Coronary Heart Disease and Coronavirus Disease 2019: Pathogenesis, Epidemiology, Association with Myocardial Revascularization

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ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) causes a hypercoagulable state with a high incidence of thrombotic complications. Patients with a history of myocardial revascularization have more severe complications due to COVID-19. Coronary stent thrombosis has become significantly more common during the COVID-19 pandemic.

AIM: The aim of our study is to analyze scientific information on the risks of stent thrombosis in patients who underwent COVID-19.

METHODS: A search was made for scientific publications in evidence-based medicine databases and web resources: PubMed, MEDLINE, UpToDate, TripDatabase, ResearchGate, and Google Scholar. Inclusion criteria were: (1) Observational studies or case series involving patients with a confirmed diagnosis of COVID-19 and myocardial infarction requiring myocardial revascularization; (2) the division of the population into survivors and non-survivors; and (3) data on the presence of the previous myocardial revascularization. Exclusion criteria: Case description and editorials/bulletins. In all articles selected for further analysis, 49 sources were considered that met the inclusion criteria and excluded duplication or repetition of information.

RESULTS: Coronavirus infection has contributed to the change in the course of myocardial infarction in patients undergoing myocardial revascularization. The incidence of stent thrombosis has a positive correlation with the severity of the coronavirus infection. The previous myocardial revascularization procedures significantly increase the risk of mortality in patients with coronavirus infection. This is especially actual for elderly patients.

CONCLUSION: One of the most vulnerable groups is elderly patients who have undergone myocardial revascularization after myocardial infarction in the past and have comorbid diseases. An analysis of scientific publications has shown that further larger-scale clinical studies are needed to confirm the hypothesis about the negative impact of coronavirus infection on stent thrombosis in patients who have undergone COVID-19.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in numerous hospitalizations, deaths, and economic hardship around the world. High virulence, infecting people even during the asymptomatic phase, and relatively high infectivity have led to the rapid transmission of this virus outside of China, leading to a pandemic [1]. The emergence of a new virus, officially known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has become a huge challenge for health-care professionals and scientists around the world [2].

Respiratory involvement ranging from a mild flu-like illness to potentially fatal acute respiratory distress syndrome or COVID-associated pneumonia is the dominant clinical manifestation of COVID-19 [3]. However, the cardiovascular manifestations of this infection have been less studied. As with respiratory infections, pre-existing cardiovascular disease (CVD) and CVD risk factors increase vulnerability to COVID-19. In addition, COVID-19 can exacerbate asymptomatic CVD and even provoke cardiac complications de novo. Some studies have shown that pre-existing CVD is a risk factor for severe infection. Thus, according to the results of published studies, patients with COVID-19 are likely to develop an acute cardiac injury, arrhythmias, blood-clotting defects, and acute stroke, which can lead to adverse outcomes [4], [5]. Studies conducted during the pandemic show that coronavirus infection often occurs in patients with coronary heart disease (CHD), which leads to a worsening of the underlying disease and increases the risk of death [6], [7].

The adverse outcomes of CHD in patients with COVID-19 are significantly higher than in the general population, which necessitates monitoring of cardiovascular status at the hospital and outpatient levels. ST-segment elevation myocardial infarction (STEMI) is one of the most significant fatal
complications of coronavirus infection. The mortality rate in this category of patients reaches 25%; the vast majority of patients have a decrease in ejection fraction; multivessel disease prevails, which requires myocardial revascularization (up to 83% of cases) [8]. In addition, during the pandemic, patients with coronavirus infection encountered significant difficulties in providing medical care for acute coronary circulation disorders due to the lengthening of the time from the onset of symptoms to the first visit to the doctor; as a result, a third of patients did not have the opportunity to timely conduct myocardial revascularization. Primary STEMI outcomes, including in-hospital death, cardiogenic shock, sustained ventricular tachycardia, or fibrillation, were also significantly worse in these patients [9], [10].

Percutaneous coronary interventions (PCIs) are a common procedure in modern cardiology practice. In total, more than 5 million PCIs have been performed worldwide. One of the rare but most serious complications of PCI (stenting, coronary artery bypass surgery [CABG], coronary angioplasty, etc.) is stent thrombosis (about 1–4% of all cases), which can lead to recurrent myocardial infarction and death of the patient [11], [12], [13]. Stent thrombosis can occur early (within 30 days after intervention), late (within a year), or very late (more than 1 year after stent implantation) [14].

It is well known that one of the most common complications of COVID-19 is venous thromboembolism [15]. Recently, studies have been conducted to determine the relationship between previous coronavirus infection and arterial thrombosis [16]. Epidemiological studies show that stent thrombosis has become significantly more common during the COVID-19 pandemic, rising to 21% of stent cases. However, a limitation of such studies is the small number of study groups of patients, and data on the prognostic impact of the previous myocardial revascularization in patients with SARS-CoV-2 infections on the course of coronary artery disease (CAD) remain very scarce to date [17], [18]. There is still insufficient data on the prevalence, clinical course, and prognosis of CAD in patients with prior revascularization who have had a coronavirus infection.

The aim of our study is to analyze scientific information on the risks of stent thrombosis in patients who underwent COVID-19.

Methods

A search was made for scientific publications in evidence-based medicine databases and web resources: PubMed, MEDLINE, UpToDate, TripDatabase, ResearchGate, and Google Scholar. Inclusion criteria were: (1) Observational studies or case series involving patients with a confirmed diagnosis of COVID-19 and myocardial infarction requiring myocardial revascularization; (2) the division of the population into survivors and non-survivors; and (3) data on the presence of the previous myocardial revascularization. Exclusion criteria: Case description and editorials/bulletins. Ethical approval and informed consent were not required because patients were not included in the study directly. The keywords for the search: “COVID-19”, “myocardial revascularization” AND “COVID-19”, “CABG”, “stent thrombosis,” AND “COVID-19”. All the articles selected for further analysis, 49 sources were considered that met the inclusion criteria and excluded duplication or repetition of information.

Results and Discussion

Influence of coronavirus infection on the course of coronary artery disease (pathogenesis and epidemiology)

A new enveloped RNA betacoronavirus causes SARS-CoV-2. Seven species of these beta coronaviruses cause infections in humans, four of which manifest as mild flu-like symptoms, and the remaining three lead to potentially fatal illnesses (Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome, and COVID-19). The respiratory organs are the main target for SARS-CoV-2, but there are also ways to damage the cardiovascular system [19], [20].

A high incidence of thromboembolic and hemorrhagic events has been reported in critically ill patients with acute respiratory distress syndrome at COVID-19 [21]. COVID-19 can lead to disruption of the coagulation cascade with an imbalance in platelet function and regulatory mechanisms of blood clotting and fibrinolysis. Clinical manifestations range from elevated laboratory markers and subclinical microthrombi to thromboembolic events, bleeding, and disseminated intravascular coagulation. After the inflammatory trigger, the activation mechanism of the coagulation cascade in COVID-19 is the tissue factor pathway, which induces endotoxin and tumor necrosis factor-mediated interleukin production and platelet activation. The subsequent massive infiltration by activated platelets can cause inflammatory infiltrates in the endothelial space, as well as thrombocytopenia [22].

The following are the general mechanisms involved in cardiovascular complications of COVID-19:

- There is direct damage to the myocardium. SARS-CoV-2 enters human cells by binding to angiotensin-converting enzyme 2 (ACE2), a membrane-bound aminopeptidase that is highly expressed in the heart and lungs [23]. ACE2 plays an important role in the...
neurohormonal regulation of the cardiovascular system both in a healthy person and in cases of various diseases. Binding of SARS-CoV-2 to ACE2 may lead to alteration of ACE2 signaling pathways resulting in acute myocardial and lung injury [24], [25].

- Systemic inflammation characterized by an acute systemic inflammatory response and cytokine storm can lead to multiple organs failure [26]. Studies have shown that patients with severe/critical course of COVID-19 have a high level of pro-inflammatory cytokines in the blood [27], [28].

- There is also an imbalance in relation to the need and supply of oxygen to the myocardium. Increased cardiometabolic demand associated with systemic infection, combined with hypoxia caused by acute respiratory disease, can disrupt the relationship between myocardial oxygen demand and supply and lead to acute myocardial injury [26].

- Another formidable condition is plaque rupture and coronary thrombosis. Systemic inflammation, as well as increased pressure due to increased coronary blood flow, can accelerate plaque rupture, leading to acute myocardial infarction. The prothrombotic environment during systemic inflammation exacerbates the situation increasing the risks of thrombosis [29].

- Various antiviral drugs, corticosteroids, and other treatments used in the treatment of COVID-19 can also have a detrimental effect on the cardiovascular system [30].

- Electrolyte imbalance can occur in any critical systemic disease and cause arrhythmia, especially in patients with pre-existing cardiac disease. Of particular concern is hypokalemia in COVID-19 due to the interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system [31]. Hypokalemia increases vulnerability to various tachyarrhythmias. An analysis of scientific publications showed that the prevalence of CVDs among patients who died from COVID 19 was as follows: Acute heart disease (52%), hypertension (51%), arrhythmia (37%), heart failure (27%), ischemic heart disease (23%), and other CVDs (23%) (Figure 1) [32].

The results of the analysis of studies of complications from the cardiovascular system in patients with COVID-19 are shown in Figure 2. The most common complication of infection was the progression of hypertension, which was observed in 30% of patients [32].

**Biochemical manifestations of coronavirus disease 2019 (changes in laboratory tests)**

The severe course of coronavirus infection is characterized by an increase in some biochemical parameters responsible for inflammatory reactions (ferritin and C-reactive protein), thrombus formation (D-dimer, fibrinogen, and prolongation of PT), and damage to myocardial muscle tissue (troponin and creatine phosphokinase). Serum ferritin levels are important in mediating the immune response that is elevated in severe cases of COVID-19, and elevated ferritin levels can trigger a cytokine storm with direct immunosuppressive and pro-inflammatory effects [33], [34], [35].

A study conducted by Spanish scientists among patients with a history of myocardial revascularization (stenting) who underwent COVID-19 described cases of stent thrombosis, which, according to their hypothesis, are associated with hypercoagulability. In laboratory studies, the following changes were observed: An increase in D-dimer (more than 500 mg/l in 100% of patients), an increase in C-reactive protein (more than 5 mg/l in 100% of patients), an increase in ferritin (more than 400 ng/ml in 75% of patients), lymphocytopenia (in 50% of patients), an increase in troponin in 100% of patients, and a decrease in glomerular filtration rate in 75% of patients [36].

Similar results were found in the other study by American scientists who examined 5700 patients with COVID-19. They observed the following changes in patient analyses: Lymphopenia (60% of patients),
increase in D-dimer (56%), ferritin (76%), C-reactive protein (79%), and lactate dehydrogenase (70%) [37].

**Prognostic risks about the course of coronary artery disease in patients with coronavirus infection who underwent myocardial revascularization**

The previous myocardial revascularization procedures significantly increase the risk of mortality in patients with coronavirus infection, according to a study conducted by Italian scientists in 2021. A history of revascularization has been present in approximately 2–5% of patients with COVID-19. Despite the relatively low prevalence of prior revascularization among patients with COVID-19, this event significantly increases the risk of short-term mortality, with odds ratios ranging from 1.8 to 12.8 [38]. This statement is supported by the results of several foreign studies, which demonstrated that clinical outcomes in patients with COVID-19 are closely related to comorbidities in patients [39]. Identification of risk factors associated with poor outcomes in patients with COVID-19 remains critical to identifying vulnerable populations [40]. This is especially actual for elderly patients with pre-existing CVD and a history of revascularization, who need proper treatment, prevention, and close monitoring in case of infection [41]. Such monitoring should be carried out based on the creation of specialized multicenter registries of patients with CAD with a history of interventions who have undergone COVID-19 [42], [43].

Table 1 presents data from studies to assess the risk of stent thrombosis after COVID-19. A significant limitation of the present study is the paucity of such prior publications. Data from a systematic review that included 17 cases of stent thrombosis in men aged 65 years after COVID-19 showed that more than 85% of them were hospitalized for recurrent myocardial infarction. Half of the patients had a very late type of thrombosis. The main localization of the thrombus was the left anterior descending (LAD) artery, 30% of patients had thrombosis of the right coronary artery, and in one case, thrombosis of a double coronary stent was found. The mortality rate in this study exceeded 35%. Predisposing factors for thrombosis were the presence of concomitant diabetes mellitus, chronic kidney disease, and multiple atherosclerotic vascular lesions. The presence of a stent in a coronary artery is considered by the authors as a local stasis factor contributing to thrombosis [44].

Similar results were obtained in a study including 50 STEMI patients hospitalized for primary PCI at the peak of the COVID-19 outbreak in Italy. At admission, the test for COVID-19 was positive in 24 patients. The patients with COVID-19 had significantly higher incidence of myocardial dysfunction (ejection fraction <30% in 45.8% vs. 19.2%). All patients underwent emergency angiography and PCI. Despite a higher incidence of persistent stent thrombosis in the COVID-19 group (47.6% vs. 11.5%), the outcome of PCI was similar in both study groups. In-hospital mortality was 41.7% and 3.8% in patients who tested positive for COVID-19.

Table 1: Comparative characteristics of the studies included the patients with stent thrombosis associated with coronavirus disease 2019

<table>
<thead>
<tr>
<th>Publication, design of study</th>
<th>Country</th>
<th>Patients</th>
<th>Type of MI</th>
<th>Comorbidities</th>
<th>Types of stent thrombosis</th>
<th>Localization of stent thrombosis</th>
<th>Mortality rate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sierra et al., 2022, Systematic review</td>
<td>Worldwide</td>
<td>17 male patients with stent thrombosis after COVID-19 in mean age 65 years</td>
<td>STEMI 82.4% NSTEMI 17.6%</td>
<td>DM 41.2%, CKD 11.8%, HTN 52.9%</td>
<td>Acute 23.5%, subacute 23.5%, late 5.9%, very late 47.1%</td>
<td>LAD&gt;50%, RCA</td>
<td>35.3%</td>
<td>ARDS, multi-organ failure</td>
</tr>
<tr>
<td>Pellegrini D. et al., 2021, Observational study</td>
<td>Italy</td>
<td>50 patients, 24 of them were COVID-19 patients in mean age 69.6 years, 83% male</td>
<td>STEMI 100%</td>
<td>HTN 70.8%, DM 41.7%, stroke 8.3%, PAD 16.7%, previous MI 55%, RF 20.8%</td>
<td>Acute 100%</td>
<td>LAD 61.9%, RCA 14.3%, Lcx 9.5%</td>
<td>41.7%</td>
<td>ARDS 16.7%, multi-organ failure, Cardiac arrest, cardiogenic shock 4.2%, DIC 4.2%, stroke 12.5%, Pulmonary embolism 4.2, bleeding 20.0%, ARF 20.5%</td>
</tr>
<tr>
<td>Rodriguez-Leor O. et al., 2021, Cohort study based on nationwide registry</td>
<td>Spain</td>
<td>1010 STEMI patients, 91 had COVID-19 (9.0%)</td>
<td>STEMI 100%</td>
<td>N/A</td>
<td>Acute 100%</td>
<td>N/A</td>
<td>23.1% vs. 5.7% in patients without COVID-19</td>
<td>Stent thrombosis (3.3% vs. 0.8%, P = 0.020) and cardiogenic shock development after PCI</td>
</tr>
<tr>
<td>Choudry F. et al., 2020, Single-center, observational study</td>
<td>UK</td>
<td>115 patients with IM, 39 of them with COVID-19 in mean age 61.4 years, 84.6% male. 4 (10.3%) had a stent thrombosis</td>
<td>STEMI 100%</td>
<td>HTN 71.8%, DM 46.2%, smoking history 61.6%, previous MI 15.4%, previous PCI 23.1%</td>
<td>Acute 100%</td>
<td>LAD 100%</td>
<td>17.9% vs. 6.5% in patients without COVID-19</td>
<td>COVID-19, Cardiac arrest, cardiogenic shock, acute heart failure</td>
</tr>
<tr>
<td>Prieto-Lobato A. et al., 2020, Clinical case series</td>
<td>Spain</td>
<td>4 male patients in mean age 72.7 years</td>
<td>STEMI 50% NSTEMI 50%</td>
<td>HTN 75%, DM 50%, LVD 75%, CKD 50%, PAD 25%</td>
<td>Acute 25%, very late type 75%</td>
<td>LAD 50% Lcx 25% RCA 25%</td>
<td>0%</td>
<td>Acute heart failure 25%, chronic heart failure 25%</td>
</tr>
<tr>
<td>Hamada A. et al., 2020, Retrospective multicenter, medical chart review</td>
<td>Israel, Lithuania, Spain</td>
<td>19 patients with primary PCI. Stent thrombosis occurred in 4 patients (21%)</td>
<td>STEMI 100%</td>
<td>HTN 84%, DM 11%, previous PCI 11%, CKD 94%, COPD 11%, PAD 11%</td>
<td>Acute 100%</td>
<td>N/A</td>
<td>26%</td>
<td>ARDS 37%, Septic shock 11%</td>
</tr>
</tbody>
</table>

and negative for COVID-19, respectively. Respiratory failure was the leading cause of death (80%) in the COVID-19 patient group [45].

In a study by Rodriguez-Leor et al., the increase in in-hospital mortality due to stent thrombosis in patients with COVID-19 increased to 23.1% compared to 5.7% in patients without coronavirus infection. The intervention was significantly more often accompanied by the development of cardiogenic shock (9.9 and 0.9%, respectively) [17]. When comparing mortality rates in the study groups, we must certainly take into account the fact that coronavirus infection in itself carries a high threat to life. COVID-19, by triggering the inflammatory process, leads to the creation of prothrombotic conditions and an increased risk of stent thrombosis.

In another study (Choudry F, 2020), among patients admitted to the hospital for STEMI with confirmed coronavirus infection, mortality rates were significantly higher than in the group without COVID-19, although they did not have a statistically significant difference (p = 0.1). All cases of stent thrombosis were acute and localized in the LAD artery. In the group of infected patients, myocardial damage with a decrease in the left ventricular function was more pronounced than in the comparison group. COVID-positive patients more often had diabetes, hypertension, and changes in blood analysis presented a systemic inflammatory response (lymphopenia, elevated D-dimers, and C-reactive protein levels) compared with COVID-19-negative patients [46].

The study by Prieto-Lobato A, 2020 included four asymptomatic male patients with coronavirus infection. There were no deaths in this case series. A limitation of this study was the very small number of patients, one of whom was 49 years of age. Half of the patients had non-ST elevation myocardial infarction [36].

In a four-country, multicenter study included 19 STEMI patients with severe coronavirus infection, the mortality rate reached 26%. All cases of stent thrombosis were acute. The main cause of death was a complication from COVID-19 [18].

The results of our study indicate that coronavirus infection has contributed to the change in the course of myocardial infarction in patients undergoing myocardial revascularization. The incidence of stent thrombosis has a positive correlation with the severity of the coronavirus infection. At the same time, we should understand that both the revascularization procedure and COVID-19 itself significantly increase the risks of adverse outcomes. In addition, in the context of the coronavirus pandemic, patients’ access to cardiac surgery was very difficult, and thrombolysis was preferred among revascularization methods to protect medical staff from prolonged contact with infected patients [18].

There is still very little data on the prevalence and impact of the previous stenting on the severity of the condition in patients with coronavirus infection, which significantly limits research in this area. All of the studies that we analyzed are highly heterogeneous and include a small number of patients. However, these data suggest a poorer prognosis and higher risk of mortality in patients with COVID-19-related myocardial revascularization.

The clinical outcome, taking into account the advanced age of patients, included in the studies we analyzed, largely depends on the burden of comorbidities, which include, first of all, hypertension (52.9–84.0%), diabetes mellitus (up to 50%) and chronic kidney disease. Understanding the risk factors for stent thrombosis are important to identify individuals at risk for adverse outcomes, especially patients with pre-existing CVD, among patients with coronavirus infection [38]. Such patients require careful monitoring, priority treatment, and prevention. The most vulnerable group, in this case, is elderly patients with the previous myocardial revascularization.

Conclusion

The COVID-19 pandemic has affected millions of patients and poses a major health threat worldwide. In a large number of patients with COVID-19, a pre-existing CVD progresses or develops new heart disease. One of the most vulnerable groups is elderly patients who have undergone myocardial revascularization after myocardial infarction in the past and have concomitant diseases. An analysis of scientific publications has shown that further larger-scale clinical studies are needed to confirm the hypothesis about the negative impact of coronavirus infection on stent thrombosis in patients who have undergone COVID-19.

References


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