COVID-19 and the Incidence of Acute Myocardial Injury

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Abstract

Cardiovascular manifestations are frequent in COVID-19 infection and are predictive of adverse outcomes. Elevated cardiac biomarkers are common findings in patients with cardiovascular comorbidities and severe COVID-19 infection. Troponin, inflammatory and thrombotic markers may also improve risk prediction in COVID-19. In our comprehensive review, we provide an overview of the incidence, potential mechanisms and outcome of acute cardiac injury in COVID-19. Thereby, we discuss coagulation abnormalities in sepsis and altered immune response as contributing factors favoring myocardial injury. We further highlight the role of endothelial damage in the pathophysiological concepts. Finally, observational studies addressing the incidence of myocardial infarction during COVID-19 pandemic are discussed.

Keywords

- COVID-19
- myocardial infarction
- cardiac injury
- troponin

Introduction

The current global pandemic of the coronavirus disease 2019 (COVID-19) presents a severe burden to healthcare services and economy. Up to this point, there are more than 231 million confirmed cases worldwide. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects predominantly the respiratory tract; however, extrapulmonary manifestations and multiple-organ involvement are also common.[1] Among individuals, clinical presentation varies from asymptomatic subclinical infection, mild afebrile respiratory symptoms to pneumonia, and acute respiratory distress syndrome (ARDS). Cardiac biomarkers, including troponin and brain-natriuretic peptide, which reflect myocardial injury and dysfunction are commonly elevated in patients hospitalized with COVID-19.[2,3] Recent studies by Majure et al. and Lombardi et al. showed that elevated troponin levels in COVID 19 patients are associated with increased mortality rates.[4,5] Furthermore, there is increasing evidence that preexisting cardiovascular metabolic diseases may affect the prognosis.[6] Known cardiovascular diseases such as hypertension, coronary heart disease, and congestive heart failure result in higher probability of infection with SARS-CoV-2 and a more severe course of COVID-19. In this review, we will focus on the incidence and pathophysiologic mechanism of cardiac injury and their implications for prognosis in COVID-19 patients.

Methods

The PubMed database was searched by the authors for literature published between February 2020 and April 2021 using the following search terms: “COVID-19” and “incidence myocardial infarction” or “cardiac injury.” The title and abstract contents of the identified articles were reviewed and assessed for eligibility. Cross-references from relevant studies were added. The search was restricted to studies in English language.

Results

Our search yielded 1,499 results. After removing review articles, opinion letters, animal studies, duplications, and articles not relevant to cardiology, 212 studies were identified for full-text analysis. Of these, 20 studies were selected in our review for further analysis and their study characteristics are listed in ►Table 1. Each study defined cardiac injury as elevation of serum troponin level above the 99th percentile upper reference limit according to the Fourth Universal Definition of Myocardial Infarction.[7] For the definition of

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Table 1 Summary of studies reporting cardiac biomarkers and acute myocardial injury or acute myocardial infarction in hospitalized patients with confirmed SARS-CoV-2 infection

Study	Type of study	Number of patients, age, gender, location	Study period	Cardiovascular comorbidities	Criteria for acute myocardial infarction/injury and prevalence
Cao et al.[50]	Retrospective observational study, single-center	Total population: 244 patients Age, mean: 62.6 y 111 females (45.5%) Wuhan, China	Feb 6 to Feb 21, 2020	HTN: 30.7% DM: 14.8%	hs cTnI > 40 ng/L, 18%
Cecconi et al.[52]	Retrospective cohort study, single center	Total population: 206 patients Age, mean: 63.9 y 70 females (29.3%) Milan, Italy	22 Feb to Mar 22, 2020	HTN: 50.2% DM: 21.8% CAD: 16.7%	hs cTnI > 19.8 ng/L, 27.7%
Chen et al.[2]	Retrospective case series, single center	Total population: 274 patients Age, mean: 62 y 103 females (38%) Wuhan, China	Jan 13 to Feb 12, 2020	HTN: 34% DM: 17% CAD: 8%	hs cTnI > 15.6 pg/mL, 41%
Cummings et al.[53]	Prospective cohort study, multicenter	Total population: 1,150 patients, 257 were critically ill Age, mean: 62 y 86 females (33%) New York, the United States	Mar 2 to Apr 1, 2020	HTN: 63% DM: 36% Chronic cardiac disease: 19%	hs cTnT median = 19 (IQR: 9–52) ng/L
Guo et al.[54]	Retrospective case series, single center	Total population: 187 patients Age, mean: 58.5 y 96 females (51.3%) Wuhan, China	Jan 23 to Feb 23, 2020	HTN: 32.6% DM: 15% CAD: 11.2%	hs cTnT > 99th percentile, 27.8%
Huang et al.[55]	Prospective cohort study, single center	Total population: 41 patients Age, mean: 49 y 11 females (27%) Wuhan, China	Dec 16, 2019, to Jan 2, 2020	HTN: 15% DM: 20% CAD: 15%	hs cTnI > 28 pg/mL, new changes in ECG/echo, 12%
Karbalai Saleh et al.[12]	Retrospective cohort study, single center	Total population: 386 patients Age, mean: 59.5 y 150 females (38.9%) Tehran, Iran	Mar to May 2020	HTN: 36.8% DM: 34.5% CAD: 6.4%	hs cTnI > 99th percentile, men: > 26 ng/mL, women: > 11 ng/mL, 29,8%

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Table 1 (*Continued*)

Study	Type of study	Number of patients, age, gender, location	Study period	Cardiovascular comorbidities	Criteria for acute myocardial infarction/injury and prevalence
Lala et al.[56]	Retrospective cohort study, multicenter	Total population: 2,736 patients Age, mean: 66.4 y 1,106 females (40.4%) New York, United States	Feb 27 to Apr 12, 2020	HTN: 38.9% DM: 26.3% CAD: 16.6%	hs cTnT > 0.03 ng/mL, 36.0%
Lombardi et al.[5]	Retrospective observational study, multicenter	Total population: 614 patients Age, mean: 67 y 179 females (29.2%) Italy	Mar 1 to Apr 9, 2020	HTN: 57.5% DM: 24.3% CAD: 22.5%	hs cTnI/cTnT > 99th percentile, 45.3%
Lopes et al.[8]	Randomized clinical trial	Total population: 659 patients Age, mean: 55.1 y 266 females (40.4%) Brazil	Apr 9 to Jul 26, 2020	HTN: 100% DM: 32% CAD: 4.6%	Elevated troponin/CK-MB and new ECG/echo changes, 6.1%
Majure et al.[4]	Retrospective observational study, multicenter	Total population: 6,247 patients Age, mean: 66 y 2,507 females (40%) New York, United States	Mar 1 to Apr 27, 2020	HTN: 60% DM: 36% CAD: 13%	hs cTnI > 0.045 ng/mL, hs cTNT > 19 ng/L, ECG, 29.1%
Metkus et al.[14]	Retrospective cohort study, multicenter	Total population: 243 patients Age, mean: 62.8 y 95 females (39.1%) United States	Mar 15 to Jun 11, 2020	HTN: 61% DM: 19%	hs cTnI > 26 ng/L, 51.0%
Ni et al.[57]	Retrospective cohort study, single center	Total population: 176 patients Age, mean: 67 y 75 females (42.6%) Wuhan, China	Jan 28 and Mar 16, 2020	HTN: 49.4% DM: 26.7% CAD: 14.2%	hs cTnI > 99th percentile, 27.8%
Qin et al.[11]	Retrospective cohort study, multicenter	Total population: 3,219 patients Age, mean: 57 y 1,684 females (52.3%) Hubei Province, China	Dec 31 to Mar 4, 2020	HTN: 27.8% DM: 12.8% CAD: 6.4%	hs cTnI or CK-MB > 99th percentile, >26.2 ng/dL or >25 U/L, 6.5 and 5.1%

Table 1 (*Continued*)

Study	Type of study	Number of patients, age, gender, location	Study period	Cardiovascular comorbidities	Criteria for acute myocardial infarction/injury and prevalence
Shi et al.[10]	Retrospective cohort study, single center	Total population: 671 patients Age, mean: 63 y 349 females (52%) Wuhan, China	Mar to May 2020	HTN: 29.7% DM: 14.5% CAD: 25.1%	hs cTnI > 0.04 ng/mL, 15.8%
Si et al.[58]	Retrospective cohort study, single center	Total population: 170 patients Age, mean: 63 y 77 females (45.3%) Wuhan, China	Jan 29 to Mar 8, 2020	HTN: 55.9% DM: 21.8% CAD: 17.6%	hs cTnI > 26.2 pg/mL, 14.7%
Wang et al.[59]	Retrospective cohort study, single center	Total population: 222 patients Age, mean: 63 y 109 females (49.1%) Wuhan, China	Feb 10 to Mar 28, 2020	HTN: 23% DM: 13.5% CAD: 6.7%	hs cTnI > 34.2 pg/mL, 15.8%
Wei et al.[3]	Prospective cohort study, multicenter	Total population: 101 patients Age, mean: 49 y 47 females (46.5%) Wuhan, China	Jan 16 to Mar 10, 2020	HTN: 21% DM: 13.9% CAD: 5%	hs cTnT > 14 pg/mL, 15.8%
Yang et al.[60]	Retrospective observational study, single center	Total population: 52 patients Age, mean: 59.7 y 17 females (33%) Wuhan, China	Late Dec 2019 to Jan 26, 2020	DM: 17% CCD: 10%	hs cTnI > 28 pg/mL, 23.0%
Zhou et al.[9]	Retrospective cohort study, multicenter	Total population: 191 patients Age, mean: 56 y 72 females (38%) Wuhan, China	Dec 29 to Jan 31, 2020	HTN: 30% DM: 19% CAD: 8%	hs cTnI > 28 pg/mL, new changes in ECG/echo, 17%

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; hs cTnI, high-sensitivity cardiac troponin I; hs cTnT, high-sensitivity cardiac troponin T; HTN, hypertension.

acute myocardial infarction, Lopes et al. required, in addition to elevation of cardiac biomarkers, consistent clinical presentation as well as electrocardiographic or imaging test evidence.[8] Specific cutoff criteria for cardiac biomarkers are also listed in ►Table 1.

In 19 studies including a total of 14,745 patients, the pooled overall prevalence of acute myocardial injury among hospitalized COVID-19 patients was 26.8% (3,947 patients). According to Lombardi et al., predictors of cardiac injury are age and comorbidities such as hypertension, heart failure, and coronary artery disease.[5] The prevalence of acute myocardial injury ranged from 6.5 to 51% in the selected studies. Univariable analysis by Zhou et al. revealed a significant association between high-sensitivity cardiac troponin I and intrahospital mortality. Additional noteworthy findings in this study were the clearly elevated levels of coagulopathy or systemic inflammation-associated markers, such as D-dimer, interleukin (IL)-6, and procalcitonin, in nonsurvivors.[9] Furthermore, a multivariable analysis of 671 patients by Shi et al. confirmed an independent association of myocardial injury with an increased risk for mortality in patients with COVID-19.[10] In another retrospective cohort study, both high-sensitivity cardiac troponin I (hazards ratio: 7.12, $p < 0.001$) and CK-MB (hazards ratio: 4.86, $p < 0.001$) were found independently associated with increased 28-day all-cause mortality.[11]

►Fig. 1 illustrates the significantly increased risk of death in patients with elevated cardiac injury markers and COVID-19 in selected studies. Karbalai Saleh et al. reported that in patients with cardiac injury, elevated troponin coincided with higher levels of inflammatory makers like white blood cell count or C-reactive protein levels when compared with COVID-19 patients without cardiac injury.[12] Li et al. found a close correlation of immune dysregulation and myocardial injury in 182 COVID-19 patients.[13] White blood cell count, neutrophil percentage, CD3+ T cell counts, CD4+ T cell counts, CD8+ T cell counts, NK cell counts, and procalcitonin were independently associated with myocardial injury and showed a predictive ability in the multivariate logistic regression when compared with cases without myocardial injury.

Discussion

Myocardial injury is prevalent in COVID-19-positive patients and is predictive of adverse outcomes.[3] Metkus et al. reported a greater than twofold risk of mortality in critical ill patients with myocardial injury.[14] Previous reports also identified higher levels of the myocardial distress markers such as troponin I or N-terminal pro-B-type natriuretic peptide (NT-proBNP) to be highly predictive for respiratory failure.[8] By using nationwide registers in Denmark, Modin et al. provided evidence that COVID-19 may be associated with an increased risk of ischemic cardiovascular events.[15] The incidence of acute myocardial infarction 14 days after a positive test for COVID-19 was approximately five times higher when compared with the 180 days prior to the COVID-19 diagnosis.

The exact pathophysiology of myocardial injury induced by SARS-CoV-2 is not clearly understood, but seems to be associated with severe inflammatory response, coronary microvascular ischemia, direct injury of the cardiomyocytes, and cytokine-mediated plaque destabilization.[16,17] Furthermore, hypoxemia caused by respiratory failure and hemodynamic instability may favor particularly type 2 myocardial infarction caused by a mismatch of oxygen supply and demand. To meet the universal definition of myocardial infarction type 2, evidence of ischemic myocardial infarction, clinical presentation, and ECG and imaging are mandatory. Nonischemic myocardial injury may be more common in

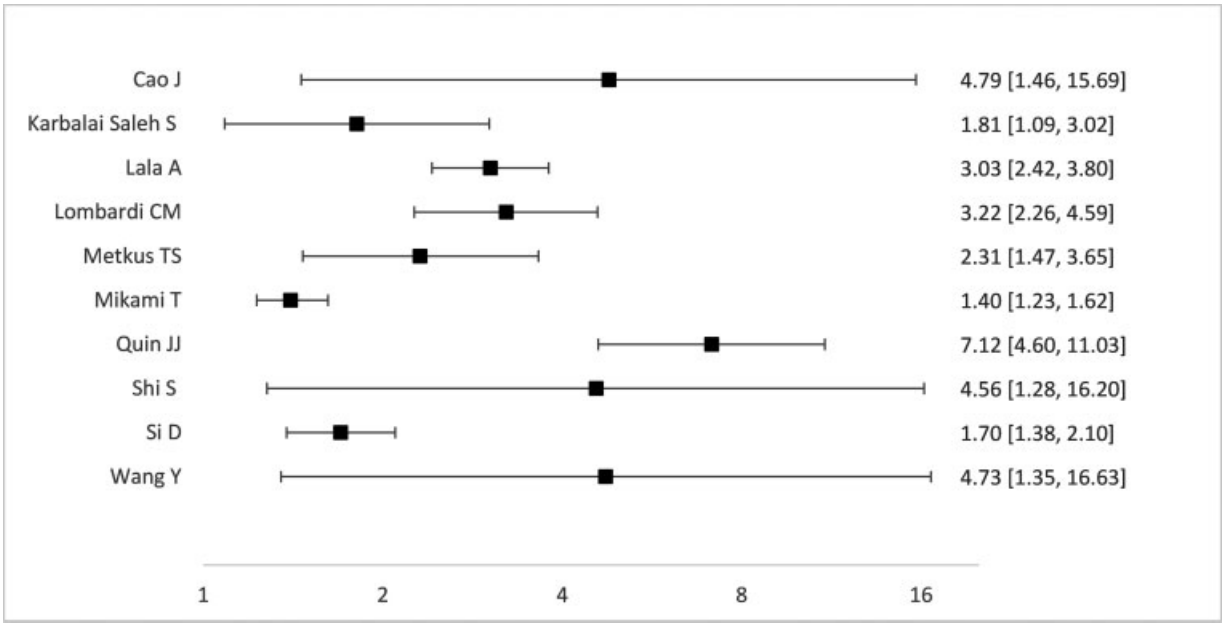

Fig. 1 Forest plot of risk of mortality for patients with cardiac injury and COVID-19.

COVID-19. In addition to cardiac causes of nonischemic myocardial injury such as myocarditis or stress cardiomyopathy, the focus in COVID-19 may be primarily on noncardiac entities such as critical illness, severe sepsis, or pulmonary hypertension due to acute pulmonary embolism. Increased levels of troponin I and NT pro-BNP are indicative for acute myocardial stress related to the elevation of the pulmonary artery pressure and right ventricular dysfunction in patients with severe COVID-19 presentations.[18]

Elevations in cardiac troponin are also present in septic patients and correlate with the occurrence of impaired left ventricular function.[19,20] Potential mechanisms are summarized in ►Fig. 2.

Potential Mechanisms of COVID-19-Associated Myocardial Injury

Numerous potential pathophysiological mechanisms of troponin elevation in COVID-19 patients are conceivable. Severe systemic inflammation and hypercoagulopathy are key factors in the pathophysiology of SARS-CoV-2 infection and thus another trigger of cardiovascular events. Additionally, abnormal endothelial function may increase the risk of atherosclerotic plaque disruption and myocardial infarction.[21] In detail, high levels of proinflammatory cytokines, such as IL-6, IL-1, or tumor necrosis factor-α (TNF-α), induce macrophage infiltration in the vascular wall and alter the thrombotic/fibrinolytic balance that promote the tendency for clotting. IL-1 and TNF-α also suppress intrinsic anticoagulant pathways.[22]

A cytokine storm profile can be found in some critical ill adults, characterized by severe systemic elevation of proinflammatory cytokines and chemokines.[23] The cytokine storm originates from activated TH1 cells, followed by macrophages and neutrophils infiltration, which are activated by SARS-CoV-2 after entering the respiratory epithelium. Hirano and Murakami et al. found the angiotensin 2 pathway as a potential mechanism for the uncontrolled inflammatory response and the cytokine storm.[24] These proinflammatory mediators and cytokines also affect the endothelium and vascular homeostasis.

Tissue factor, expressed by stimulated endothelial cells, activates the coagulation system by the initiation of thrombin formation via activation of factor VII and X.[21] The endothelial cells further release von Willebrand factor causing platelet aggregation. Together with a reduced release of prostacyclin and an increased production of plasminogen activator inhibitor-1 (PAI-1), blood clotting and thrombus accumulation are promoted.[21] The thrombogenicity and hemostatic imbalance related to SARS-CoV-2 infection are associated with a higher prevalence of thromboembolic cardiovascular complications.[25–27] Particularly, altered platelet function and vascular inflammation contribute to thrombotic complications. Zaid et al. provided evidence that hyperactivated platelets in COVID-19 patients favor a procoagulatory state due to inflammatory mediator release.[28] Interaction of platelet receptor GPIIb/IIIa with corresponding neutrophil receptors induces the release of neutrophil extracellular traps (NETs). NETs are found in microvascular thrombi and play a role in vessel occlusion and tissue damage in COVID-19.[29,30] Increased production of prothrombotic platelet-activating antibodies in response to SARS-CoV-2 was described by Althaus et al. in severe COVID-19 infection.[31]

Another potential mechanism is the direct myocardial damage by SARS-CoV-2, since it uses the human angiotensin-converting enzyme 2 (ACE-2) receptor for cellular entry mediated by its surface spike proteins. Taking etymological

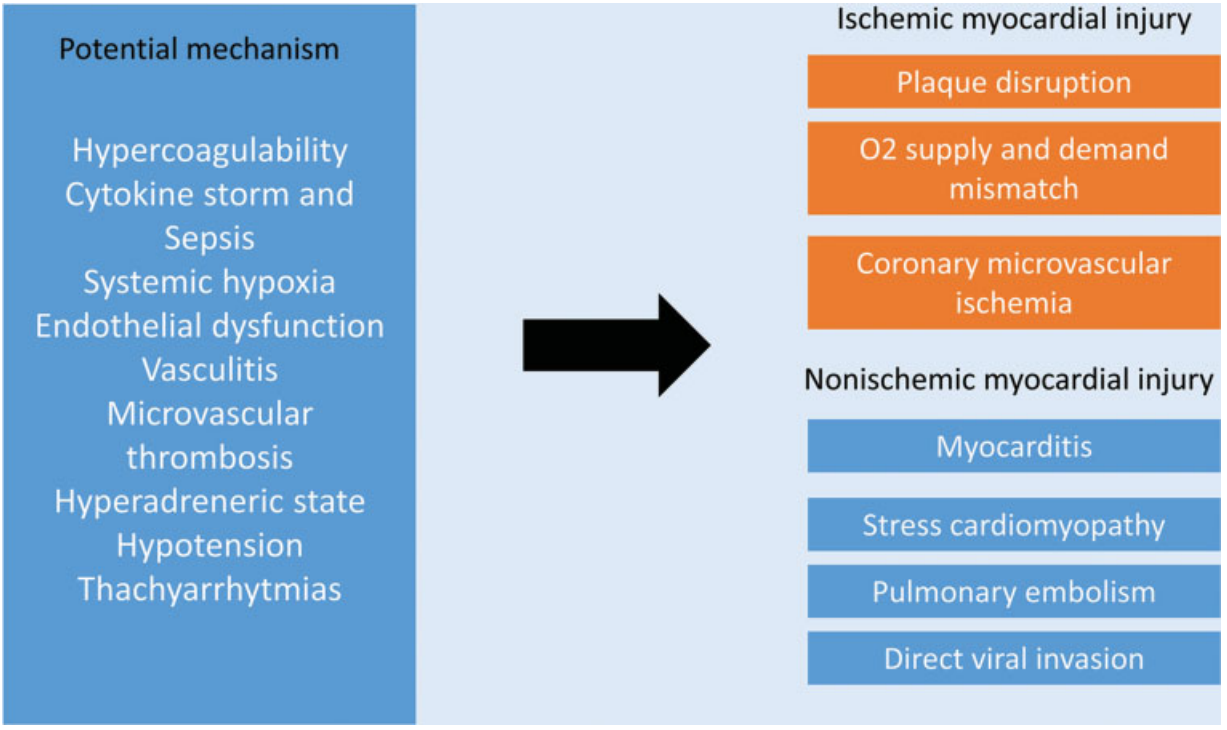

Fig. 2 Potential mechanisms of increased cardiac troponin levels above the 99th percentile upper reference limit (URL) in COVID-19.

aspects into account, corona in Latin means “garland” or “crown” referring to the presence of its spike-like capsid under the electron microscope.[32] ACE-2, a metallopeptidase, plays a crucial role in cardiovascular homeostasis and is expressed on the surface of multiple tissues like the respiratory epithelial in the lung, in cardiomyocytes and pericytes of human hearts, the kidney, the brain, and especially in vascular endothelial cells.[33,34] The cardioprotective effects of ACE-2 were first described by Crackower et al., as they observed a severe left ventricular dysfunction in ACE-2 knockout mice.[35] The loss of ACE-2 also raised the expression levels of hypoxia-regulated genes, indicating a myocardial stunning due to chronic hypoxia similar to coronary artery disease. SARS-CoV-2 appears to downregulate the ACE-2 by fusing with the membrane receptor on the entry and removing it from the surface.[36] Thus, downregulation of ACE-2 by SARS-CoV-2 may be linked with cardiac dysfunction and heart failure. In addition, ACE inhibitors appear to increase cardiac ACE-2 gene expression and could theoretically contribute to an increased vulnerability to infection.[37] However, large cohort studies by Li et al. and Mancia et al. could not confirm an association between the use of ACE inhibitors or angiotensin-receptor blockers with the risk of infection and the severity of COVID-19.[38,39] In animal models, ACE-2-dependent myocardial infection occurred after pulmonary infection with other coronaviruses, raising the possibility of direct damage of myocardium and vascular endothelium by the virus.[16] During the Toronto SARS outbreak, Oudit et al. detected viral RNA in 35% of autopsied heart samples. Immunohistochemical analysis further revealed increased myocardial macrophage infiltration in SARS-positive hearts. In contrast, autopsy studies found cardiac cell necrosis, but lymphocytic myocarditis could not be detected in postmortem heart samples of COVID-19 patients.[40] However, magnetic resonance imaging (MRI) reports confirmed diffuse subepicardial contrast enhancement associated with myocardial edema in many patients with COVID-19.[41] The cardiac MRI is an additional noninvasive diagnostic tool for the detection of possible cardiac involvement and may be useful for risk stratification and prognostication. In patients who have recovered from COVID-19, especially myocardial edema and fibrosis were found.[42] This remodeling process may lead to reduced contractility in the long term.

Despite these interactions, there are also noncardiac causes of myocardial injury including pulmonary embolism and underlying critical illness, sepsis, and multisystem organ dysfunction, which could be responsible for the majority of cardiac damage.

During the COVID-19 pandemic, several studies reported a decrease in the incidence of hospitalization for acute myocardial infarction worldwide.[43–49] Among patients with non-ST segment elevation myocardial infarction (NSTEMI) and STEMI, Solomon et al. noticed a decline by up to 48% in the weekly rates in March and April 2020 in northern California compared with the same week in 2019.[43] In an Italian nationwide observational survey, De Rosa et al. found a reduction of 48.4% in hospital admissions for AMI throughout March 12 to 19, 2020, when compared with the same period in 2019, respectively, for non-STEMI of 65.1% reduction and for STEMI of 26.5%.[46] Another retrospective analysis of 15 hospitals in northern Italy by De Filippo et al. observed a significant reduction in hospital admissions for ACS per day during COVID-19 pandemic compared with 2019 (18.9 vs. 13.3 daily admissions, $p < 0.001$).[44] The ongoing French Cohort of Myocardial Infarction Evaluation (FRENCHIE) registry, in which 21 centers participated, was recently analyzed by Mesnier et al. According to their findings, admissions for acute myocardial infarction decreased by 30% from 686 to 481 between 4 weeks prior to and 4 weeks after the lockdown.[48] The reduction was significant for both, STEMI (24%, incidence rate ratio: 0.72 [95% CI: 0.62–0.85]) and non-STEMI (35%; 0.64 [0.55–0.76]). In Germany, the incidence and fatality rates from COVID-19 were low in March to June 2020 and a total of 207 admissions for myocardial infarction were registered in Berlin during the weeks 11 to 14, with a 19.5% reduction (95% CI: 3.0–33.0) compared with the corresponding period in 2019 ($p = 0.021$).[49] The reduction of hospitalizations for STEMI was 9 and 28% for non-STEMI. Based on similar results in the reduction of AMI admissions in several countries, the severity of the COVID-19 pandemic can at best have a minor impact. The reasons behind the overall decrease are various and system- and patient-related factors may be partially responsible. One of the main reasons could be the fear of potential infection with the SARS-CoV-2 at the hospital. Also, the government advised the population to stay at home and minimize contact with others to a minimum. A considerable number of patients may stay in self-isolation and not attend healthcare services unless in a life-threatening emergency. Additionally, changes in physical activity may be associated with angina pectoris burden during quarantine periods. Recently, a single-center observational study by Fardman et al. indicated a post-COVID-19 rebound effect.[51] In this study, a noticeable increase in hospitalizations for acute myocardial infarction after the first wave of the COVID-19 pandemic in April and May 2020 was observed.

Conclusion

Cardiac complications are common in COVID-19 and associated with adverse prognosis. Systemic inflammation and prothrombotic activity are related to myocardial injury, particularly acute myocardial infarction type 2 and non-ischemic myocardial infarction. Due to its prognostic value, troponin should be assessed at the time of hospital admission in COVID-19 patients for risk stratification.

Conflict of Interests

The authors declare that they have no conflict of interest.

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