

# Comprehensive Review of Cardiovascular Complications of Coronavirus Disease 2019 and Beneficial Treatments

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**Abstract:** Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 and was first reported in December 2019 in Wuhan, China. Since then, it caused a global pandemic with 212,324,054 confirmed cases and 4,440,840 deaths worldwide as of August 22, 2021. The disease spectrum of COVID-19 ranges from asymptomatic subclinical infection to clinical manifestations predominantly affecting the respiratory system. However, it is now evident that COVID-19 is a multiorgan disease with a broad spectrum of manifestations leading to multiple organ injuries including the cardiovascular system. We review studies that have shown that the relationship between cardiovascular diseases and COVID-19 is indeed bidirectional, implicating that preexisting cardiovascular comorbidities increase the morbidity and mortality of COVID-19, and newly emerging cardiac injuries occur in the settings of acute COVID-19 in patients with no preexisting cardiovascular disease. We present the most up-to-date literature summary to explore the incidence of new-onset cardiac complications of coronavirus and their role in predicting the severity of COVID-19. We review the association of elevated troponin with the severity of COVID-19 disease, which includes mild compared to severe disease, in nonintensive care unit compared to intensive care unit patients and in those discharged from the hospital compared to those who die. The role of serum troponin levels in predicting prognosis are compared in survivors and non-survivors. The association between COVID-19 disease and myocarditis, heart failure and coagulopathy are reviewed. Finally, an update on beneficial treatments is discussed.

**Key Words:** SARS-CoV-2, cardiovascular disease, troponin, mortality, Covid-19  
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Coronavirus disease 2019 (COVID-19) is caused by a single-strand RNA enveloped virus that belongs to the family of coronaviridae and emerged in December 2019 in Wuhan, China. It rapidly spread globally and was declared by the World Health Organization (WHO) as a public health emergency of international concern and pandemic on March 11, 2020.<sup>1</sup> COVID-19 predominantly presents with respiratory symptoms, given that it is named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The clinical presentations of COVID-19 vary from an asymptomatic carrier state to severe pneumonia, to acute respiratory distress syndrome (ARDS), multiorgan failure, and death.<sup>2</sup> Globally, the total number of confirmed infected cases was 212,324,054, which resulted in

4,440,340 deaths as of August 22, 2021.<sup>3</sup> In addition to presenting as only a respiratory infection, COVID-19 exhibits a wide variety of extrapulmonary involvement.<sup>4</sup> Pathophysiologic mechanisms of acute COVID-19 include direct viral toxicity; endothelial damage and microvascular injury; immune system dysregulation and stimulation of a hyperinflammatory state; hypercoagulability with resultant in situ thrombosis and macrothrombosis; and maladaptation of the angiotensin-converting enzyme 2 (ACE-2) pathway.<sup>2</sup> Mortality of COVID-19 is attributed to various conditions such as septic shock, renal failure, ARDS, and acute cardiac injury. Earlier reports of COVID-19 manifestations revealed cardiac injury as a common and important complication of coronavirus.<sup>5,6</sup> There is a bidirectional interaction between cardiovascular disease (CVD) and pathophysiology of COVID-19. Preexisting cardiovascular comorbidities increase the risk of severe COVID-19. Alternatively, coronavirus infection is suggested to affect the cardiovascular system and lead to newly developed cardiac complications. However, little is known about the potential mechanisms of cardiac injury and its relationship with morbidity and mortality. This urges us to pay special attention to the cardiac manifestations of COVID-19. As the pandemic continues, more evidence is becoming available directing the epidemiological findings and complications of the disease. Herein, we present the most updated comprehensive review of the literature for the aims of exploring the incidence of new-onset cardiac complications of coronavirus and their role in predicting the severity and mortality of the disease. This review alerts physicians to the importance of cardiovascular involvement in COVID-19, early detection of patients at risk for poor outcomes and treatments proven in randomized trials.

## METHODS

### Search Strategy

The review was conducted by searching PubMed for relevant studies of cardiovascular complications using the following search terms: [COVID-19(MeSH Terms)] OR [SARS-CoV-2] OR [COVID-19(Title/Abstract)] OR [coronavirus(MeSH Terms)] OR [coronavirus(Title/Abstract)] AND [cardiac(MeSH Terms)] OR [cardiac(Title/Abstract)] OR [heart(Title/Abstract)] OR [heart(MeSH Terms)] OR [myocardial(Title/Abstract)] OR [myocardial(MeSH Terms)] OR [myocarditis(Title/Abstract)] OR [myocarditis(MeSH Terms)] OR [myocardial infarction(Title/Abstract)] OR [myocardial infarction(MeSH Terms)] OR [heart failure(Title/Abstract)] OR [heart failure(MeSH Terms)] OR [cardiac complication(Title/Abstract)].

Search results were de-duplicated in EndNote X6, and the titles and abstracts were screened by two researchers for their relevance. We also screened the bibliographies of the included articles manually. Subsequently, the full texts of screened studies were retrieved and reviewed thoroughly according to the inclusion and exclusion criteria. The eligibility of studies was assessed based on the following criteria: (1) all studies published as an original article in peer-reviewed journals; (2) participants diagnosed with COVID-19; and (3) reporting the prevalence of cardiac complications, cardiac troponin I (cTnI), severity, and mortality. Two authors independently

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reviewed the full text of selected articles against the eligibility criteria. The literature search was started on June 25th, 2020, updated throughout the study, and finalized on May 12, 2021.

### Data Extraction

Data extraction was carried out on studies that fulfilled the inclusion criteria by two independent investigators using a predefined standardized extraction form. The primary outcome was new-onset cardiac complications of SARS-CoV-2. The secondary outcome was the association of cardiac injury with the severity and mortality of SARS-CoV-2. The extracted information included basic information on title of the study, author’s affiliation and sponsor, geographical location of study, sample size, sampling method, perspective of the study, participant characteristics including age, sex, number of deaths, cardiac complications, range and cut-off point of cTnI, and other available characteristics.

Cardiac injury was defined as cTnI elevation >99th percentile and/or new abnormalities in electrocardiography and echocardiography. According to the guidelines for diagnosis and management of COVID-19 issued by the National Health Commission of China, severe COVID-19 cases were characterized by the presence of any of the following: respiratory distress, respiratory frequency  $\geq 33$  times/min, oxygen saturation less than 93% in a resting state, or partial arterial oxygen pressure/oxygen absorption concentration (FiO<sub>2</sub>)  $\leq 300$  mm Hg (1 mm Hg = 0.133 kilopascal). Critically ill was defined with the following conditions: respiratory failure requiring mechanical ventilation and shock or transfer to the intensive care unit (ICU) due to organ failure other than respiratory failure. The respiratory support treatment for severe patients was medium-flow nasal cannula (5 L/min) whereas critical-type patients received noninvasive ventilation and/or invasive mechanical ventilation.

## RESULTS

### Demographic and Clinical Characteristics

The literature search yielded 1290 records using the search terms of which 1002 records were excluded after title/abstracts screening and duplication removal. Subsequently, full-texts of the remaining 288 studies were assessed for eligibility and a total of 220 were excluded for the following reasons: (1) no outcome of interest; (2) specific population (cancer cases or pregnancy); and (3) articles written in languages other than English. Altogether, 68 studies of cardiovascular complications comprising 144,528 cases with confirmed COVID-19 were recruited between December 16th, 2019 and December 31, 2020 (Fig. 1). The baseline characteristics of the included studies are demonstrated in Supplemental Digital Content Table 1 <http://links.lww.com/CIR/A35>.

### ASSOCIATION OF ELEVATED TROPONIN LEVELS WITH SEVERITY OF COVID-19 DISEASE

Multiple studies reported myocardial injury, defined as an increased level of troponin above the 99th percentile, as one of the most common complications of COVID-19. In 92 deceased cases with COVID-19, the most common complication after ARDS was myocardial injury with an incidence rate of 34.1%.<sup>7</sup> Among 1000 COVID-19 patients, the most common complication was cardiac injury (11.6%) followed by shock (8.1%) and acute liver injury (6.4%).<sup>8</sup> Among 312 hospitalized patients >65-years old with COVID-19, acute cardiac injury was the most common complication (33%) outside the lungs, and patients with severe illness were more likely to present with cardiac complications compared to mild cases (62.9% vs 17.9%, respectively,  $P = 0.038$ ).<sup>9</sup> The incidence of cardiac injury ranged from 1% in recovered individuals to 69.2% in ICU

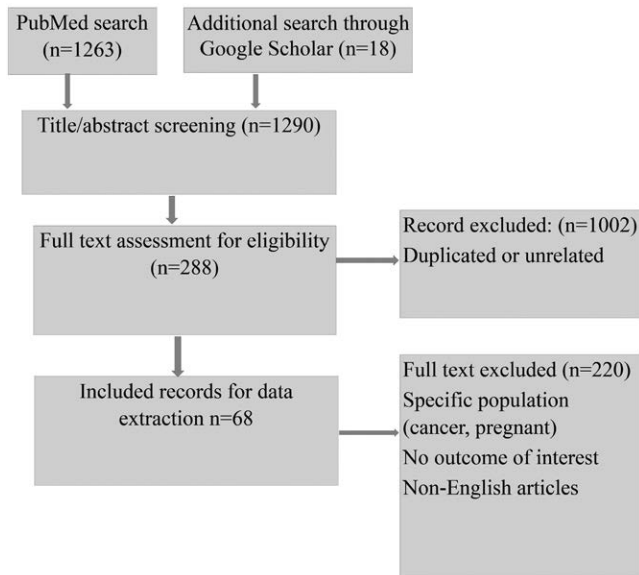


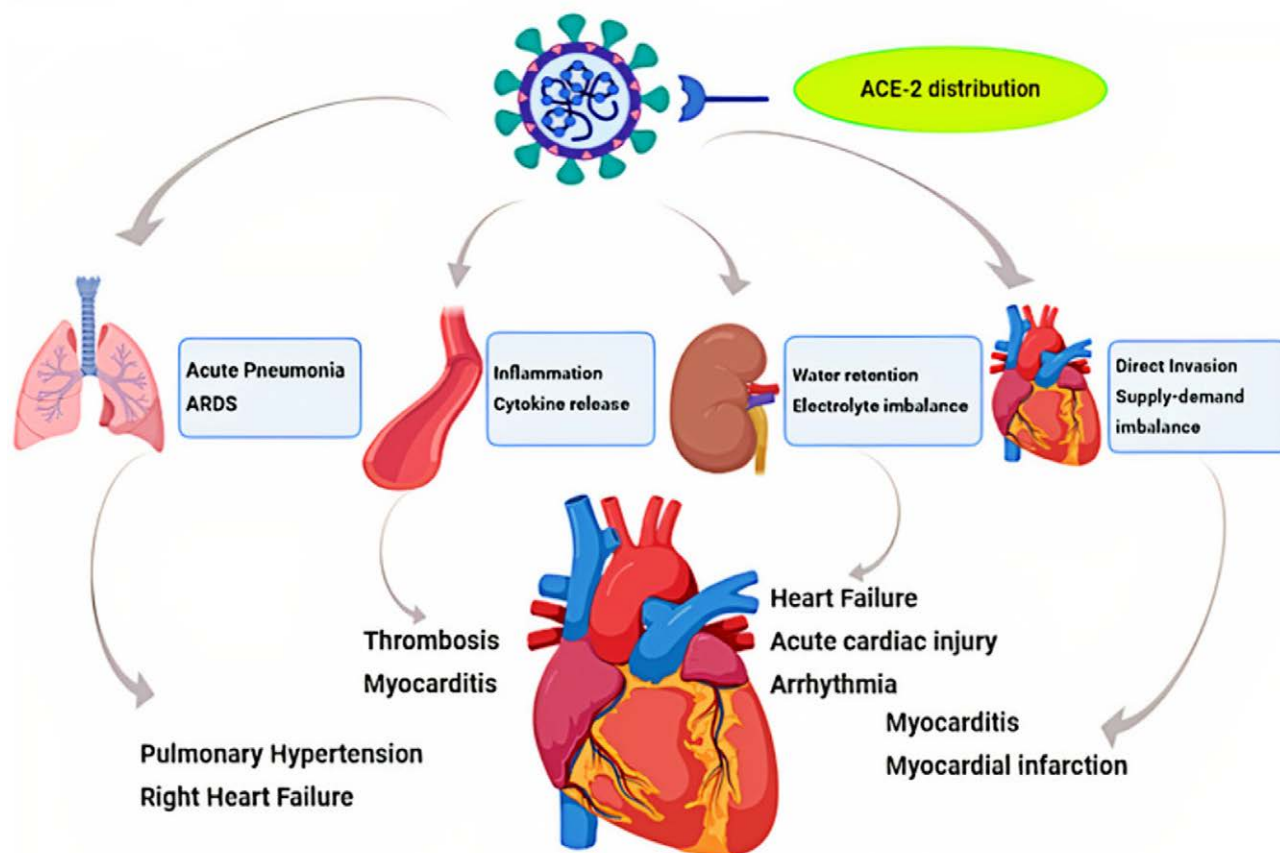
FIGURE 1. Flow diagram summarizing the method of selecting studies to review.

admitted and 74.1% in those  $\geq 60$ -years old.<sup>10–12</sup> A higher incidence of cardiac complications was noted with increasing age (4% in age <60 years vs 12.5% in age 60–74 years vs 31% in age  $\geq 75$  years).<sup>8</sup>

Two studies provided evidence of myocardial injury associated with SARS-CoV-2 in children. In 58 children who met the criteria of pediatric inflammatory multisystem syndrome associated with SARS-CoV-2, 68% had an elevated cTnI.<sup>13</sup> In nine pediatric patients positive for COVID-19, five children had an elevated level of cTnI, mild to moderate ventricular dysfunction on echocardiography, and ST-segment abnormalities on the electrocardiogram.<sup>14</sup> Although the cardiac manifestations mimicked Kawasaki disease, the clinical patterns of infected children did not meet all criteria required for classic or atypical Kawasaki disease; thus, cardiac involvement was in part due to COVID-19-related pediatric multisystem inflammatory syndrome.

Potential mechanisms of cardiac injury include direct viral invasion, hypoxia-induced cytokine release and inflammation, instability and rupture of atherosclerotic plaque.<sup>15,16</sup> The most recognized mechanism for the pathogenesis of SARS-CoV-2 infection is through the ACE-2 receptor (Fig. 2). ACE-2 is predominantly expressed in the lower respiratory tract and to some extent in other tissues such as cardiomyocytes and endothelial cells.<sup>1,17</sup>

Cardiac involvement in COVID-19 is accompanied with a more severe clinical course. Cardiac injury could be either a new-onset complication of SARS-CoV-2 or an exacerbation of preexisting cardiovascular comorbidities. In a multivariable logistic regression model, risk factors predicting the development of cardiac injury consisted of older age, history of hypertension, chronic heart disease, chronic renal disease, and high level of C-reactive protein (CRP).<sup>18</sup> Higher workload in hypoxic states and myocardial demand triggered by acute viral infections account for the higher rates of acute cardiac injury and hemodynamic deterioration in patients who have underlying CVD such as heart failure, congenital heart disease, and coronary artery disease.<sup>19,20</sup> In patients who had neither preexisting comorbidity nor acute cardiac injury, the mortality rate was nearly half of those with CVD comorbidities and normal cTnI level (7.62% vs 13.33%, respectively).<sup>21</sup> The mortality rate was 37.5% in patients with elevated troponin but without a prior history of CVD.<sup>21</sup> The highest rate of death was observed in patients with both new-onset and underlying cardiac disease (69.4%).



**FIGURE 2.** SARS-CoV-2 infection is associated with new onset cardiovascular disease including heart failure, acute cardiac injury, myocardial infarction, myocarditis, arrhythmias, and coagulopathies. SARS-CoV-2 infects multiple organs mainly through the ACE-2 receptor. This could subsequently result in the development of cardiac injury with the following mechanisms: direct viral invasion of cardiomyocytes; renal function impairment leading to electrolyte abnormalities and water retention; inflammatory response and cytokine release; and respiratory damage, which causes increasing myocardial demand and hypoxia-induced oxidative stress. ACE-2 indicates angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Table 1 summarizes the characteristics of studies stratified by mild and severe disease, non-ICU admission versus ICU admission, and discharge versus death. Among 671 patients with severe COVID-19, the incidence of myocardial injury evidenced by elevated cTn level was 15.8% with a significant difference between survivors and non-survivors (9.7% vs 75.8%;  $P < 0.001$ ) (Table 1).<sup>18</sup> Other studies summarized in Table 1 reported a higher incidence of elevated troponin levels in those who died compared to those who were discharged from the hospital.<sup>12,23,25,28,30,32,36,37</sup> Moreover, Harmouch et al<sup>25</sup> noted cardiac injury as an independent risk factor predicting mortality. They reported cardiac injury in 20% of 560 individuals with COVID-19 with a significantly higher incidence rate in nonsurvivors compared to survivors (51.5% vs 15.1%,  $P < 0.001$ ) (Table 1).

Table 1 also reports higher rates of elevated troponin levels in those with severe compared to mild disease. Among 548 COVID-19 patients, the incidence of cardiac injury was significantly higher in severe compared to mild cases (34.9% vs 9%) (Table 1).<sup>27</sup> Other studies noted in Table 1 reported similar findings.<sup>9,22,24,27,33–35</sup> Rates were also higher in those admitted to the ICU compared to non-ICU patients (Table 1).<sup>10,26,31</sup> In another report on 273 COVID-19 patients, the serum level of four cardiac biomarkers including creatinine kinase-MB, cTnI, myohemoglobin, and N-terminal pro-B-type natriuretic peptide (NT-ProBNP) was positively correlated with an increasing severity of COVID-19.<sup>24</sup>

### The Role of Troponin I Level in Predicting Prognosis

Studies have indicated that quantifying the serum level of cTnI has clinical significance in predicting the prognosis in COVID-19. Among studies that measured mortality as an outcome of COVID-19, the level of cTnI was significantly higher in nonsurvivors compared to survivors. The characteristics of those studies are summarized in Table 2.<sup>18,23,28–30,32,36,38–45,47</sup> Among 101 COVID-19 cases, those with high-sensitivity troponin T (TnT)  $\geq 14$  pg/mL were more likely to require ICU admission (62.5% vs 24.7%), mechanical ventilation (43.5% vs 4.7%), and have a fatal outcome (18.8% vs 0%) compared to patients with high-sensitivity-TnT  $< 14$  pg/mL.<sup>48</sup>

In a report of 182 confirmed cases of COVID-19, patients with an elevated cTnI value had an odds ratio (OR) of poor outcomes including mortality, requiring intubation, ARDS/acute renal failure, and acute kidney injury of 25.81 [95% confidence interval (CI), 6.61–80.74], 30.94 (95% CI, 8.44–94.88), 7.43 (95% CI, 1.96–25.12), and 15.83 (95% CI, 4.54–53.56), respectively (Table 2).<sup>40</sup> Ciceri et al<sup>38</sup> described the clinical characteristics of 410 patients with COVID-19 in Milan, Italy. When comparing the level of laboratory parameters in three subgroups of patients according to their outcome (discharged, hospitalized, or death), a significantly higher level of cTnI was observed in nonsurvivors compared to the hospitalized and discharged groups: 25.20 [interquartile range (IQR), 13.80–62.05] ng/L

**TABLE 1.** Incidence of Elevated Troponin in COVID-19 Cases

First Author	Number Patients	Mild Disease	Severe Disease	Non-ICU (noncritically ill)	ICU (critically ill)	Discharged Group	Death Group
Deng Q <sup>22</sup>	112	2.2%	46.3%	-	-	-	-
Deng Y <sup>12</sup>	225	-	-	-	-	0.9%	59.6%
Du <sup>23</sup>	179	-	-	-	-	17.9%	61.5%
Han <sup>24</sup>	273	5.05%	23.3%	-	-	-	-
Harmouch <sup>25</sup>	560	-	-	-	-	15.1%	51.5%
Hong <sup>10</sup>	98	-	-	2.4%	69.2%	-	-
Huang <sup>26</sup>	41	-	-	4%	31%	-	-
Li X <sup>27</sup>	548	9%	34.9%	-	-	-	-
Li T <sup>9</sup>	312	17.9%	62.9%	-	-	-	-
Ni <sup>28</sup>	179	-	-	-	-	12.07%	58.33%
Nie <sup>29</sup>	311	-	-	-	-	6%	81.9%
Pan <sup>30</sup>	124	-	-	-	-	42.9%	53.9%
Shi <sup>18</sup>	671	-	-	-	-	9.7%	75.8%
Wang <sup>31</sup>	138	-	-	2%	22.2%	-	-
Wang <sup>32</sup>	107	-	-	-	-	4.5%;	42.1%;
Yang <sup>33</sup>	136	2.9%-	24.2%	-	-	-	-
Zhao <sup>34</sup>	91	9.8%	26.7%	-	-	-	-
Zheng <sup>35</sup>	99	1.7%	6.7%	-	-	-	-
Zhou <sup>36</sup>	191	-	-	-	-	1%	59%
Zou <sup>37</sup>	154	-	-	-	-	10.78%	65.38%

ICU indicates intensive care unit.

versus 9.05 (IQR, 7.3–24.6) ng/L and 9.85 (IQR, 5.57–20.25) ng/L, respectively,  $P < 0.001$  (Table 2).

Several studies using multivariate modeling have shown that an elevated Tn level is an independent predictor of mortality. In a retrospective study of 3219 patients admitted to multiple centers with a COVID-19 diagnosis, elevated high-sensitive cTnI was associated with 28-day mortality [hazard ratio (HR), 7.12; 95% CI, 4.60–11.03;  $P < 0.001$ ] after adjusting for age, sex, hypertension, diabetes, coronary heart disease, and cerebrovascular disease.<sup>43</sup> Of note, the cut-off value of high-sensitive cTnI for COVID-19 mortality prediction was found to be approximately 50% lower than the standard laboratory cut-off value, suggesting that a redefinition of cardiac biomarker levels might improve their accuracy in predicting mortality from COVID-19.<sup>43</sup> In a large cohort study of 2736 patients with COVID-19, 36% of patients had elevated troponin at the time of admission.<sup>41</sup> Heart failure, atrial fibrillation, and coronary artery disease were more prevalent in patients with a higher concentration of TnI ( $>0.09$  ng/mL) compared to normal values. Even a small elevation of TnI to 0.03–0.09 ng/mL significantly increased the risk of mortality [adjusted hazard ratio (aHR), 1.75; 95% CI, 1.37–2.24;  $P < 0.001$ ] with higher values (cTnI  $> 0.09$ ) associated with higher risk (aHR, 3.03; 95% CI, 2.42–3.80) (Table 2).<sup>41</sup> These results also suggest that intermediate levels of Tn are important in predicting mortality.

Among 311 patients with COVID-19, the nonsurvivors had a higher concentration of cTnI compared to those who survived [median, IQR: 32.5 ng/L, (11.4–304.4 ng/L) vs 2.8 ng/L (1.5–5.8 ng/L), respectively] (Table 2).<sup>29</sup> In multivariate logistic regression analysis, an elevated cTnI level was an independent predictor of mortality (OR, 1.92; 95% CI, 1.4–2.59) (Table 2). Among 176 COVID-19 cases with a mortality rate of 34%, the proportion of patients with elevated cTnI was higher in nonsurvivors compared with survivors (58.33% vs 12.07%, respectively).<sup>28</sup> Multivariable logistic regression

models revealed that an elevated cTnI increased the risk of death with an OR of 6.93; (95% CI, 1.83–26.22;  $P = 0.0044$ ) after adjustment for sex, age, fever, severity status, comorbidities, background use of ACE inhibitors or angiotensin II receptor blockers, laboratory parameters, and glucocorticoid treatment (Table 2). Similarly, in a large prospective cohort of 5279 cases that identified risk factors for severe outcomes, the cTnI value was higher in critically ill compared to discharged patients with COVID-19: 0.07 ng/mL (IQR, 0.01–0.10) versus 0.02 (IQR, 0.01–0.10), respectively.<sup>49</sup> In multivariate analysis, an elevated level of cTnI ( $>1$  ng/mL) was independently associated with increased risk of critical illness (HR, 4.78; 95% CI, 2.10–10.9;  $P < 0.001$ ), and the highest rate of death was observed in patients with both new-onset and underlying cardiac disease (69.4%).<sup>49</sup> In the study of Du et al<sup>22</sup> on 179 patients with COVID-19, risk factors predicting mortality were age  $\geq 65$  years, preexisting concurrent cardiovascular or cerebrovascular diseases, CD8+ T-cells  $\leq 75$  cells/ $\mu$ L, and cTnI  $\geq 0.05$  ng/mL. Multivariable logistic regression analysis indicated that elevated cTnI ( $\geq 0.05$ ) was associated with an increased risk of mortality (OR: 4.077; 95% CI, 1.166–14.253;  $P < 0.001$ ) (Table 2). When subjects were matched by age, sex, and comorbidities for those who died compared to survivors, cTnI  $\geq 0.05$  ng/mL remained an independent risk factor for mortality (OR, 7.200; 95% CI, 1.518–34.139;  $P < 0.013$ ).<sup>22</sup>

In line with these results, several meta-analyses examined the role of elevated Tn in predicting COVID-19-related mortality. In a meta-analysis of eight studies with 1429 patients and 374 deaths, patients with elevated Tn levels had a significantly higher in-hospital mortality than those with normal troponin levels (unadjusted OR, 21.15; 95% CI, 10.19–43.94; heterogeneity:  $I^2 = 70.5\%$ ,  $P = 0.001$ ).<sup>20</sup> In a meta-analysis of Santoso et al,<sup>50</sup> elevation of cardiac troponin was associated with a higher rate of mortality [relative risk (RR): 7.95; 95% CI, 5.12–12.34,  $P < 0.001$ ] as well as a more severe form

**TABLE 2.** Comparison of Serum Troponin Level Between the Survivor and Nonsurvivor Groups

First Author	No. Patients	Total Mortality	Troponin Level, Median [IQR]		P-value*	OR or HR (95% CI) of Elevated cTnI for Mortality
			Discharged	Death		
Ciceri <sup>38</sup> (ng/L)	410	23%	9.85 [5.57–20.25]	25.20 [13.80–62.05]	<0.001	
Du <sup>23</sup> (ng/L)	179	11.7%	0.0 [0.0–0.0] (17.9%)	0.1 [0.0–0.8] (61.5%)	<0.001	OR: 4.077; 95% CI: 1.166–14.253; <i>P</i> < 0.001
Fan <sup>39</sup> (U/L)	73	64.3%	3.5 [1.8–4.1]	16.6 [10.1–40.8]	0.001	OR: 1.208 (1.077–1.355); <i>P</i> < 0.0001
Franks <sup>40</sup>	182	18.7%	-	-	-	HR: 25.81 (95% CI, 6.61–80.74)
Lala <sup>41</sup>	2736	18.5%	-	-	-	cTnI > 0.03–0.09 ng/mL: HR 1.75; (95% CI, 1.37–2.24; <i>P</i> < 0.001); cTnI > 0.09 ng/mL: HR 3.03; (95% CI, 2.42–3.80)
Majure <sup>42</sup>	6247	21%				cTnI 1–3 URL: 2.06 (95% CI, 1.68–2.53; <i>P</i> < 0.001); cTnI > 3 URL: 4.51 (95% CI, 3.66–5.54); <i>P</i> < 0.001
Ni <sup>28</sup>	176	34%	12.07%†	58.33%†		OR: 6.93 (95% CI, 1.83–26.22); <i>P</i> = 0.0044
Nie <sup>29</sup> (ng/L)	311	35.6%	2.8 [1.5–5.8]	32.5 [11.4–304.4]	-	OR: 1.92 (1.41–2.59)
Pan <sup>30</sup> (μg/L)	124	71.8%	9.9 [3.4–57.1]	24.1 [9.8–155.8]	0.006	OR: 1.561 (0.709–3.435); <i>P</i> = 0.268
Qin <sup>43</sup>	3219	6%	-	-	-	HR: 7.12 (95% CI, 4.60–11.03); <i>P</i> < 0.001
Rath <sup>44</sup> (ng/dl)	123	13%	0.14 [0.05, 0.29]	0.24 [0.16, 0.120]	0.023	-
Ruan <sup>45</sup> (pg/mL)	150	45%	3.5‡	30.3‡	<0.001	-
Sabatino <sup>46</sup> (ng/dL)	76	-	0.14	0.24	-	-
Shi <sup>18</sup> (pg/mL)	671	9%	6 [6–11]	23.5 [4.2–199.6]	<0.001	OR: 1.28 (1.07–1.46); <i>P</i> = 0.004
Wang <sup>32</sup> (pg/mL)	107	17.7%	1.1‡	26.3‡	<0.001	
Zhou <sup>36</sup> (pg/mL)	191	28.2%	3 [1.1–5.5]	22.2 [5.6–83.1]	<0.0001	>28 pg/mL; OR: 80.07 (10.34–620.36); <i>P</i> < 0.0001

cTnI indicates cardiac troponin I; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OR, odds ratio.

\**P*-value compares discharged to death group.

†% Patients with elevated cTnI.

‡% Patients with cTnI > 26.2 pg/ml.

of disease and need for ICU care. In a meta-analysis of 14 studies with 3175 patients, elevated Tn was associated with higher risk of mortality (risk ratio: 7.79; 95% CI, 4.69–13.01; *I*<sup>2</sup> = 58%), ICU admission (RR: 4.06; 95% CI, 1.50–10.97; *I*<sup>2</sup> = 61%), mechanical ventilation (RR: 5.53; 95% CI, 3.09–9.91; *I*<sup>2</sup> = 0%), and developing coagulopathy (RR: 3.86; 95% CI, 2.81–5.32; *I*<sup>2</sup> = 0%).<sup>51</sup>

A Swedish registry study from February 1, 2020 to September 14, 2020 matched 86,742 patients with COVID-19 to 348,481 control individuals without COVID-19. In the matched cohort study, the OR for acute myocardial infarction was 6.61 (95% CI: 3.56–12.20) and for ischemic stroke was 6.74 (95% CI: 3.71–12.20) in the 2 weeks following COVID-19.<sup>52</sup> These findings suggest that COVID-19 is a risk factor for acute myocardial infarction and ischemic stroke and emphasize the need for vaccination.

### Potential Mechanisms for Cardiac Injury

Altogether, it is evident that acute cardiac injury, represented as elevated cardiac troponin, has a positive association with fatal outcome in COVID-19 patients. Although mechanisms are unclear, studies suggest that cytokine storm and inflammation may be involved. Several studies demonstrated that the rise in cTnI in COVID-19 patients is consistent with increases in inflammatory markers such as ferritin, interleukin (IL)-6, and lactate dehydrogenase, indicating a contribution of the inflammatory response in developing new-onset cardiac complications of COVID-19.<sup>53</sup> Cecconi et al<sup>54</sup> assessed predictors of clinical deterioration indicated by ICU admission or death in 239 COVID-19 patients in Italy. They reported that an increase in IL-6, procalcitonin, cTnI, and D-dimer was associated with an increased risk of clinical deterioration. Among 73 COVID-19 patients, the level of cTnI in nonsurvivors was significantly higher

compared to survivors [16.6 U/L (IQR, 10.1–40.8 U/L) vs 3.5 U/L (IQR, 1.8–4.1 U/L); *P* < 0.001] with the normal range of 0–28 U/L.<sup>39</sup> Every one unit elevation of cTnI was associated with an increased risk of mortality by 20.8%. Multivariable logistic regression analysis revealed that the independent prediction of cTnI with mortality disappeared after adjusting for the inflammatory (CRP and IL-6 level) and coagulation index (D-dimer level). This finding led them to conclude that COVID-19-related cardiac injury may be in part due to an inflammatory response and abnormal coagulation function.

Elevated levels of Tn, D-dimer (>230 ng/ml), and CRP (>50) predicted risk for in-hospital events. In 2261 subjects at hospital admissions, 16.8% (486) had myocardial injury, 77.5% had an elevated D-dimer, and 78.1% had a CRP > 50 mg/L.<sup>55</sup> Elevation of all three biomarkers reflected myocardial injury, coagulation, and inflammation and were present in 334 patients (11.5%). In logistic regression, COVID-19 patients with 1, 2, and 3 elevated biomarkers had threefold, sixfold, and 11-fold higher adjusted odds of death compared to those with no elevated biomarkers at admission. Those with normal cTn and D-dimer and CRP < 50 mg/L (*n* = 196, 6.8%) were at low risk of critical illness and in-hospital mortality.

A large study examining 6247 hospitalized COVID-19 patients confirmed the role of troponin assessment in risk stratification. In multivariate logistic regression analysis, including covariates of age, sex, race, ethnicity, hypertension, coronary artery disease, heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and levels of alanine aminotransferase and serum creatinine, patients with an elevated cTnI had approximately a two to fourfold increased risk of mortality, with odds of death for mildly elevated troponin level (1–3 ng/mL) of 2.06

(95% CI, 1.68–2.53;  $P < 0.001$ ) and for severely elevated troponin level ( $>3$  ng/mL) of 4.51 (95% CI, 3.66–5.54;  $P < 0.001$ ), compared to a normal troponin (Table 2).<sup>42</sup> Another key finding of their study was an incremental increase of acute phase and inflammatory markers (CRP, IL-6, and ferritin) with increasing level of troponin, suggesting a role of inflammation and cytokine storm as an underlying mechanism of cardiac injury in COVID-19.

Taken together, these findings suggest that myocardial injury in COVID-19 may be driven by a cytokine-induced vascular inflammatory response. To examine this further, the multicenter Oxford Risk Factors And Non-Invasive Imaging Study (ORFAN) carried out coronary computed tomography angiography (CCTA) and RNA sequencing in 435 patients with and without COVID-19.<sup>56</sup> Those with COVID-19 were enrolled in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, randomized, controlled, open-label, platform trial in which more than 27,000 hospitalized adults with clinically suspected or confirmed SARS-CoV-2 infection from 177 sites in the UK between April 14, 2020 and January 24, 2021 were randomly assigned to one of the several treatment groups.<sup>57</sup> The ORFAN investigators reported that COVID-19 induced vascular inflammation causing cytokine upregulation led to changes in perivascular adipose tissue.<sup>56</sup> When RNA sequencing was combined with analysis of radiographic images using artificial intelligence, this inflammation was associated with a novel radiotranscriptomic signature (C19-RS) that was significantly more prevalent in COVID-19 patients [adjusted OR of 2.97 (95% CI, 1.43–6.27),  $P = 0.004$ ]. C19-RS had prognostic value for in-hospital mortality in COVID-19 with HRs of 3.31 [95% CI, 1.49–7.33],  $P = 0.003$ ] and 2.58 [95% CI, 1.10–6.05],  $P = 0.028$ ] in two external testing cohorts, respectively, after correction for clinical factors and biochemical biomarkers of inflammation (white blood cell count and hs-CRP) and troponin levels. Moreover, the corrected HR for in-hospital mortality was 8.24 (95%CI, 2.16–31.36),  $P = 0.002$  for those who received no treatment with dexamethasone, a potent anti-inflammatory corticosteroid, but only 2.27 (95%CI, 0.69–7.55),  $P = 0.18$  in those who received dexamethasone after the test, suggesting that anti-inflammatory treatment may be modifying the natural history of COVID-19 infection by improving outcomes specifically in those patients with high vascular inflammation.<sup>56</sup> These results support a role of vascular inflammation in COVID-19 and that the risk can be reduced with dexamethasone.

## MYOCARDITIS

As with other viral infections, SARS-CoV-2 can be complicated by myocarditis.<sup>58</sup> The underlying mechanisms are suggested to be due to both direct invasion of the virus in cardiomyocytes, possibly via ACE-2 receptors, and indirectly through cytokine release and inflammatory responses (Fig. 2).<sup>59,60</sup>

In a retrospective study of 112 patients, 14 (12.5%) presented evidence of myocarditis defined as elevation of cTnI level and abnormal echocardiographic findings.<sup>22</sup> cTnI was increased threefold ( $>0.12$  ng/mL) in 28.6% of cases during hospitalization and peaked significantly one week preceding death. The most common echocardiographic abnormalities were reduced left ventricular ejection fraction (LVEF)  $< 50\%$  in 5.4% of patients, segmental wall motion abnormalities in 4.5%, and wall thickness  $>10$  mm in 2.7%. A significantly higher incidence of myocarditis was noted in the severe group compared to nonsevere cases (19.4% vs 2.2%,  $P < 0.01$ ).<sup>22</sup>

In a prospective observational cohort in Germany of 100 patients who recently recovered from COVID-19, cardiac magnetic resonance (CMR) imaging performed at a median of 71 days (IQR, 64–92) after positive COVID-19 testing detected ongoing myocardial inflammation (defined as abnormal native T1 and T2 measures on CMR) in 60% of patients ( $n = 60$ ) independent of

preexisting conditions, morbidity and mortality of the acute illness, and time from the original diagnosis.<sup>61</sup>

In a retrospective multicenter study on the causes of 68 deaths among 150 cases of COVID-19, five (7%) patients revealed features of fulminant myocarditis associated with rapid progression to severe disease, and 22% had evidence of both respiratory and circulatory failure in the death group.<sup>45</sup> A higher risk of mortality was noted in patients with underlying CVD ( $P < 0.001$ ).

Of 148 admitted COVID-19 patients (mean age  $64 \pm 12$  years) with Tn elevation (32% requiring ventilator support), LVEF assessed by CMR imaging was normal in 89% (LVEF =  $67\% \pm 11\%$ ) at 2 months after discharge.<sup>62</sup> Late gadolinium enhancement and/or ischemia were present in 54%. Of these, 26% had myocarditis, 19% had infarction, 26% had inducible ischemia, and 6% had evidence of both infarction and ischemia.

In a study of 26 competitive college athletes [mean (SD) age, 19.5 (1.5) years; 15 male (57.7%)] with mild symptoms (sore throat, shortness of breath, myalgias and/or fever) or asymptomatic SARS-CoV-2 infection undergoing MRI imaging, 15% had features suggestive of myocarditis and an additional eight (30.8%) had late gadolinium enhancement suggesting previous myocardial injury.<sup>63</sup> Recommendations for competitive athletes with cardiovascular complications related to COVID-19 include abstinence from competitive sports or aerobic activity for 3–6 months until resolution of myocardial inflammation by cardiac MRI or troponin normalization.

In a cross-sectional study of screening in 789 professional athletes with COVID-19 infection to determine whether it was safe to return-to-play, only five (0.6%) had imaging evidence of inflammatory heart disease resulting in restriction from play.<sup>64</sup> The screening included Tn testing, ECG, and resting echo. Mean (SD) age was 25 (3) years. A total of 460 were symptomatic and 329 were asymptomatic or minimally symptomatic. Screening was done at a mean (SD) of 19 (17) days after a positive test. A total of 30 had an abnormal finding: six (0.8%) had a positive Tn  $>99\%$ , 10 (1.3%) had an abnormal ECG, and 20 (2.5%) had an abnormal echo with left ventricular (LV) dysfunction.<sup>64</sup> Of these 30 patients, 27 underwent MRI with myocarditis identified in three and pericarditis identified in two. These data suggest that in the outpatient setting in professional athletes, cardiac complications are rare.

## Myocarditis After mRNA Vaccination

In data from the Vaccine Adverse Event Reporting System (VAERS) through June 11, 2021, there were 1226 reports of probable myocarditis or pericarditis cases after approximately 300 million COVID-19 mRNA vaccine doses among 12- to 39-year-olds after the second vaccine dose of the two COVID-19 mRNA vaccines from Pfizer-BioNTech and Moderna.<sup>65</sup> Out of 484 cases among age  $\leq 29$  years reviewed by the Centers for Disease Control, 86% had chest pain occurring approximately 2–3 days after the second mRNA vaccine dose; 64% had elevated cardiac troponin levels that hit their peak at around 3 days postvaccination and 17% had abnormal cardiac imaging.<sup>66</sup> ST-segment elevations were present in ECGs in most cases. Cardiac MRI findings were abnormal in all patients undergoing MRI with findings suggestive of myocarditis such as late gadolinium enhancement and myocardial edema. Males were affected more than females with 16.9 versus 3.2 cases per million doses, respectively. Echocardiograms were abnormal in 40% of cases, with a few people having LVEF under 50%. BNP or NT-proBNP levels were only mildly elevated in two-thirds of patients.<sup>66</sup> There was no evidence of thrombotic events, thrombocytopenia, or disseminated intravascular coagulation. COVID-19 PCR tests were all negative. Treatment included nonsteroidal anti-inflammatory drugs, steroids, and colchicine. A few were treated with intravenous (IV) immunoglobulin and aspirin, and those with LV dysfunction were given beta-blocker and/or angiotensin converting enzyme inhibitor therapy. With

or without treatment, the clinical course appeared mild and almost all patients had their symptoms resolve and imaging and laboratory findings improve.<sup>66</sup> A potential mechanism for the development of myocarditis in uninfected patients getting an mRNA vaccine is that the immune system may detect the mRNA as an antigen, resulting in activation of pro-inflammatory cascades and immunological pathways, which may play a role in development of myocarditis as part of a systemic reaction in certain individuals.<sup>66</sup>

## HEART FAILURE

Heart failure has been considered as a common cardiac complication of COVID-19 and one of the major risk factors of mortality in severe cases. Either preexisting CVD disease or newly developed cardiac injury could lead to heart failure, defined by elevated NT-ProBNP and reduced LVEF.

In an early report of COVID-19 cases in the USA, 13% of patients displayed features of new-onset heart failure. In the study of Vasudev et al,<sup>67</sup> bedside echocardiography of 45 critically ill patients with COVID-19 revealed evidence of LV dysfunction, elevated pulmonary pressure, and reduced right ventricular (RV) ejection fraction in 31%, 24%, and 11% of total cases, respectively. These echocardiographic findings were instrumental in determining treatment strategies.

In a study of 54 severe and critically ill cases with COVID-19, serum levels of NT-ProBNP were elevated in 55.6% of all cases and were significantly higher in critically ill compared to severe cases.<sup>5</sup> According to the echocardiographic findings, three out of 15 (20%) critically ill patients developed new-onset heart failure of whom two patients died. In a retrospective analysis of 191 patients in Wuhan, China, 23% of patients developed heart failure with a frequency significantly higher in the nonsurvivor group compared to the survivor group (52% vs 12%;  $P < 0.0001$ ), suggesting heart failure as a risk factor predicting mortality in COVID-19.<sup>37</sup> Similarly, in another study of 21 ICU-admitted COVID-19 patients, 33.3% demonstrated evidence of cardiomyopathy.<sup>68</sup> COVID-19 patients with no previous history of systolic dysfunction had a significant decrease in LV systolic function and clinical signs of cardiogenic shock with an elevation of troponin I and creatinine kinase biomarkers and decrease of central venous oxygen saturation to  $<70\%$ .

In a prospective study enrolling 123 COVID-19 cases, impaired LVEF, RV function, and tricuspid regurgitation were associated with a higher rate of mortality.<sup>44</sup> LVEF at admission correlated with the serum level of cTnI and NT-ProBNP ( $r = -0.367$ ,  $P < 0.001$  and  $r = -0.485$ ,  $P < 0.001$ , respectively). In another study evaluating echocardiographic manifestations of 100 serial COVID-19 cases, 32% had a normal echocardiogram at baseline whereas 68% (68) had at least one abnormality: 39% had RV dilation and dysfunction; 16% had LV diastolic dysfunction; and 10% had LV systolic dysfunction.<sup>69</sup> Of those patients with either an elevated troponin (20% of patients) or a worse clinical condition, LV systolic function was similar to patients with a normal troponin or better clinical condition, but RV function was impaired. Clinical deterioration occurred in 20 patients (20%) with the most common echocardiographic abnormality being RV function deterioration (12 patients), followed by LV systolic and diastolic deterioration (five patients). Five of these patients had deep femoral vein thrombosis. These findings suggest that troponin elevations can result from isolated RV dysfunction that could result from increased pulmonary vascular resistance in the setting of COVID-19-induced hypoxemia or pneumonia or vascular lung disease.<sup>69</sup>

In a study of children with multisystem inflammatory syndrome associated with SARS-CoV-2, echocardiographic evaluation in 33 pediatric patients with COVID-19 revealed cardiomegaly in 30% and decreased LVEF ( $<50\%$  and  $<30\%$  in 65.5% and 12.5%, respectively). However, echocardiographic findings revealed complete recovery in 95% of the children by hospital days 4–7.<sup>70</sup>

Among 1,212,153 patients with a history of heart failure in the Premier Healthcare Database, 24.2% of patients hospitalized with COVID-19 between April 1, 2020 and September 30, 2020 died in hospital compared to 2.6% of those hospitalized with acute heart failure and no COVID-19 infection. Male sex (adjusted OR: 1.26; 95% CI, 1.13–1.40) and morbid obesity (adjusted OR: 1.25; 95% CI, 1.07–1.46) were associated with greater odds of in-hospital mortality, along with age (adjusted OR: 1.35; 95% CI, 1.29–1.42 per 10 years).<sup>71</sup> Nearly one in four died during hospitalization. Black and Hispanic patients were overrepresented, but race was not a predictor of in-hospital mortality or the need for mechanical ventilation. Thus, patients with a history of heart failure who develop COVID-19 face a remarkably higher risk than those with acute heart failure but no COVID infection.

In a population-based, retrospective analysis of 6439 patients admitted with a confirmed COVID-19 positive PCR test between February 27, 2020 and June 26, 2020 at Mount Sinai Health System hospitals in New York, 37 (0.6%) with no prior history of heart failure developed heart failure during their hospitalization.<sup>72</sup> Of those 37, eight (22%) had no previous CVD or risk factors while 14 had a history of previous heart disease, and 15 had no heart disease but at least one risk factor for it. The eight with no prior history had a mean age of 43, lower BMI, and fewer comorbidities but a higher rate of cardiogenic shock. Those with a history or risk factors for heart disease had a mean age of 73.

A meta-analysis confirmed the role of NT-ProBNP as an independent risk factor for mortality and a marker of poor prognosis in COVID-19 patients.<sup>43</sup> Potential mechanisms underlying ventricular wall stress, which lead to the release of NT-ProBNP, include hypoxia-induced pulmonary hypertension, medication such as vasopressors, systemic inflammatory response, and direct pathogen-induced cardiac injury.<sup>73</sup> However, further extended studies are warranted to identify the exact mechanisms and the prognostic role of heart failure to identify the optimal cardiac evaluation and to tailor treatment strategies in COVID-19 patients.

## COAGULOPATHY

Venous and arterial microthrombosis and macrothrombosis are common manifestations of COVID-19. A total of 28% of critically ill patients with COVID-19 are estimated to have venous thromboembolism (VTE), the most common complication.<sup>74,75</sup> Mechanisms include direct endothelial invasion of the virus via ACE-2 receptors,<sup>76–80</sup> complement activation,<sup>81–83</sup> platelet activation and platelet-leukocyte interactions,<sup>84–86</sup> neutrophil extracellular traps,<sup>82,87,88</sup> release of pro-inflammatory cytokines,<sup>89</sup> prolonged immobilization, disruption of normal coagulant pathways,<sup>90</sup> and hypoxia,<sup>91</sup> similar to the pathophysiology of thrombotic microangiopathy syndromes.<sup>92</sup> In a study evaluating the histopathological spectrum of cardiopulmonary complications in 14 deceased COVID-19 cases, the key finding was thromboembolic pulmonary vascular occlusion including capillary thrombi in 78.6% of cases.<sup>93</sup> Also, mid-sized pulmonary artery thrombi were reported in 35.7%, which eventually led to pulmonary infarct, hemorrhage, and superimposed bacterial infection. Neutrophil extracellular traps have recently been reported in pulmonary vessels and coronary thrombosis and proposed as a mechanism for ST elevation myocardial infarction and thrombosis in COVID-19 patients.<sup>94</sup>

Potential mechanisms for the high risk for thrombotic arterial and venous occlusion may also be due to development of antiphospholipid (aPL) antibodies. aPL syndrome is an acquired and potentially life-threatening thrombophilia in which patients develop pathogenic autoantibodies targeting phospholipids and phospholipid-binding proteins (aPL antibodies). aPL autoantibodies were present in 52% of serum samples from 172 patients hospitalized with COVID-19 using the manufacturer's threshold and in 30% using a more stringent

cutoff ( $\geq 40$  ELISA-specific units).<sup>95</sup> Higher titers of aPL antibodies were associated with neutrophil hyperactivity, including the release of neutrophil extracellular traps, higher platelet counts, more severe respiratory disease, and lower clinically estimated glomerular filtration rate.<sup>95</sup> Purified antibodies isolated from patients with COVID-19 promoted neutrophil extracellular trap release from neutrophils isolated from healthy individuals and accelerated venous thrombosis in two mouse models.<sup>95</sup> These findings suggest that half of the patients hospitalized with COVID-19 become at least transiently positive for aPL antibodies and that these autoantibodies are potentially pathogenic. Together, these findings suggest that autoantibodies should be considered as a potential therapeutic target in severe COVID-19.

In a multicenter retrospective report of 191 patients, the incidence of coagulopathy was 19% with higher rates in nonsurvivors compared to survivors (50% vs 7%, respectively,  $P < 0.0001$ ). Multivariate logistic regression analysis revealed elevated D-dimer  $> 1 \mu\text{g/ml}$  as the strongest risk factor for a higher rate of in-hospital mortality (HR: 18.42; 95% CI, 2.64–128.55,  $P = 0.0033$ ).<sup>36</sup>

Klok et al<sup>96</sup> demonstrated an incidence rate of thrombotic complications in 138 COVID-19 ICU patients to be as high as 31% of which the most frequent thrombotic event was pulmonary embolism (PE) (81%). Similarly, in the report of Inciardi et al<sup>97</sup> on 99 COVID-19 patients, after ARDS, the most common complications were venous thromboembolism and arterial thromboembolism (12% and 3%, respectively) with a higher incidence in patients with cardiac underlying comorbidities compared to those with noncardiac comorbidities (23% vs 6%, respectively). In the study of Guo et al,<sup>17</sup> acute coagulopathy was more frequent in patients with higher cTnI levels compared to normal levels (65.8% vs 20%, respectively). Bompard et al<sup>98</sup> reported an association of coagulopathy with more severe disease and poor outcomes of COVID-19. Among 137 patients, the overall cumulative incidence rate of PE was 24%, and the rate of ICU admission and mechanical ventilation were remarkably higher in positive PE patients compared to non-PE patients (38% vs 12%,  $P < 0.001$  and 31% vs 8%,  $P < 0.001$ , respectively).<sup>98</sup>

Since hypercoagulability and thromboembolism are prominent features of severe COVID-19 and ongoing anticoagulant use might be protective, a nationwide register-based cohort study of outpatients in Sweden from February to May 2020 examined dual oral anticoagulant use ( $n = 103,703$ ) and reported that it was not associated with reduced risk of hospital admission for COVID-19 [aHR: 95% CI, 1.00 (0.75–1.33) vs nonuse atrial fibrillation comparator ( $n = 36,875$ ); and aHR: 0.94 (0.80–1.10) vs nonuse CVD comparator ( $n = 355,699$ )], or ICU admission or death due to COVID-19 [aHRs: 0.76 (0.51–1.12) and 0.90 (0.71–1.15), respectively].<sup>99</sup> Therefore, ongoing dual oral anticoagulant use was not associated with reduced risk of severe COVID-19, indicating that prognosis would not be modified by early outpatient dual oral anticoagulant use initiation.

In The Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically ill Patients with COVID-19 (INSPIRATION) randomized clinical trial of 562 patients with COVID-19 admitted to the ICU, no difference was observed in venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days in those randomized to the intermediate-dose prophylactic anticoagulation group (enoxaparin 1 mg/kg daily) versus those in the standard-dose prophylactic anticoagulation group (enoxaparin, 40 mg daily), 45.7% versus 44.1%, respectively, (OR, 1.06) but intermediate dose had more bleeding complications.<sup>100,101</sup> Therefore, use of standard-dose thromboprophylaxis when using enoxaparin is recommended in critically ill ICU patients with COVID-19.

Among 2219 noncritically ill COVID-19 patients not in the ICU randomized in the ACTIV-4a, ATTACC, and REMAP-CAP trials, therapeutic-dose heparin increased organ support-free days and reduced need for ventilation at day 21 as compared with usual-care thromboprophylaxis (probability of 98.6% with adjusted OR, 1.27;

95% credible interval, 1.03–1.58).<sup>102</sup> The adjusted absolute between-group difference in survival until hospital discharge without organ support favoring therapeutic-dose anticoagulation was 4.0 percentage points (95% credible interval, 0.5–7.2). The final probability of the superiority of therapeutic-dose anticoagulation over usual-care thromboprophylaxis was 97.3% in the high D-dimer cohort, 92.9% in the low D-dimer cohort, and 97.3% in the unknown D-dimer cohort.<sup>102</sup> Major bleeding occurred in 1.9% of the patients receiving therapeutic-dose anticoagulation and in 0.9% of those receiving usual-care thromboprophylaxis. However, in critically ill COVID-19 patients in the ICU, there was no difference in organ support-free days or survival to hospital discharge between the two treatment groups, and the trial was stopped for futility. The percentage of patients who survived to hospital discharge was similar in the two groups (62.7% and 64.5%, respectively; adjusted OR, 0.84; 95% credible interval, 0.64–1.11).<sup>103</sup> Major bleeding occurred in 3.8% of the patients assigned to therapeutic-dose anticoagulation and in 2.3% of those assigned to usual-care pharmacologic thromboprophylaxis; therefore, therapeutic-dose heparin is recommended in non-ICU patients but not in ICU patients. For confirmed venous thromboembolism, therapeutic anticoagulation is recommended for  $\geq 3$  months.<sup>104</sup>

## BENEFICIAL TREATMENTS

Treatments for COVID-19 have evolved rapidly from randomized trials. In this section, we summarize the most recent developments. Most treatments used mortality or progression to needing intubation as a primary endpoint. Although the trials did not specifically address prevention of cardiovascular complications, it should be kept in mind that treatments that aim to prevent mortality or progression to needing intubation may also prevent cardiovascular complications. Therefore, it is important for the practitioner to be aware of available treatments in order to prevent adverse outcomes and presumably prevent cardiovascular complications.

### TREATMENTS WITH PROVEN BENEFIT IN OUTPATIENTS

#### Prophylaxis to Prevent COVID in Exposed Outpatients: Casirivimab With Imdevimab

Participants ( $\geq 12$  years of age) were randomly assigned within 96 hours after a household contact received a diagnosis of SARS-CoV-2 infection to receive 1200 mg of a monoclonal antibody cocktail of casirivimab with imdevimab (REGEN-COV) by subcutaneous injection or matching placebo. Symptomatic SARS-CoV-2 infection developed in 11 of 753 participants in the REGEN-COV group (1.5%) and in 59 of 752 participants in the placebo group (7.8%) [relative risk reduction (RRR) (1 minus the RR), 81.4%;  $P < 0.001$ ].<sup>105</sup> In weeks 2–4, two out of 753 participants in the REGEN-COV group (0.3%) and 27 of 752 participants in the placebo group (3.6%) had symptomatic SARS-CoV-2 infection (RRR, 92.6%).<sup>105</sup> REGEN-COV also prevented symptomatic and asymptomatic infections (RRR, 66.4%). Overall, either asymptomatic or symptomatic COVID-19 developed in 36 participants in the Regeneron group (4.8%) and in 107 participants in the placebo group (14.2%; RRR, 66.4%; OR, 0.31). Among symptomatic infected participants, the median time to resolution of symptoms was 2 weeks shorter with REGEN-COV than with placebo (1.2 weeks and 3.2 weeks, respectively), and the duration of a high viral load ( $>104$  copies per milliliter) was shorter (0.4 weeks and 1.3 weeks, respectively).<sup>105</sup> No dose-limiting toxic effects of REGEN-COV were noted. Therefore, the NIH has recommended a single subcutaneous dose of Regeneron's antibody cocktail to prevent symptomatic COVID-19, reduce the incidence of asymptomatic SARS-CoV-2 infection and reduce the duration of



symptomatic disease.<sup>106</sup> Moreover, the cocktail, REGEN-COV, has the potential to be used as a long-term prophylaxis in individuals at risk for COVID-19.

### Treatment for Covid-Positive Outpatients: Casirivimab With Imdevimab

The REGEN-COV antibody cocktail of casirivimab with imdevimab lowered rates of hospital admission and/or death by day 28 by 70% (1200 mg IV) and 71% (2400 mg IV) compared to placebo in 4567 infected outpatients.<sup>107</sup> The FDA granted emergency use authorization for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Both doses of the intervention were also associated with a shorter median time to symptom resolution (10 days vs 14 days with placebo).<sup>107</sup>

## TREATMENTS WITH PROVEN BENEFIT FOR HOSPITALIZED PATIENTS

### Casirivimab With Imdevimab

In a randomized, controlled, open-label platform trial of the RECOVERY Trial between September 18, 2020 and May 22, 2021, a total of 9785 hospitalized patients were randomly allocated to receive usual care plus REGEN-COV (casirivimab 4 g and imdevimab 4 g) by IV infusion or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients, and 1360 (14%) patients with unknown baseline antibody status.<sup>108</sup> In the seronegative patients, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0.80; 95% CI, 0.70–0.91;  $P = 0.0010$ ). In an analysis involving all randomized patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (rate ratio 0.94; 95% CI 0.86–1.03;  $P = 0.17$ ).<sup>108</sup> The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients ( $P$  value for heterogeneity = 0.001). Duration of hospital stay was shorter in seronegative patients randomized to the antibody cocktail versus usual care (4 vs 17 days, respectively), and more seronegative patients were discharged alive by day 28 (64% vs 58%). Therefore, in patients hospitalized with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab (REGEN-COV) reduced 28-day mortality among patients who were seronegative at baseline.

### Dexamethasone

As noted earlier, dexamethasone is a corticosteroid with potent anti-inflammatory effects. In the RECOVERY trial, 2104 patients were assigned to receive oral or IV dexamethasone (at a dose of 6 mg once daily) for up to 10 days and 4321 were randomized to receive usual care alone.<sup>57</sup> Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% CI, 0.75–0.93;  $P < 0.001$ ). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs 41.4%, respectively; rate ratio, 0.64; 95% CI, 0.51–0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs 26.2%, respectively; rate ratio, 0.82; 95% CI, 0.72–0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs 14.0%, respectively; rate ratio, 1.19; 95% CI, 0.92–1.55).<sup>57</sup> Therefore, dexamethasone use in those who required mechanical ventilation cut the risk of death by about 35% compared

with usual care. Overall mortality also was lower in all hospitalized patients who received the drug.<sup>57</sup> On the basis of these results, the NIH recommends dexamethasone for those who need supplemental oxygen, high-flow or noninvasive ventilation, and mechanical ventilation or extracorporeal membrane oxygenation but recommends against dexamethasone for those hospitalized but not on supplemental oxygen or receiving respiratory support.<sup>109</sup>

### Remdesivir

Remdesivir is an antiviral that prevents SARS-CoV-2 from replicating by binding to RNA-dependent RNA polymerase, a key enzyme the virus needs to propagate. The Adaptive COVID-19 Treatment Trial (ACTT-1), a randomized, double-blind, placebo-controlled trial of 541 hospitalized subjects with COVID-19 pneumonia randomized to IV remdesivir, reported that those receiving remdesivir had a median recovery time of 10 days (95% CI, 9–11) versus 15 days (95% CI, 13–18) for 521 subjects randomized to placebo (rate ratio for recovery, 1.29; 95% CI, 1.12–1.49;  $P < 0.001$ ).<sup>110</sup> The Kaplan-Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (HR, 0.73; 95% CI, 0.52–1.03). Remdesivir was approved in October 2020 for hospitalized COVID-19 patients aged 12 years and above who weigh at least 88 lbs and recently for hospitalized pediatric patients under 12 years who weigh at least 7.7 lbs.<sup>109</sup> NIH guidelines recommend the use of remdesivir in hospitalized patients who require supplemental oxygen, either on its own, or in combination with dexamethasone.<sup>109</sup> For those requiring high-flow or noninvasive ventilation, NIH recommends remdesivir only in combination with dexamethasone.

### Remdesivir and Baricitinib

Baricitinib is an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2, which was predicted with the use of artificial intelligence to be a potential therapeutic agent against SARS-CoV-2. In a randomized trial of 1033 hospitalized patients, those randomized to remdesivir and baricitinib had a median time to recovery of 7 days (95% CI, 6–8), compared to 8 days in those on remdesivir alone (rate ratio for recovery, 1.16; 95% CI, 1.01–1.32;  $P = 0.03$ ), and a 30% higher odds of improvement in clinical status at day 15 compared to those on remdesivir alone (OR, 1.3; 95% CI, 1.0–1.6).<sup>111</sup> The 28-day mortality was 5.1% in the combination group and 7.8% in the control group at 28 days (HR: 0.65; 95% CI, 0.39–1.09). Those receiving high-flow oxygen or noninvasive ventilation had a time to recovery of 10 days with the combination compared to 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10–2.08).

In the phase 3 COV-BARRIER study, a randomized, double-blind, placebo-controlled study of hospitalized patients, patients randomized to baricitinib 4 mg once daily were less likely to progress to ventilation or death (OR = 0.85; 95% CI, 0.67–1.08).<sup>112</sup> The addition of baricitinib to standard care was associated with a 39% reduced risk for death at day 28. Based on these results, the FDA has authorized emergency use of baricitinib alone for the treatment of patients aged 2 years and older who are hospitalized with COVID-19 and require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.<sup>112</sup>

### Monoclonal Antibodies

#### Tocilizumab

Tocilizumab is a monoclonal antibody directed against IL-6. In a randomized trial of 131 patients with COVID-19 pneumonia requiring oxygen support but not admitted to the ICU, fewer patients randomized to tocilizumab needed noninvasive ventilation or mechanical ventilation or died in the tocilizumab group at day 14, (12%) (95% CI, –28% to 4%) than in the usual care group

(24% vs 36%, median posterior HR 0.58; 90% credible interval, 0.33–1.00).<sup>113</sup> The HR for mechanical ventilation or death was 0.58 (90% credible interval, 0.30–1.09). At day 28, seven patients had died in the tocilizumab group and eight in the usual care group (adjusted HR, 0.92; 95% CI, 0.33–2.53). Serious adverse events occurred in 20 (32%) patients in the tocilizumab group and 29 (43%) in the usual care group ( $P = 0.21$ ).

In the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) study of patients in the ICU receiving noninvasive or invasive oxygenation, inotrope or vasopressor support, 353 patients were randomized to tocilizumab, 48 to sarilumab (IL-6 antagonist), and 402 to control.<sup>114</sup> The median number of organ support-free days was 10 (IQR, –1 to 16) in the tocilizumab group, 11 (IQR, 0–16) in the sarilumab group, and 0 (IQR, –1 to 15) in the control group. Ninety-day survival was significantly better in the pooled group of tocilizumab and sarilumab yielding a hazard ratio for the comparison with the control group of 1.61 (95% credible interval, 1.25–2.08) and a posterior probability of superiority to control of more than 99.9%. All secondary analyses supported efficacy of these IL-6 receptor antagonists.

In the RECOVERY trial, hospitalized patients were eligible for random assignment to tocilizumab versus usual care if they had hypoxia (oxygen saturation <92% on room air or requirement for supplemental oxygen), systemic inflammation (CRP  $\geq 75$  mg/L), and no clear evidence of an active infection other than SARS-CoV-2.<sup>115</sup> A total of 4116 adults were randomly assigned to tocilizumab ( $n = 2022$ ) or usual care ( $n = 2094$ ), several times more patients than in all previous randomized trials of tocilizumab combined. In both groups, 82% were receiving systemic corticosteroids at the time of random assignment, in contrast to some earlier tocilizumab trials. The primary outcome, all-cause mortality within 28 days of random assignment, occurred in 35% of patients allocated to usual care and 31% of patients allocated to tocilizumab (rate ratio 0.85; 95% CI, 0.76–0.95;  $P = 0.0028$ ). Patients in the tocilizumab group were also more likely to be discharged from the hospital within 28 days than patients in the usual care group.

The NIH has recommended using tocilizumab in combination with dexamethasone in certain hospitalized COVID patients exhibiting rapid respiratory decompensation and includes those who have been admitted to the ICU within the previous 24 hours who require invasive mechanical ventilation, noninvasive mechanical ventilation or high-flow nasal cannula oxygen, or patients outside the ICU with rapidly increasing oxygen needs who require noninvasive ventilation or high-flow oxygen and have significantly increased markers of inflammation.<sup>116</sup> NIH states that tocilizumab should be avoided for “significantly” immunocompromised patients.

A prospective meta-analysis of 27 randomized trials of IL-6 antagonists included 10,930 patients [median age, 61 years (range of medians, 52–68 years), of whom 3560 (33%) were women]. By 28 days, there were 1407 deaths among 6449 patients randomized to IL-6 antagonists and 1158 deaths among 4481 patients randomized to usual care or placebo [summary OR, 0.86 (95% CI, 0.79–0.95);  $P = 0.003$  based on a fixed-effects meta-analysis].<sup>117</sup> This corresponds to an absolute mortality risk of 22% for IL-6 antagonists compared with an assumed mortality risk of 25% for usual care or placebo. The corresponding summary ORs were 0.83 (95% CI, 0.74–0.92;  $P < 0.001$ ) for tocilizumab and 1.08 (95% CI, 0.86–1.36;  $P = 0.52$ ) for sarilumab. The summary ORs for the association with mortality compared with usual care or placebo in those receiving corticosteroids were 0.77 (95% CI, 0.68–0.87) for tocilizumab and 0.92 (95% CI, 0.61–1.38) for sarilumab. The ORs for the association with progression to invasive mechanical ventilation or death compared with usual care or placebo were 0.77 (95% CI, 0.70–0.85) for all IL-6 antagonists, 0.74 (95% CI, 0.66–0.82) for tocilizumab, and 1.00

(95% CI, 0.74–1.34) for sarilumab. Secondary infections by 28 days occurred in 21.9% of patients treated with IL-6 antagonists versus 17.6% of patients treated with usual care or placebo (OR accounting for trial sample sizes, 0.99; 95% CI, 0.85–1.16). These results provide support for the NIH’s recommendation to use tocilizumab in combination with dexamethasone in hospitalized patients requiring oxygen delivery or intubation.<sup>116</sup>

## TREATMENTS WITHOUT PROVEN BENEFIT

### Convalescent Plasma

On February 25, 2021, the DSMB halted the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients, which was being conducted at 47 hospital emergency departments across the US and had enrolled 511 subjects with mild to moderate symptoms of COVID-19, due to an interim analysis not showing benefit, although there was no harm.<sup>118</sup> In the RECOVERY trial among 11,558 patients randomized to convalescent plasma or usual care, no significant difference in 28-day mortality was observed between the convalescent plasma and usual care groups [1399 (24%) vs 1408 (24%); rate ratio 1.00, 95% CI, 0.93–1.07;  $P = 0.95$ ].<sup>119</sup> The 28-day mortality rate ratio was similar in all prespecified subgroups of patients. Allocation to convalescent plasma had no significant effect on the proportion of patients discharged from hospital within 28 days in the convalescent plasma or usual care groups [3832 (66%) vs 3822 (66%), respectively; rate ratio 0.99, 95% CI, 0.94–1.03;  $P = 0.57$ ]. Among those not on invasive mechanical ventilation at randomization, there was no significant difference in the proportion progressing to invasive mechanical ventilation or death [1568 (29%) of 5493 patients in the convalescent plasma group vs 1568 (29%) of 5448 patients in the usual care group; rate ratio 0.99, 95% CI, 0.93–1.05;  $P = 0.79$ ].<sup>119</sup> Therefore, high-titer convalescent plasma has not improved survival or other prespecified clinical outcomes in two randomized trials.

Other treatments without benefit in randomized, controlled trials include vitamin D, Ivermectin, and hydroxychloroquine.<sup>47,120,121</sup>

The ACC has provided a link for clinical guidance for the global cardiovascular care of COVID-19 patients: <https://www.acc.org/latest-in-cardiology/features/accs-coronavirus-disease-2019-covid-19-hub#sort=%40commonsorddate%20descending>

## CONCLUSIONS

In this systematic review, we provided the most recent evidence regarding the high incidence of new-onset cardiac complications following SARS-CoV-2 and its association with increased mortality. There are several mechanisms involved in developing cardiac injury including inflammation and cytokine storm, hypoxemia and direct viral invasion. We also highlighted the significance of troponin level as a fundamental consideration in evaluating the prognosis of COVID-19. Finally, we review randomized trials supporting treatments for COVID-19. This review draws attention to the importance of understanding the effect of COVID-19 on the cardiovascular system to provide optimal medical care and appropriate triage in an effort to improve patients’ outcomes, which can be severely affected by cardiac complications.

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