Cardiovascular complications of COVID-19

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A B S T R A C T

Cardiac injury associated with coronavirus disease 2019 (COVID-19) is associated with high fatality rates. We reviewed the literature on COVID-19-related cardiovascular complications to elucidate the putative causes, diagnosis, and management of cardiovascular complications of COVID-19. Putative causes of these cardiovascular complications include cytokine storm, myocarditis, coronary plaque rupture, hypercoagulability, stress cardiomyopathy or combinations thereof. Cardiac troponin, D-dimer, and N-terminal pro B-type natriuretic peptide levels all provide prognostic information on COVID-19-related cardiovascular complications: elevated levels correlate with poorer prognosis. Coronary thrombosis due to COVID-19 may be associated with a higher thrombus burden than that from other causes. Hypercoagulability can be extremely challenging to treat, and in the absence of contra-indications, thromboprophylaxis is generally indicated in intensive care unit patients. With the exception of percutaneous coronary intervention for acute myocardial infarction, there are no specific treatments for COVID-19-related cardiovascular complications and management is primarily supportive. Whether antiviral therapies, coupled with monoclonal antibodies administered early in the course of COVID-19 illness will prevent severe cardiovascular complications remains to be seen.

Hong Kong Med J 2022;28:249–56
https://doi.org/10.12809/hkmj209217

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This article was published on 31 May 2022 at www.hkmj.org.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a contagious respiratory illness which can cause serious complications including stroke, kidney failure, and cardiovascular complications.[1] Cardiovascular complications are a major risk factor for COVID-19 mortality.[2-4] The aim of this paper was to review the literature, published by December 2020, in order to elucidate the risk factors, putative causes, diagnosis, and management of cardiovascular complications of COVID-19.

Incidence, risk factors and mortality in patients with COVID-19

Incidence

Two early studies on COVID-19 reported that 20% to 28% of patients with COVID-19 had cardiac injury associated with cardiac dysfunction and arrhythmias.[2,3] In a cohort of 416 patients hospitalised with confirmed COVID-19, cardiac injury was reported to occur in 19.7%, and was associated with an unexpectedly high risk of mortality during hospitalisation. Symptoms of COVID-19 were more severe when accompanied by cardiac injury; the mortality rate was higher among patients with cardiac injury than among those without (51.2% vs 4.5%).[2]

Risk factors: age, sex, and co-morbidities

Independently, in another cohort of 187 patients, those with cardiac injury were more likely to be male, older and to have more co-morbidities including diabetes, hypertension, coronary artery disease, chronic kidney disease, chronic lung disease, etc. Severe COVID-19 infections were also potentially associated with cardiac arrhythmias and the need for mechanical ventilation. The mortality during hospitalisation was 7.62% for patients without underlying cardiovascular disease and normal cardiac troponin (c-TN) levels, but as high as 69.44% for those with underlying cardiovascular disease and elevated c-TN.[3]

In another report of 72 314 cases (44 672 confirmed) of COVID-19, the crude mortality rate was 2.3%.[4] For octogenarians, the case fatality rate was 14.8%. A history of coronary artery disease was present in 4.2% of all cases, but in 22.7% of fatal cases. Case fatality rates were 10.5% for coronary artery disease, 7.3% for diabetes, and 6% for hypertension. Risk of COVID-19 death is highest among the oldest and lowest among the youngest populations. Compared with those aged 18 to 29 years, people aged 75 to 84 years and those

2019冠狀病毒病的心血管併發症

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2019冠狀病毒病（COVID-19）可導致心臟損傷與高死亡率。我們審查了相關COVID-19心血管併發症的文獻，以闡明該病引起心血管併發症的推定原因、危險因素，診斷和治療。這些心血管併發症的推定原因包括細胞因子風暴、心肌炎、冠狀動脈斑塊撕裂、高凝狀態、應激性心肌病或以上組合。心肌肌鈣蛋白、D-二聚體和N末端B型利鈉肽前體水平均能夠提供COVID-19相關心血管併發症的臨床預後信息：個別或組合水平升高與較差的預後存在關聯。與普通病例相比，COVID-19引起的心肌梗塞與較高血栓負擔相關。治療COVID-19引起的高凝狀態通常極具挑戰性，在沒有禁忌症的情況下，需要深切治療的患者都應接受預防性抗凝治療。急性心梗患者的治理，除了經皮冠狀動脈介入術，主要是提供常規支持性的心梗治療，而沒有其他特定針對COVID-19相關心血管併發症的措施。在COVID-19病發後盡早處方抗病毒藥物或單克隆抗體能否預防嚴重心血管併發症則未有定案。

aged ≥85 years have 200-times and 630-times, respectively, higher average death rates.[5]

In a retrospective study of 393 patients, the prevalence of obesity and male sex also appears to be higher in patients with COVID-19 who developed severe symptoms compared with those who did not.[6]

Putative causes of cardiovascular complications in patients with COVID-19

Cardiovascular complications of COVID-19 are generally associated with poor prognosis. Therefore, prevention and treatment of COVID-19 should be considered a priority. To that end, an understanding of the possible pathogenetic mechanisms resulting in myocardial injury would be helpful. Putative causes of cardiovascular complications in patients with COVID-19 include: cytokine storm, myocarditis, extreme physical and emotional stress, ischaemic injury caused by cardiac microangiopathy or macrovascular coronary artery disease, hypercoagulopathy, right heart strain, and cor pulmonale associated with adult respiratory distress syndrome.

Cytokine storm

In addition to direct viral damage, uncontrolled inflammation or 'cytokine storm'—indicated by high levels of inflammatory markers including C-reactive protein (CRP), ferritin, and D-dimer, and increased levels of inflammatory cytokines and chemokines—has been reported in patients with COVID-19.[7,8] However, the exact pathogenetic relevance of cytokine storm has yet to be confirmed.[9]

Myocarditis

Myocardial inflammation (myocarditis) is evidenced by elevated c-TN level in some patients[10] and autopsy data show mononuclear infiltrate in the myocardium, with related cardiomyocyte necrosis.[11] Although there have been case reports of myocarditis in patients with COVID-19, it is unclear whether myocarditis is caused by direct viral invasion or an uncontrolled inflammatory response.[10,12]

In a cohort study of 39 autopsy cases of COVID-19, cardiac infection with COVID-19 was frequently found; however, overt myocarditis was not observed in the acute phase.[13] In contrast, another study reported on the detection of SARS-CoV-2 genomes in endomyocardial biopsies.[14]

A cardiac magnetic resonance (MR) imaging study of 100 patients recently recovered from COVID-19 reported cardiac involvement in 78% of them, with evidence of ongoing myocardial inflammation in 60% of them. Such involvement appeared independent of pre-existing conditions, severity, overall course of the acute illness, and the time from diagnosis.[13] Of 26 competitive athletes, four (15.4%) had cardiac MR findings suggestive of myocarditis and eight additional athletes (30.8%) exhibited late gadolinium enhancement without T2 elevation suggestive of prior myocardial injury.[15]

In a study of 145 student athletes with COVID-19 who were either asymptomatic or had mild to moderate symptoms during acute infection, cardiac MR findings (at a median of 15 days after a positive test result for COVID-19) were consistent with myocarditis in only two patients (1.4%), based on updated Lake Louise criteria.[16]

In contrast, preliminary data based on a small autopsy study of 40 patients showed that cardiac injury results more from clotting than from inflammation; microthrombi were frequent, whereas none of the patients had myocarditis.[17] While this observation has implications for thromboprophylaxis, whether COVID-19 can cause a viral myocarditis is yet to be confirmed.

Physical and emotional stress

Cases of typical stress cardiomyopathy have also been reported,[18] suggesting that both physical and emotional stress may be in part contributory to some cases of cardiovascular complications of COVID-19.

Ischaemic injury

In some patients, ST-segment elevation myocardial infarction (STEMI) may be the first clinical manifestation of COVID-19.[19] However, patients with c-TN elevations may not have epicardial coronary artery obstruction at angiography. In a case series of 18 patients with COVID-19 with STEMI, nine patients underwent coronary angiography; six

of them (67%) had obstructive disease. A total of 13 patients died in the hospital (4 due to fatal myocardial infarction and 9 due to noncoronary myocardial injury).[20] In contrast, patients with COVID-19 with STEMI had more thrombus burden and required more anticoagulation than patients with no COVID-19 infection.[21] Very-late stent thrombosis has also been reported with patients with COVID-19 and can be one of the presenting features of COVID-19 in those with a history of coronary stenting.[22]

Hypercoagulopathy

Coronavirus disease 2019 is associated with a hypercoagulable state.[23] Although the pathogenesis is not completely understood, the following may be observed: elevated fibrinogen and D-dimer; prolongation of both the prothrombin time and activated partial thromboplastin time; and mild thrombocytosis or thrombocytopenia. Major adverse cardiovascular events, and symptomatic thromboembolism, occur frequently in patients with COVID-19, especially among those in the intensive care unit (ICU), even after thromboprophylaxis.[24]

Stroke

Unchecked vascular thrombosis may result in neurological complications. In a case series of 214 patients with COVID-19, neurological symptoms were seen in 36.4% of patients and were more common in patients with severe infection.[25] A retrospective study of 214 patients reported six patients with acute stroke, of which five were ischaemic stroke.[26] Stroke has also been reported in younger patients (aged 33-49 years) with COVID-19.[27]

Thromboembolism

Post-mortem studies of 12 patients have reported pulmonary embolism as the direct cause of death in four patients (33%) and deep venous thrombosis in seven patients (58%).[28] The risk for venous thromboembolism is markedly elevated with prevalence up to 32%,[24,29,30] highest with patients in the ICU.[30] In a large study involving 3334 consecutive hospitalised patients with COVID-19, among 829 patients in the ICU, 29.4% had a thrombotic event (13.6% venous and 18.6% arterial).[30] Although low-dose anticoagulation has been used for thromboprophylaxis, in a series of 184 critically ill patients with COVID-19, 31% suffered clinically significant thrombotic complications despite low-dose nadroparin.[31]

Thrombocytopenia

A meta-analysis demonstrated thrombocytopenia in patients with severe disease is associated with increased risk of COVID-19 mortality.[32] How thrombocytopenia should be factored into the decision to prescribe anticoagulant therapy has yet to be studied.

Cor pulmonale, right heart strain, pulmonary hypertension

An echocardiographic study of 110 COVID-19 cases noted right ventricular dilation in 31% of patients.[33] Another study demonstrated that when compared with those in the lowest quartile, patients with the highest right ventricular longitudinal strain quartile had an increased risk of elevated D-dimer and CRP levels, acute cardiac injury, acute respiratory distress syndrome, deep vein thrombosis as well as mortality.[34] Acute cor pulmonale, right heart strain, and/or pulmonary hypertension should always be considered in critically ill patients with COVID-19.[35]

Other significant cardiac issues in COVID-19

Arrhythmias

Early data suggested an incidence of 16.7% arrhythmias among hospitalised patients with COVID-19 and 44.4% of ICU admissions.[36] A multicentre study of 192 patients with COVID-19 reported a prevalence of 12.5% for atrial fibrillation among hospitalised patients with COVID-19.[37] Another study evaluating 115 patients with COVID-19 reported atrial tachyarrhythmia in 16.5% of patients, with atrial fibrillation being the most common (63%).[38] Those with atrial tachyarrhythmia had higher CRP and D-dimer levels compared with those without atrial tachyarrhythmia. Among 393 patients with COVID-19, atrial arrhythmias were more common among patients on ventilators (18.5% vs 1.9%).[6] In another study of 700 patients with COVID-19, nine patients experienced cardiac arrest. All cardiac arrests occurred in patients in the ICU. No patients experienced sustained monomorphic ventricular tachycardia, ventricular fibrillation, or complete heart block. Twenty-five patients had atrial fibrillation, nine had significant bradyarrhythmia, and 10 had non-sustained ventricular tachycardia.[39] Among 187 patients with COVID-19, when compared with patients with normal c-TN levels, those with elevated c-TN levels developed more frequent malignant arrhythmias (17.3% vs 1.5%), including ventricular tachycardia/ventricular fibrillation.[3]

Heart failure

Patients with cardiovascular disease and heart failure are more susceptible to COVID-19 and have a more severe clinical course once infected.[40,41] In two studies of patients with COVID-19 hospitalised in Wuhan, heart failure was identified as a complication

in about 50% of the fatalities.[42] In a retrospective multicentred study, among 8383 patients with heart failure who were hospitalised with COVID-19, nearly one in four died during hospitalisation.[43] Evidently, heart failure in patients with COVID-19 may be triggered or aggravated by the acute infection in patients with pre-existing cardiovascular disease or incident acute myocardial insult.

Cardiac arrest

Malignant tachyarrhythmias resulting in cardiac arrest present a dilemma for caregivers. The outcomes of out-of-hospital cardiac arrest were worse during the first weeks of the COVID-19 pandemic in the United States, and this was observed not only in areas with high case-fatality rates but also ones with lower rates.[44] In a retrospective study of 136 patients with COVID-19, 119 (87.5%) had a respiratory cause for their cardiac arrest, and the initial rhythm was asystole in 89.7%, pulseless electrical activity in 4.4%, and shockable in 5.9%. The return-of-spontaneous-circulation rate was 13.2% and 30-day survival rate was only 2.9%.[45] In another study of 54 patients with COVID-19, the mortality rate following cardiopulmonary resuscitation was even worse (100%). The initial rhythm was non-shockable for 52 patients (96.3%), with pulseless electrical activity being the most common (81.5%). Although the return-of-spontaneous-circulation rate was achieved in 29 patients (53.7%), none survived to be discharged home.[46]

Prognostic laboratory parameters for cardiovascular complications in patients with COVID-19

Prognostic parameters for cardiovascular complications in patients with COVID-19 include c-TN level, D-dimer level, and N-terminal pro B-type natriuretic peptide (NT-proBNP) level.

Cardiac troponin level

Increases in c-TN level indicative of myocardial injury is common in patients with COVID-19 and is associated with adverse outcomes such as arrhythmias and death. The risk of cardiac injury, as diagnosed by increased c-TN levels (>99th percentile), was found in up to 22% of patients in the ICU, and in 59% of those that died.[36] In another study of 2736 patients with COVID-19, c-TN elevation was observed in 36%, and c-TN elevation (>0.09 ng/dL) appears to triple the mortality risk.[47] Other studies of patients with COVID-19 have also demonstrated a poorer prognosis, including mortality, in patients with c-TN elevation.[41,48] Both c-TN and NT-proBNP levels were documented to be elevated significantly during the course of hospitalisation among those who eventually died, but no dynamic changes were observed among the survivors.[3] Moreover, patients with COVID-19 with myocardial injury who also have transthoracic echocardiography abnormalities had a higher mortality risk.[49]

D-dimer level

Elevated D-dimer levels were higher among patients with COVID-19 and was correlated with a poorer prognosis. Multivariate analysis showed increasing odds of in-hospital death associated with D-dimer value above 1 μg/mL.[50] In a study of 343 patients with COVID-19, D-dimer levels ≥2.0 μg/mL had a higher incidence of mortality compared with those with D-dimer levels <2.0 μg/mL (12/67 vs 1/267, P<0.001).[51] A markedly elevated D-dimer (>6 times the upper limit of normal) is a consistent predictor of thrombotic events and poor overall prognosis.[52] Indeed, the International Society on Thrombosis and Haemostasis has advised that for patients who have markedly raised D-dimers (arbitrarily defined as three- to four-fold increase), admission to hospital should be considered even in the absence of other severe symptoms.[53] The importance of D-dimer is emphasised in several other international guidelines.[52-55]

N-terminal pro B-type natriuretic peptide level

As a biomarker of heart failure, NT-proBNP levels are commonly elevated in hospitalised patients with COVID-19, particularly in those with elevated c-TN levels. The report by Shi et al[2] showed that NT-proBNP levels were significantly higher in patients with elevated c-TN levels than in those without c-TN elevation (1689 vs 139 pg/mL). A study of 3219 hospitalised patients with COVID-19, elevated c-TN was detected in 6.5%, and an elevated NT-proBNP level in 12.9%.[56] The adjusted hazard ratio for 28-day mortality for c-TN was 7.12 and for NT-proBNP 5.11, confirming that elevated NT-proBNP levels also carry prognostic information. Although NT-proBNP provides corroborating laboratory information on heart failure, the caveat is that NT-proBNP levels increase with age and with various other conditions including renal failure, thus compromising its utility in older patients with confounding variables.

Management of cardiovascular complications of COVID-19

Coronary thrombosis

The approach to the diagnosis and management of STEMI in patients with COVID-19 is similar to that for patients without (Table 1). The approaches endorsed by the American College of Cardiology are recommended[57]: their emphasis is on patient

selection for the cardiac catheterisation laboratory, resource allocation, and protection of the interventional team and other healthcare workers involved in caring for the COVID-19 patient.

On occasion, it is reasonable to liberalise the use of intravenous thrombolytic therapy relative to primary percutaneous coronary intervention. Intravenous thrombolytic therapy can be considered for a relatively stable patient with STEMI and COVID-19. Obviously, in those STEMI patients who are critically ill with COVID-19, the decision to reperfuse with either primary percutaneous coronary intervention or intravenous thrombolytic therapy should be individualised, and contingent upon hospital resources. In this regard, the consensus statement from the Taiwan Society of Cardiology is both pragmatic and reasonable.[58]

In the event that primary percutaneous coronary intervention is to be performed, maximum personal protective equipment is essential. Intubation, suction, and cardiopulmonary resuscitation all result in aerosolisation of respiratory secretions and increase the risks to the hospital staff. Patients already intubated pose less of an infectious risk. Hence patients with COVID-19 or suspected COVID-19 requiring intubation should be intubated prior to arrival to the catheterisation suite.

In the treatment of STEMI patients, an early Hong Kong study reported that both the "symptom onset to first medical contact" and the "door-to-device" times pertaining to primary percutaneous coronary intervention were reported to be substantially prolonged.[59]

Studies from both England[60] and the United States[61] have confirmed that hospital admissions for acute coronary syndrome declined by 40% to 48% in the early days of COVID-19. It is likely that patients with acute coronary syndromes avoided attending hospital during this period.

TABLE 1. Approach to COVID-19-related acute myocardial injury

Clinical suspicion of acute cardiac injury
• Measure cardiac troponin, NT-proBNP, D-dimer
• 12-lead ECG
• Echocardiogram
Diagnosis and monitoring of acute cardiac injury
• ECG changes of myocardial injury/infarction
• Elevated c-TN
• Symptoms
• Telemetry
Look out for cardiac complications
• Arrhythmias
• Thrombo-embolic events
• Heart failure, cardiogenic shock
• Myopericarditis, pericardial effusion
Consult cardiologist on
• Treatment (anticoagulants, antiplatelets, nitrates, etc)
• Need for further tests and imaging
• Acute coronary syndrome, may need percutaneous intervention

Abbreviations: COVID-19 = coronavirus disease 2019; c-TN = cardiac troponin; ECG = electrocardiogram; NT-proBNP = N-terminal pro B-type natriuretic peptide

Heart failure

Standard indications for use of various agents for treatment of heart failure apply to patients with COVID-19. The coexistence of heart failure and COVID-19 complicates diagnosis and management because of overlapping chest findings; however, there are notable differences in chest computed tomography between heart failure and COVID-19 pneumonia, such as lesion distribution/morphology, and pulmonary vein engorgement, which can all help to differentiate between the two.[62]

Cardiopulmonary resuscitation

Cardiopulmonary resuscitation poses a very high risk for viral spread, and full personal protective equipment should be provided. Immediate intubation should be prioritised in order to minimise the duration of any aerosolisation. While awaiting intubation, bag/mask ventilation with filter is advised.

Hypercoagulopathy

Several international guidelines have issued recommendations advocating chemoprophylaxis in all hospitalised patients with COVID-19,[63-66] in the absence of both contra-indications and bleeding complications (Table 2). In the event thromboprophylaxis is deemed indicated, low-molecular-weight heparin is preferred, but unfractionated heparin can be used if low-molecular-weight heparin is unavailable or if kidney function is severely impaired. Low-molecular-weight heparin may be preferred over unfractionated heparin for staff safety reasons.

Athletes recovering from COVID-19

As for athletes who have recovered from COVID-19 infections, a recent expert consensus article recommended 2-week convalescence followed by no diagnostic cardiac testing if asymptomatic, and an electrocardiogram and transthoracic echocardiogram in mildly symptomatic athletes with COVID-19 to return to participate in competitive sports.[67]

TABLE 2. Current guideline recommendations for chemoprophylaxis for the prevention of thromboembolism in hospitalised patients with COVID-19 (who do not have suspected or confirmed VTE)

Patient/setting	ACCP[63]	ASH[64]	ISTH[65]	NIH[66]
Critically ill, hospitalised	Prophylactic dose of LMWH	Prophylactic dose of LMWH	Prophylactic dose of LMWH or UFH*	Routine VTE prophylaxis
Non-critically ill, hospitalised	Prophylactic dose of LMWH or fondaparinux	Prophylactic dose of LMWH	Prophylactic dose of LMWH or UFH*	Routine VTE prophylaxis
After discharge	Extended prophylaxis not recommended†	Post-discharge thromboprophylaxis being investigated in clinical trials. Balance risk vs benefit	LMWH or a DOAC for at least 2 weeks and up to 6 weeks post-hospital discharge in selected high-risk patients at low risk for bleeding	
Non-hospitalised‡	Routine prophylaxis not recommended		Routine prophylaxis not recommended	Routine prophylaxis not recommended

Abbreviations: ACCP = American College of Chest Physicians; ASH = American Society of Hematology; COVID-19 = coronavirus disease 2019; DOAC = direct oral anticoagulant; ISTH = International Society on Thrombosis and Haemostasis; LMWH = low-molecular-weight heparin; NIH = National Institutes of Health; UFH = unfractionated heparin; VTE = venous thromboembolism

* An intermediate dose of UFH or LMWH may be considered in people with morbid obesity or those in the intensive care unit

† Extended thromboprophylaxis should be considered in patients with COVID-19 at high risk for VTE but at low risk of bleeding

‡ Randomised trials that address thromboprophylaxis in out-patients with COVID-19 have not been published. All cases require individualised therapy and patients at high risk for VTE should be considered for anticoagulation

Summary

Cardiovascular complications of COVID-19 are associated with higher fatality rates. Putative causes of cardiac injury include cytokine storm, myocarditis, extreme physical and emotional stress, ischaemic injury, hypercoagulopathy, right heart strain, and cor pulmonale, or combinations thereof. Echocardiography and c-TN, D-dimer, and NT-proBNP levels all provide prognostic information. Aside from percutaneous coronary intervention for STEMI, there is no specific treatment for COVID-19-associated cardiac injury, and management is primarily supportive. Whether antiviral therapies administered early in the course of disease will prevent severe disease and cardiovascular complications associated with COVID-19 remain to be seen.

Author contributions

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All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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