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COVID-19 and cardiovascular manifestations

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Abstract. – OBJECTIVE: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as COVID-19, a viral outbreak that started in December 2019, eventually lead to a worldwide pandemic. COVID-19 usually presents with flu-like symptoms, such as headaches, dry cough, fever, fatigue, myalgia, shortness of breath, diarrhea and loss of smell or taste. However, it can also have major effects on the cardiovascular system. Based on the available relevant literature, we aimed to elaborate the possible mechanisms influencing cardiovascular damage, myocardial injury and thromboembolic disease process in particular.

MATERIALS AND METHODS: After considering our inclusion and exclusion criteria, the systematic review included 8 studies in total.

RESULTS: In general, underlying cardiovascular diseases were associated with poorer clinical outcomes. This may be due to immunological dysregulation. The disease outcomes were also positively correlated with the severity of the disease, especially with myocardial injury. Thus, cardiac biomarkers, such as Troponin T, CK-MB and myoglobin could be utilized in prediction algorithms for deciphering the clinical outcome in COVID-19 patients.

CONCLUSIONS: Venous thromboembolisms were commonly encountered complications despite the administration of thromboprophylaxis, and they mostly presented as pulmonary embolisms, warranting the need for relevant investigations in hemodynamically unstable patients. However, more studies need to be conducted to better understand the mechanisms at play and the ensuing complications, to better treat COVID-19 patients.

Key Words:
Myocardial injury, Venous thromboembolism, COVID-19, SARS-CoV-2.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreak started in late December 2019 from its epicenter in Wuhan, the capital city of the Hubei province of China. On March 11th, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. COVID-19 is transmitted by inhaling air contaminated droplets. It mostly presents with flu-like symptoms such as headaches, dry cough, fever, fatigue, myalgia, shortness of breath, diarrhea, loss of smell and or taste[1,2]. However, not only SARS-CoV-2 causes respiratory symptoms, but it could also significantly impact the cardiovascular system.

Preexisting cardiovascular diseases seem to exacerbate the condition and increase the mortality rate in patients infected with COVID-19. In addition, COVID-19 seems to contribute to the progression of cardiovascular diseases like myocardial injury, acute coronary syndrome, venous thromboembolism and arrhythmias. Clinical data from the beginning of the pandemic suggested the association between COVID-19 and the

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cardiovascular system as critically ill patients had profoundly elevated cardiac troponin levels[3]. However, the underlying mechanisms are unknown and remain hypothetical. In some cases, systemic inflammation together with the cytokine storm have been suggested to hasten the progression of the disease or induce cardiovascular damage. Angiotensin-converting enzyme 2 (ACE2), a component of the renin-angiotensin-aldosterone system (RAAS), as well as a crucial receptor protein for the entry of the SARS-CoV-2, is believed to cause the damage of the heart and vessels[3,4]. As it is, the quality of life is highly affected in patient suffering from cardiac diseases, the presence of concurrent COVID-19 infection leads to further deterioration of both psychological and physical health[5-7].

It is important to understand the viral structure, life cycle of the virus and how the immune system responds to it, in order to completely comprehend the impact of SARS-CoV-2 infection on the cardiovascular system. The focus of this review is to summarize the evolution, history and pathophysiology of SARS-CoV-2, as well as to elaborate the possible mechanisms in the involvement of cardiovascular damage based on several studies and articles published thus far.

The aim of this review was to collect and analyze studies where the following questions were addressed:

1. Does an infection with SARS-CoV-2 induce cardiovascular damage?
2. What are the cardiovascular consequences of COVID-19 infection?
3. How does SARS-CoV-2 manifest itself in the cardiovascular system?
4. What are the possible mechanisms of COVID-19's cardiovascular involvement?

Our primary focus was to summarize the pathophysiological mechanisms that generate cardiovascular implications among patients suffering from COVID-19 infection, in particular, the ensuing of myocardial injury and thromboembolic events.

Materials and Methods

Data Source and Search Strategy

This research was carried out using the Preferred Reporting Items or Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement of Page et al[8] from 2021.

A thorough search of publications was done utilizing the electronic database PubMed. Following MeSH terms "SARS-CoV-2", "COVID", "COVID-19", "SARS" or "coronavirus" were used in different combinations with "myocardial injury", "cardiac injury", "myocardial damage", "troponin ", "elevated troponin", "elevated cardiac enzymes", "cardiac biomarkers", "cardiovascular diseases", "myocardium", "Venous thromboembolism (VTE)", "thromboembolic events", "pulmonary emboli (PE)", "deep venous thrombosis (DVT)". The literature search was not limited in time and every relevant article published since the beginning of the present COVID-19 outbreak, dated through May 5th, 2021 was reviewed. Original articles, which were not written in English, German, Romanian or in Turkish were excluded. Additional relevant articles were detected from cited documents and references.

Selection Criteria

Inclusion criteria for this review included the following: (a) research study types, such as retrospective, prospective, cohort, case-control studies or meta-analysis, that listed myocardial injury with increased troponin levels in COVID-19 patients; (b) a sample size of over 10 hospitalized COVID-19 patients; (c) patients diagnosed with SARS-CoV-2 using RT-PCR technique; (d) studies mainly analyzing PE or DVT in COVID-19 patients; (e) postmortem studies of myocardial injury or VTE.

All studies, which were not mentioned in the inclusion criteria were excluded. Specifically, the exclusion criteria consisted of the following: (a) reviews and single case reports; (b) irrelevant topics and articles; (c) population overlap in different studies and meta-analysis.

Data Extraction

By applying the search terms, the PubMed search engine primarily generated a total of 899 articles. After further assessment and consideration of the inclusion and exclusion criteria, this systematic review included and analyzed a total of eight studies. The precise explanations for study exclusions are shown in the PRISMA flow diagram in Figure 1.

Results

Underlying Cardiovascular Comorbidities

Pre-existing cardiovascular disorders and comorbidities like hypertension and diabe-

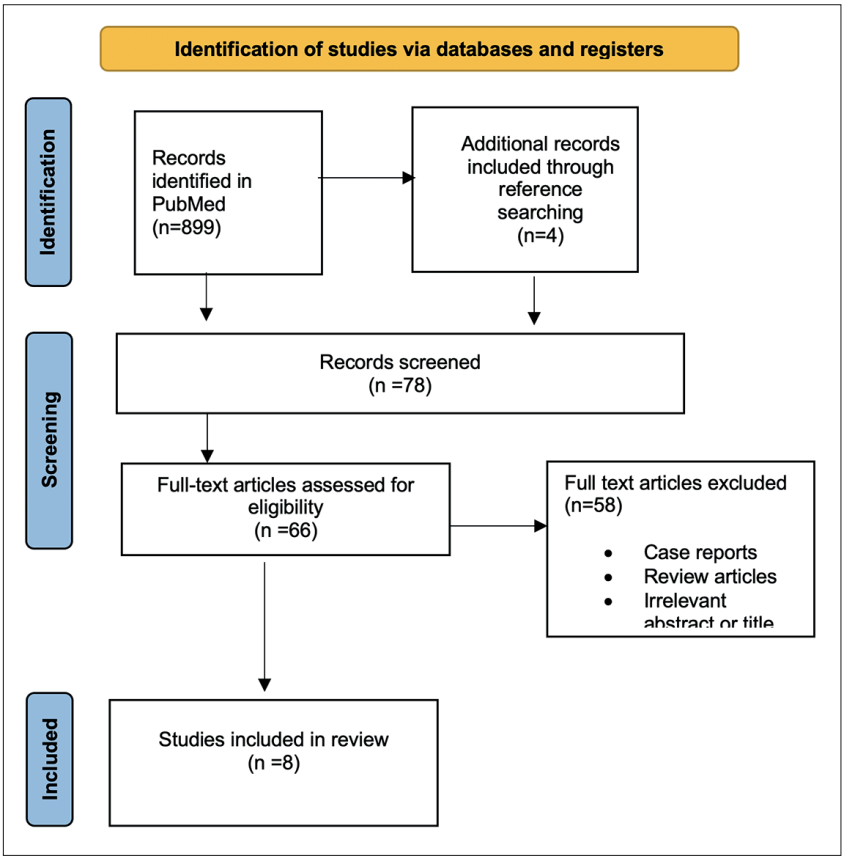

Figure 1. Identification of studies *via* databases and registers.

tes mellitus are prevalent in patients who had COVID-19. In a single-center prospective study, 77% of 201 patients with COVID-19 admitted to the Military Hospital in Rawalpindi (Pakistan) had preexisting morbidity, prevalently hypertension and diabetes (both at 17.5%)[9]. Similarly, in a cohort study[10] of 700 patients admitted between March 6, 2020, and May 19, 2020, in Pennsylvania, USA, the most common comorbid disorders reported were hypertension (50%) and diabetes mellitus (26%). The significant prevalence of those underlying conditions was also verified in the subsequent studies listed in the Table I below.

It is striking that the prevalence of underlying comorbidities was even higher in patients who were admitted to the ICU or were in critical conditions. Regardless of the type of comorbidity, the clinical outcome was worse in the presence of comorbidity than in its absence. For instance, in a retrospective study conducted in Boston, USA, 35.8% of all COVID-19 patients had hypertension. In the ICU, the prevalence was even higher, and 55.9% of all COVID-19 patients had hypertension. Likewise, there was a higher rate of diabetes in the ICU (38.8%) patients than in the regular ward (29%) or in outpatients (9.4%). It is noteworthy that the rate of comorbidities was

Table I. Prevalence of pre-existing conditions.

Study & year	City, country	Sample size	Hypertension	Cardiovascular diseases	Diabetes mellitus	Reference
Bhatla et al[10]	Philadelphia, USA	700	347 (50%)	76 (11%)	182 (26%)	10
Piazza et al[11]	Boston, USA	1114	399 (35.8%)	90 (8.1%)	201 (18%)	11
Lodigiani et al[12]	Milan, Italy	388	183 (47.2%)	54 (13.9%)	88 (22.7%)	12
Yang et al[13]	Wuhan, China	203	80 (39.4%)	9 (4,4%)	29 (14.3%)	13
Liaqat et al[9]	Rawalpindi, Pakistan	201	35 (17.5%)	30 (14.9%)	35 (17.5%)	9
Majure et al[13]	New York, USA	6247	3717 (60%)	833 (13%)	2248 (36%)	14

also higher in deceased patients. Shi et al[15] reported in a retrospective study in Wuhan (China) that 59.7% of those who died also suffered from hypertension; while among the survivors only 26.6% had hypertension. Similarly, 33.9% of the patients who died had a history of coronary heart disease *vs.* just 6.4% of the survivors[15].

Therefore, it seems that cardiovascular diseases and their risk factors, hypertension and diabetes mellitus, tend to have a negative impact on the clinical outcomes of COVID-19 patients.

Possible Mechanisms of Cardiovascular Involvement in COVID-19

Direct myocardial injury

Myocardial tissue might be directly damaged by the infiltration of SARS-CoV-2 virus. As previously stated ACE2 functions as the receptor for viral entry. The Spike protein of SARS-CoV-2 attaches with high affinity to the human cell receptor ACE2, while the Transmembrane protease serine 2 (TMPRSS2) prepares the S protein. This enables the viral entry. ACE2 and TMPRSS2 are vastly expressed in the lungs, as well as in the heart, blood vessels, kidneys and gastrointestinal smooth muscle. Hence, SARS-CoV-2 is presumably able to directly infect various cell types and tissues[16-18].

In a cohort study of successive autopsy cases in Hamburg in April 2020, Lindner et al[19] spotted in 24 out of 39 autopsies (61.6%) the genome of SARS-CoV-2 in the cardiac tissue. Apart from the presence of the virus and its progeny inside the myocardial tissue, Linder et al[19] also stated that the localization of the viral genome is not directly in the cardiomyocytes, but rather in the macrophages or interstitial cells within the cardiac tissue.

Systemic inflammation and cytokine storm

One of the challenging factors with SARS-CoV-2 infection is the broad range of disease presentation. While some patients will remain with no symptoms, others will present with mild to moderate symptoms, such as cough, fever, fatigue and dyspnea. Moreover, some individuals will display severe complications, like viral pneumonia and acute respiratory distress syndrome, which are the leading causes of death in COVID-19[17]. The diverse clinical picture and the severity of the disease are unmistakably correlated with each person's immune response[20]. In the early phase of the infection, the virus penetrates the lung tissue and multiplies quickly, while the immune system gets activated to defend against the pathogen[21]. The innate and adaptive immunity is crucial for restricting viral replication, dissemination and playing defense-based protection. At the same time, tissue injury caused by the pathogen will provoke increased production of proinflammatory cytokines, macrophages and granulocytes. Vasodilation and endothelial permeability facilitate the inflammatory processes, resulting in a cytokine storm[22]. The serum levels of pro-inflammatory cytokines and chemokines will determine the prognosis and severity of clinical symptoms. The correlation between disease severity and cytokine release syndrome can be ascertained from the retrospective analysis of the patients' plasma infected with SARS-CoV-2. It has been shown that there is an increase in interleukin (IL)-1b, interferon gamma (IFN-ɣ), monocyte chemoattractant protein (MCP)-1, inducible protein (IP)-10, macrophage inflammatory protein (MIP)-1A, MIP-1B, granulocyte colony stimulating factor (G-CSF) and tumor necrosis factor-alpha (TNF-α). Similarly, there is a higher concentration of the cytokines in patients' plasma in the intensive care unit. Furthermore, a substantial increase in plasma IL-6 is linked to severely ill patients with ARDS and cardiac injury[20,23]. It is assumed that pro-inflammatory cytokines weaken myocardial function. In some patients it has immense cardiovascular outcomes and may provoke hypotension, tachycardia and left ventricular dysfunction[21]. In others, it is cardiotoxic and may cause conduction problems, arrhythmia and cardiac injury with increased BNP serum levels[21].

Overall, these findings suggest that the virus can potentially harm the tissues and organs indirectly, *via* the ensuing pathological inflammatory reactions[20].

Downregulation of ACE2 receptors

Macrophages play an important role in the immune system, being a significant source of TNF-α. The tumor necrosis factor-α converting enzyme, a metallopeptidase also called ADAM-17, mediates the activation of TNF-α and is responsible for ectodomain excretion of ACE2. A reduction in receptor density causes ACE2 to become soluble when the virus attaches itself to the receptor. The consequent downregulation of ACE2 leads to an accumulation of angiotensin (ang) II, since one of the most important features of membrane bound ACE2 is to convert the va-

soconstrictor ang II into vasodilator angiotensin 1-7[24,25]. Due to the critical role of the ACE2 receptors in the pathogenesis of COVID-19, some clinicians have speculated that ACE inhibitors and ARBs might be favoring viral disease. Indeed, both antihypertensive medications enhance the expression of the enzyme ACE2, consequently upregulating ACE2 receptors, which may facilitate the entry of the virus[24]. For instance, in a retrospective study conducted in France, Liabeuf et al[26] tried to determine the relationship between the renin angiotensin system inhibitors (RASIs) and disease severity and mortality. Liabeuf et al[26] observed that the long-term use of RASI against hypertension was associated with a higher risk of being admitted in the ICU (OR: 2.28; 95%CI: 1.17-4.42)[26], reporting a log-rank *p*-value equal to 0.002 with the use of RASIs at baseline. In contrast, in a meta-analysis conducted by Greco et al[27], the results of 14 included studies with a total of 10,127 patients showed that the use of ACEIs and ARBs does not worsen the severity (OR: 0.88; 95% CI: 0.60-1.31) and mortality in COVID-19 (OR: 0.95; 95% CI 0.57-1.58), $p < 0.01$. The authors could not establish other favorable effects of the antihypertensive medications in COVID-19; nevertheless, they advised continuing the drugs without interruption, since these medications have proven to be beneficial in cardiovascular diseases

(CVD)[27]. On the other hand, ACE2 seems to have anti-inflammatory properties in the lungs, the blockage of AT1 receptors and the resulting rise in ACE2 activity may be protective against pulmonary inflammation[24]. The meta-analysis of Pirola et al[28] also implies that RAAS might have beneficial effects on the prognosis of COVID-19; the authors included a total of 16 studies with 24,676 patients affected by COVID-19. The statistical analysis verifies that there is no connection between ACEIs/ARBs and ICU admission or in-hospital mortality. On the contrary, the data suggested that the use of antihypertensive medication (ACEIs and ARBs) had protective effects on disease evolution and outcome. The risk of death or critical illness was reduced by 23%[28].

Definite conclusions on the impact of ACEIs/ARBs therapy on COVID-19 patients remain elusive. All published studies and available researches are retrospective observational; thus, they have limitations since the study population is not the accurate representation of the general population and generalizability is not possible. Numerous randomized controlled studies are being conducted to assess the impact of the continuation or discontinuation of the therapy with ACEIs or ARBs on the clinical outcomes of patients infected with COVID-19.

Mismatch of myocardial oxygen demand-supply

The European Society of Cardiology (ESC) defines altered oxygen supply and demand of the myocardium as a myocardial infarction (MI) type 2[29]. Diminished oxygen supply such as decreased perfusion from a fixed plaque or endothelial dysfunction, or an increase of its demand could lead to imbalance, and consequently, ischemia of the myocardium. Respiratory failure and ARDS with severe hypoxemia also commonly diminish oxygen supply in COVID-19 patients. Meanwhile, hypoxemia due to ARDS, pyrexia and tachyarrhythmia increase myocardial oxygen demand. Increased levels of Ang II will cause arteriolar vasoconstriction and subsequently severe hypertension, further increasing myocardial demand[30].

Plaque rupture and coronary thrombosis

Atherosclerotic plaque rupture will prompt MI type 1[29]. Plaques could become destabilized due to systemic inflammation, viral infection, high blood pressure and shear stress on the endothelial layer of the vessels[30]. Viral infection disrupts plaques *via* pathogen-associated molecular patterns (PAMPs); they penetrate the bloodstream and stimulate immune receptor cells within established atherosclerotic plaques. Pathogens also activate the immune system and subsequently may provoke systematic inflammation, starting the generation of active cytokines[31]. This will further induce endothelial dysfunction, leading to vasoconstriction and formation of thrombosis[32].

Nevertheless, the clinical incidence of acute coronary syndrome in the setting of COVID-19 remains unclear as cardiac catheterization has been performed only in a limited number of patients, to prevent the spread of infection among medical personnel. In addition, delaying emergency catheterization for 1-2 days in order to wait for the results of the Real Time-Reverse Transcription Polymerase Chain reaction (RT-PCR) is not admissible according to the protocol. Therefore, emergent percutaneous revascularization has been chiefly reserved for STEMIs[33].

Adverse effects of therapies

Antiviral treatment and corticosteroids used to treat COVID-19 are other substantial con-

cern due to their ill-effects on the cardiovascular system; for example, hydroxychloroquine and chloroquine have cardiotoxic adverse effects. Methylprednisolone, an anti-inflammatory, has an impact on fluid retention as well as electrolyte imbalance, and should be monitored closely[24].

Electrolyte imbalances

Systemic diseases regularly lead to electrolyte imbalances through various mechanisms; these imbalances can induce arrhythmias, particularly in patients with underlying cardiac dysfunction. For instance, COVID-19 patients may develop hypomagnesemia or hypokalemia, provoking diarrhea and nausea[34]. Diuretics could induce hypokalemia as well. Furthermore, hypokalemia raises a significant issue in COVID-19, showing a potential association between SARS-CoV-2 and RAAS. SARS-CoV-2 attaches to ACE2 in the viral entry and presumably downregulates the ACE2 expression, resulting in increased Ang II levels, which will further contribute to hypokalemia by increasing potassium elimination by the kidneys[34]. Not only can hypokalemia lead to a variety of tachyarrhythmias, e.g., ventricular tachycardia and fibrillation[30,35], but it has also shown to worsen ARDS and cardiac injury, which are frequent complications of COVID-19[34].

Diffused endothelial damage

Endothelial cells are essential in adjusting vascular homeostasis, their dysfunction will contribute to vasoconstriction, inflammation, tissue edema and hypertension[32].

ACE2 receptors as well as TMPRSS2 protease are highly expressed in the circulatory system. Viral replication and its progeny will evoke innate immunity and inflammation. Activated macrophages, releasing pro-inflammatory cytokines IL-1ß and IL-6 and disproportionate AngII activity will stimulate endothelial cells and cause endothelial dysfunction. This will further reinforce a prothrombotic state with growing endothelial permeability[21,36].

Cardiovascular Manifestations Associated with COVID-19 Infection

Myocardial injury

COVID-19 can damage the heart leading to early morbidity and mortality. Various reports[14,37,38] describe many hospitalized patients with evidence of myocardial injury. Myocardial injury is defined differently in reports, as shown in the pie chart in annex 4. 55% of published reports diagnosed MI by elevated levels of cardiac troponin I above the upper 99th percentile. Increased levels of cardiac troponin T and increased levels of hypersensitive troponin T (hs-TnT) above the 99th percentile upper reference limit (>28 pg/ml) were used in 18% of published reports. In a small number of studies, cardiac injury was defined as elevated serum levels of hypersensitive TnI above the 99th percentile upper reference limit (>28 pg/ml). (Figure 2).

The incidence of myocardial injury in the selected studies ranged from 19% to 54 %[9,14,37,38]. The occurrence of myocardial injury in patients diagnosed with COVID-19 has been associated with worse outcomes, such as further ICU admissions, cardiac complications and mortality.

In an early retrospective study in Wuhan, China, Shi et al[37] showed that cardiac injury is very common in severely ill patients with COVID-19 and in those who are deceased due to it. For instance, myocardial injury was present in 75.8% of the deceased patients. Furthermore, they found out that the raised serum levels of myocardial markers have a negative prognostic value. In an analysis done with the help of a receiver operating characteristic curve, a prediction model of in-patient fatality was established through cardiac biomarkers. CK-MB and myoglobin are considered excellent biomarkers to predict mortality, since the area under the receiver operating curve (AUC) is as high as 0.87 and 0.88 respectively. The AUC value of cTnI was 0.92, which is an excellent predictor for mortality of hospitalized patients. Old age and underlying comorbidities correlate with cardiac injury in COVID-19 patients as well[37].

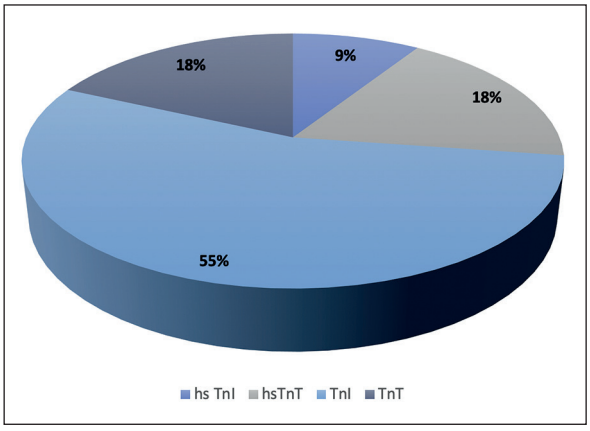

Figure 2. The percentage of reports using various biomarkers of myocardial injury.

Guo et al[38] also showed, in a retrospective case series, that myocardial injury was correlated with increased mortality in patients with COVID-19. In their laboratory findings they noticed that the inflammatory markers, such as CRP, procalcitonin and globulin, were highly raised in patients with increased TnT levels. Furthermore, cardiac markers, like NT-proBNP, CK-MB and myoglobin were also more raised in patients with elevated values of cardiac troponin. Overall, the authors observed that high levels of troponin T had a negative prognostic value. Patients with underlying comorbid cardiovascular disorders and raised TnT had a mortality rate of 69.44%. In contrast, patients without any CVD and normal values of TnT had only a mortality rate of 7.62%. Interestingly, the mortality rate was higher in patients without CVD and raised TnT values (37.50%) than in patients having an underlying CVD but normal serum TnT levels (13.33%)[38].

Majure et al[14] further confirmed that elevated troponin levels are associated with poor prognosis. In their large retrospective study of 6247 patients in New York, USA, the authors observed that increased troponin levels were highly correlated with mortality. Out of the 6,247 patients, 1,397 died (22.4%). 605 of the patients who died had normal troponin levels (43.3%), 304 of them had mildly elevated troponin levels (>1 to ≤3x) (21.8%) and 488 of them had highly increased cardiac troponin levels (>3x) (34.9%). After a multivariate data evaluation, mildly increased troponin levels were linked with higher risk of in-patient deaths [adjusted odds ratio (OR): 2.06; 95% confidence interval (CI): 1.68 to 2.53]; p <0.001. Highly increased levels of troponin were even more associated with mortality in hospitalized patients (OR: 4.51; CI 95% 3.66 to 5.54); p <0.001. Furthermore, patients with increased troponin levels were more likely to be admitted in the ICU ward and needed mechanical ventilation[14].

In a prospective study[9] performed in a Military Hospital in Pakistan, ECG and transthoracic echocardiographic findings were also conducted and analyzed. The study included 201 patients diagnosed with COVID-19, 57 of them were categorized as critical (28.4%). Troponin I levels were three times higher in critically ill patients. A logistic regression showed that the levels of troponin I (>0.12 ng/ml) were substantially higher when compared with the non-critical patients (OR: 8.14; 95% CI: 2.13-31.10); p <0.002. D-dimer levels were elevated in the critically ill group as well. Abnormal ECG findings were seen in 96.5% of the critically ill. Most abnormal ECG findings in the critical group were tachycardia, anteroseptal ST depression and atrial fibrillation. Abnormal echocardiographic findings were seen in 18.8% of all 181 patients who got a TTE testing. 25 of the critically ill subjects showed RV dilatation or dysfunction[9].

Overall, these results show that cardiac injury is not just a symptom of COVID-19, but also an indicator of the severity of the disease and predictor of unfavorable prognosis.

Venous thromboembolism (VTE)

The increased prevalence of venous thromboembolic event, such as deep vein thrombosis and pulmonary embolism, observed in patients infected with SARS-CoV-2 implies the development of a prothrombotic state, regardless of thromboprophylaxis administration. Potential mechanisms include severe inflammation, immobilization due to prolonged bed rest, intravascular devices, lack of oxygen due to a mismatch of ventilation/perfusion ratio and high prevalence of thromboembolic risk factors, such as age and obesity[11,39].

An autopsy study[40] of 12 case series in Hamburg revealed that 7 patients had deep vein thrombosis in both lower extremities (58%). Consequently, four of them developed pulmonary embolism, which was the cause of death due to the dissemination of the blood clot from the deep veins of the legs (33.3%)[40].

In a retrospective cohort study in Boston, USA, Piazza et al[11] tried to determine the prevalence of arterial and venous thromboembolic events in 1,114 patients infected with SARS-CoV-2. The authors identified that the incidence of VTE was the highest in the ICU followed by hospitalized patients and outpatients. ICU admissions were associated with a high rate of COVID-19 related complications such as pneumonia (96.5%) and ARDS (78.8%); even though 89.4% of the ICU patients received antithrombotic prophylaxis. After 30 days, major arterial or venous thromboembolic events occurred in 35.3% patients while major cardiovascular events occurred in 45.9% and symptomatic VTE occurred in 27% of the patients admitted in the ICU. ARDS also increased the probability of major arterial and venous thromboembolic events, major cardiovascular events and symptomatic VTE. Piazza et al[11] further established that the patients infected with SARS-CoV-2 in the ICU ward had increased levels of D-dimers, fibrinogen, IL-6 and hs-CRP

serum levels[11].

Furthermore, Piazza et al[11] reported the association of ICU admissions with more frequent VTE events[11]. In contrast to that, Poyiadji et al[41] observed, in their retrospective cohort study of 328 patients in Detroit, that acute PE can also develop in patients who do not need ICU admission. They also noticed several risk factors predisposing to VTE in COVID-19 patients. All patients with a greater body mass index (BMI) than 30 kg/m^2 and increased D-dimers were associated with 2.7-fold and 4.8-fold increased odds of developing PE, respectively. Elevated C-reactive protein was identified as another risk factor as well. Thus, SARS-CoV-2 patients with increased D-dimer values and augmented inflammatory responses are more vulnerable to develop PE. Moreover, the authors discovered that patients getting statin therapy before hospitalization were less likely to develop VTE, suggesting that statin therapy has protective effects on thromboembolic events[41].

In another retrospective study in Northern-West Italy, Longhitano et al[42] observed a high prevalence of VTE events despite prophylaxis against thrombosis in the ICU department. All the ICU patients with ARDS related to COVID-19 received Enoxaparin, a low molecular weight heparin (LMWH) for the prevention of thrombosis. Out of 62 patients, 12 developed VTE (19.3%), 11 of them got PE (17.7%) and one of them had DVT in the lower extremity (1.61%). Longhitano et al[42] noticed that VTE happened typically after six days in the ICU and 14 days after the appearance of symptoms[42].

Similarly, Middeldorp et al[43], in a cohort study of 198 patients in Amsterdam, noted that the patients with COVID-19 admitted in the ICU were at a higher risk of developing VTE. Out of the 198 patients, 75 were transferred to the ICU ward (37.9%). Although antithrombotic prophylaxis was given to all patients with COVID-19, VTE occurred in 39 patients (19.7%). Out of those 39 patients, 35 were ICU patients (89.7%); thus, the amount of VTE in ICU patients was markedly higher[43].

Concurrently, a retrospective cohort study in Milan analyzed the prevalence of thromboembolic events and other cardiovascular incidents in 388 COVID-19 patients. 16 out of the 44 patients who underwent diagnostic imaging for VTE tested positive for either DVT, PE, thrombosis in the inferior vena cava, stroke without atrial fibrillation or NSTEMI (36.3%). Pulmonary embolism was diagnosed in 63% of all patients with VTE, representing the majority of complications caused by thrombosis. Notably, the VTE diagnosis in 50% of those 16 patients was already confirmed in the first 24 hours of hospitalization. Hence, Lodigiani et al[12] suggested the VTE as one of the early symptoms of COVID-19 that may be deemed as an important feature of COVID-19's clinical picture.

In a multicenter prospective cohort study, Helms et al[44] compared the prevalence of VTE among 150 patients having ARDS due to COVID-19 and 145 patients having ARDS unrelated to COVID-19. The result demonstrated that the patients with ARDS secondary to COVID-19 were more prone to thromboembolic events (11.7 *vs.* 2.1%), especially with higher incidence of PE (11.7% *vs.* 2.1%)[44].

Finally, in a recent large retrospective observational study involving a population of 10,871 patients diagnosed with COVID-19 in New York, USA, 118 patients were diagnosed with symptomatic VTE (1.09%). Among those 118 patients, 101 had PE (85.6%). Furthermore, Poyiadji et al[41] and Giannis et al[45] recognized the protective effects of statins and antiplatelet therapy against VTE in two separate studies, as they decreased VTE's incidence.

Discussion

The overall findings show that the underlying cardiovascular comorbidities, such as hypertension and diabetes mellitus are associated with poorer clinical outcomes. Piazza et al[11] reported that their prevalence was higher in critically ill patients. In an alternative study, Shi et al[37] stated that more than 50% of the deceased patients suffered from hypertension. Similarly, Liaqat et al[9] showed that there was a positive correlation between underlying comorbidities and the disease progression. A plausible theory as to why underlying comorbidities exacerbate the disease, despite being successfully managed, is the immunological dysregulation during viral infection[24].

We also found that myocardial injury in hospitalized patients is positively correlated with the severity and mortality; supporting the statement of various studies including Guo et al[38], which stated that myocardial injury is a predictor of poor prognosis[9,14,37]. In addition, the prevalence of VTE in hospitalized patients was high regardless of thromboprophylaxis, especially in the ICU-ward. The possible COVID-19 mechanisms

that could cause CVD include direct myocardial injury, systemic inflammation together with cytokine storm, downregulation of ACE2 receptors, abnormal myocardial oxygen demand-supply, plaque rupture with resulting coronary thrombosis, adverse effects of several therapies intended to treat COVID-19, electrolyte imbalances as well as endothelial damage.

Although some studies demonstrated that CVD are predictors of increased mortality in hospital patients, Guo et al[38] found that 16% of the patients with pre-existing CVD but normal troponin T values had comparatively better outcomes. On the other hand, patients with underlying comorbid CVD and elevated TnT had a mortality rate of nearly 70%[38]. These findings indicate that cardiac biomarkers should be assessed in individuals with CVD who get infected with SARS-CoV-2 to evaluate the risk stratification, and thereby, initiate early management.

The prevalence of myocardial injury in examined studies varied from 19% to 54%[9,14,37,38]. Majure et al[14] also noted that the real incidence of cardiac damage among in-hospital patients might be lower, since troponin values are not evaluated in every patient; additionally, their fatality was also lower than that of those who had the troponin levels determined.

Even though VTE was commonly found in patients with COVID-19 and has been linked to unfavorable outcomes, its true prevalence is unclear. Incidences of VTE in examined studies ranged from 1.09% to 58%[40,45]. The huge difference in the prevalence of VTE may be attributed to the sample size in the different studies or to the severity of the illnesses in the research population.

As Middeldorp et al[43] also explained, the diagnosis of VTE is quite challenging in patients suffering with COVID-19, since many symptoms, such as dyspnea, may be missed while diagnosing COVID-19. The assessment of lower extremities for DVT is not the primary focus of the physicians in the ICU department as well[43]. Wichmann et al[40] further affirms that PE should be always considered in hemodynamically unstable patients with COVID-19.

The ongoing reviews evaluating the effects of COVID-19 on the cardiovascular system are limited by several factors, as most conducted studies are case control studies, case series, retrospective or prospective cohort and autopsy studies. These studies can have selection and information biases. Furthermore, small sample sizes have also restricted the generalizability of the results. For example, in the autopsy study of Lindner et al[19], clinical data were scarce and inadequate to establish whether a cytokine storm is associated with heart dysfunction during and following the disease. Moreover, the sample size included only 39 cases[19]. Another example is the retrospective cohort study of Lodigiani et al[12] where the authors state that the results might have some limitations regarding the patients' outcomes since the research included patients just from the beginning of the outbreak in Europe, at a time when there was a lack of experience and knowledge about COVID-19. Therefore, it is difficult to distinguish whether thromboembolic events had a major role in the high mortality rate[12]. Furthermore, definitive conclusions about the effects of the antihypertensive treatment with ACEIs/ARBs in COVID-19 patients remain elusive; even though meta-analyses are available, the data obtained is from the retrospective studies. Numerous randomized controlled trials are being done to conclude the effects of the therapy with ACEIs and ARBs on the clinical outcomes of COVID-19 patients, as randomized controlled trials are the gold standard for strong evidence and least amount of bias.

Conclusions

The infection with SARS-CoV-2 causes extensive damage to the cardiovascular system. Myocardial injury becomes evident by troponin level elevations, cardiac arrhythmias, and to some extent by ventricular impairment. Currently, it is unclear if these findings are simply linked to the poor outcomes or if they specifically lead to the mortality of these patients.

VTE is a common complication in patients hospitalized due to COVID-19 and mostly manifests as PE. Therefore, imaging should be recommended even if there is minimal suspicion of VTE. Also, long term effects on the cardiovascular system, and subsequently, the wellbeing of the patients, will remain uncertain and need further studies.

Therefore, more studies need to be performed to better understand the mechanisms involved in COVID-19 and its effects on CVD, as well as to better treat COVID-19 patients with such complications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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