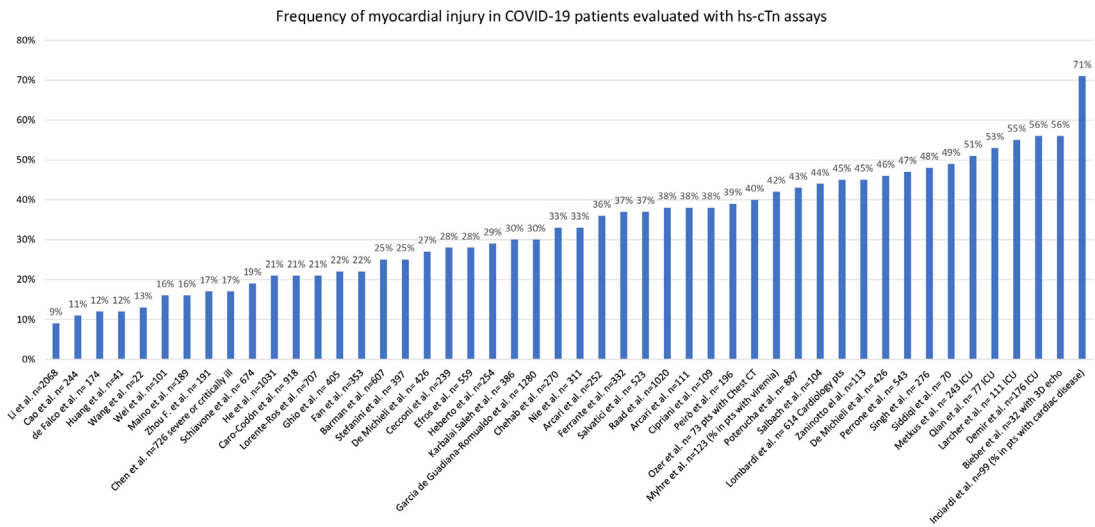


Fig. 2. Frequency of myocardial injury in multiple studies based on hs-cTn values. Details about different studies' population, the assays used, and a complete list of references are available on [Table 1](#).

Kini and colleagues²⁵ evaluated hs-cTnI measurements between 72h before and 48h after the COVID19 diagnosis and classified patients as suffering from chronic myocardial injury or acute myocardial injury (>20% or >50% delta with elevated or normal baseline cTn, respectively). They found that both types of myocardial injury were associated with increased mortality at 30 days and 6 months even after multivariable adjustment. However, among patients less than 65 years and those without known coronary artery disease, acute myocardial injury was associated with a worse prognosis at 6 months. It was associated with a more pronounced inflammatory status, more ischemic risk factors such as intracoronary thrombosis and more oxygen supply-demand imbalance due to sepsis, but also more nonischemic conditions, like myocarditis, PE, and Takotsubo syndrome. In contrast, patients with chronic myocardial injury had more chronic comorbidities, including CKD and HF. Nuzzi and colleagues⁵³ evaluated hs-cTn measurements (either T or I) within 24 h of admission and, subsequently, again between 24 and 48 h. They categorized patients in 4 groups: normal (troponin <99th URL at both assessments), normal-elevated (normal cTn at admission and elevated thereafter), elevated-normal or elevated (ie, cTn>99th URL at both measurements). Patients with incident myocardial injury, with persistent elevated cTn, and with elevated cTn only at admission had a higher risk of death compared with those with normal cTn at both evaluations. By multivariable analysis, patients that developed myocardial injury

had the highest mortality risk. A smaller study²⁴ showed that patients with significant variation in concentrations of hs-cTnI ($\Delta \geq 20\%$), and at least one value ≥ 99 th sex-specific URL had longer hospital stays, more aggressive disease, and more often needed admission to ICU. Therefore, the data seem to indicate an adjunctive prognostic role for serial sampling although the populations that benefit most from this monitoring are a matter of debate.

Adjunctive Role of Cardiac Troponin in Risk Stratification

The role of very low hs-cTn concentrations to facilitate the identification of low-risk patients with a favorable prognosis has been demonstrated for both hs-cTnT²⁷ and hs-cTnI.⁵⁴ Patients with very low values at presentation (<6 ng/L for Roche hs-cTnT and < 5 ng/L for Abbott hs-cTnI) are at low risk for mortality and adverse events. Particularly, a single hs-cTnT less than 6 ng/L identified 26% of patients with COVID-19 without mortality and a low risk of major adverse events among patients presenting to the ED.²⁷ Similarly, an initial hs-cTnI less than 5 ng/L identified 33% of patients at low risk with 97.8% sensitivity and 99.2% negative predictive value in a hospitalized cohort.⁵⁴ These findings are similar to what is suggested for ruling-out MI, and likely occur because very low hs-cTn concentrations represent an objective measure to identify younger patients with fewer comorbidities.

Conversely, whether cTn increases enhance risk stratification in patients with COVID-19 remains a matter of debate. Omland and colleagues⁵⁵ reported that in multivariable models adjusting for clinical variables and a severity of illness score, only ferritin and lactate dehydrogenase (but not cTn) were significant predictors of a composite outcome of hospital mortality and admission to the ICU for mechanical ventilation and lasting greater than 24 hours in consecutive unselected COVID-19 patients. In our Padova study,⁵⁴ in patients with COVID-19 presenting through the ED, hs-cTnI was a significant predictor of mortality for patients with lower Acute Physiology and Chronic Health Evaluation II (APACHE II) score but not in those with higher (>13) APACHE score. One could argue that in those that are more critically ill, the adjunctive role of cTn in predicting outcomes is more limited. However, hs-cTn can help to identify those who are less severely ill but are also at risk. Moreover, its use may be more clinically convenient than a more complex multivariable model. It may also be the case that many studies were based on cTn concentrations obtained for clinical reasons, potentially biasing the analysis.

When to Measure Cardiac Troponin and What to Do if It Is Elevated?

The European Society of Cardiology Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association developed a document discussing the significance and the proper use of cTn in COVID-19.⁵⁶ There is a paucity of evidence regarding the appropriate response to finding an increased hs-cTn concentration. If a type 1 MI is suspected, established diagnostic algorithms for rule-out and/or rule-in of MI should be deployed according to current guidelines.⁵⁶ However, given that in most patients with COVID-19 a type 1 MI is not present, these individuals rarely undergo coronary angiography. Indeed, in critically ill patients with septic shock and/or ARDS, cTn increases are more likely due to critical illness with or without hemodynamic impairment, resulting in myocardial injury or, if ischemia is present, type 2 MI.⁵⁶ Data on the appropriate therapy for type 2 MI in the critically ill are scarce and this is even more true for patients with COVID-19, constituting an important research gap.⁵⁷

PROGNOSTIC IMPLICATIONS

Most studies have correlated myocardial injury with a poor in hospital outcome and short term mortality, regardless of the presence of known concomitant cardiovascular disease.^{58,59} Conversely, cTn

concentrations remain within the normal range in most survivors.⁵⁶ The incidence of myocardial injury increases with greater severity of illness and with the development of ARDS.⁵⁶ Regarding the consequences of myocardial injury in COVID-19, Kotecha and colleagues⁶⁰ performed cardiac magnetic resonance (CMR) in 148 patients with such injury who recovered from severe COVID-19 after a median of 68 days. They found late gadolinium enhancement and/or ischemia in 54% of patients. This included myocarditis-like scar in 26%, infarction and/or ischemia in 22%, and dual pathology in 6%. Myocarditis-like injury was limited in extent and had minimal functional consequences; however, in 30% signs of active myocarditis persisted. Of the patients with an ischemic injury pattern, 66% had no history of coronary disease suggesting pre-existing silent disease or de novo COVID-19-related changes. Puntmann and colleagues⁶¹ performed CMR after a median of 71 days in 100 recovered patients with COVID-19 (including two-thirds of patients that recovered at home). hs-TnT was detectable in 71 patients and elevated (>13.9 pg/mL) in 5 patients. CMR revealed cardiac involvement in 78 patients and ongoing myocardial inflammation in 60. Hs-cTnT was significantly correlated with native T1 mapping, native T2 mapping, and LV mass.

Data regarding long-term consequences of myocardial injury in those who survived COVID-19 are scarce. A prospective exercise echocardiographic evaluation of 48 patients 6 months after COVID-19 disease (some of whom had experienced myocardial injury⁶²) revealed that exercise induced a significant increase in the average E/e' ratio and systolic pulmonary artery pressure in those who had suffered myocardial injury.

SUMMARY

Myocardial injury, defined as cTn increases above the assay-specific 99th percentile, is frequent in patients with COVID-19. It correlates with adverse events and short-term mortality. Most increases seem related to chronic cardiovascular conditions and acute nonischemic myocardial injury, similarly to that reported in severely ill patients. However, some studies with advanced cardiac imaging and long-term follow-up indicate that myocardial injury might be associated with long-term structural abnormalities and worse cardiac performance. Except for patients suffering from type 1 MI, the appropriate treatment of patients with COVID-19 with myocardial injury remains case-specific and further investigations are necessary to understand how to improve outcomes in this population.

CLINICS CARE POINTS

- Myocardial injury is common in patients with COVID-19 infection, but its frequency varies widely based on the population studied and the cTn assay and threshold used.
- Even though COVID-19 patients can present with type 1 or type 2 MI, acute and chronic myocardial injury (cTn increases above the 99th percentile without clinical evidence of acute myocardial ischemia) are the most common reasons for cTn increases.
- Regardless of the mechanism, myocardial injury, and the magnitude of cTn increases have prognostic significance.

DISCLOSURE

Dr Y. Sandoval has previously served on the Advisory Boards for Roche Diagnostics and Abbott Diagnostics without personal compensation. He has also been a speaker without personal financial compensation for Abbott Diagnostics. Dr A.S. Jaffe has consulted or presently consults for most of the major diagnostics companies, including Beckman-Coulter, Abbott, Siemens, Ortho Diagnostics, ET Healthcare, Roche, Radiometer, Sphingotec, RCE, and Amgen and Novartis. Dr L. De Michieli has nothing to disclose.

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