


# Management of acute coronary syndrome in the context of coronavirus disease 2019

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## Abstract

Coronavirus disease 2019 (COVID-19) is still developing worldwide. The prognosis of the disease will become worse and mortality will be even higher when it is combined with cardiovascular disease. Furthermore, COVID-19 is highly infectious and requires strict isolation measures. For acute coronary syndromes (ACS), a common cardiovascular disease, infection may aggravate the occurrence and development of ACS, making the management of more difficult. It will be an enormous challenge for clinical practice to deal with ACS in this setting of COVID-19.

Aim to reduce the mortality of ACS patients during the epidemic of COVID-19 by standardizing procedures as much as possible.

Pubmed and other relevant databases were searched to retrieve articles on COVID-19 and articles on ACS management strategies during previous influenza epidemics. The data was described and synthesized to summarize the diagnosis and management strategy of ACS, the preparation of catheter laboratory, and the protection of the medical staff in the context of COVID-19. Ethical approval is not required in this study, because it is a review with no recourse to patient identifiable information.

Standardized diagnosis and treatment advice can help reduce the mortality of COVID-19 patients with ACS. In the absence of contraindications, the third generation of thrombolytic drugs should be the first choice for thrombolytic treatment in the isolation ward. For patients who have to receive PCI, this article provides detailed protective measures to avoid nosocomial infection.

**Abbreviations:** ACE 2 = angiotensin converting enzyme 2, ACS = acute coronary syndromes, COVID-19 = Coronavirus disease 2019, PCI = percutaneous coronary intervention, SARS-CoV = Severe Acute Respiratory Syndrome Coronavirus, STEMI = ST-segment elevation myocardial infarction.

**Keywords:** acute coronary syndromes, coronary artery disease, coronavirus disease 2019, percutaneous coronary intervention, SARS-CoV-2

## 1. Introduction

Since December 2019, an outbreak of pneumonia caused by a novel coronavirus has spread rapidly around the world. Full-length genome sequencing results showed that the consistency of novel coronavirus genome share 79.6% sequence identity to

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV),<sup>[1]</sup> which is considered to be a coronavirus related to SARS-CoV called SARS-CoV-2, and was subsequently named COVID-19 by World Health Organization. Notably, it was confirmed that SARS-CoV-2 infects alveoli of human body through the binding domain of angiotensin converting enzyme 2 (ACE 2) receptor.<sup>[1,2]</sup> However, the ACE 2 is widely expressed in the cardiovascular system, causing acute myocardial injury.<sup>[3]</sup> Emerging evidence has shown that the SARS-CoV-2 infection causes not only the typical respiratory symptoms but also the cardiovascular symptoms, including chest tightness, palpitations, chest pain, and other manifestations, especially serious myocardial injury, thus aggravating the condition and affecting the prognosis.<sup>[4-7]</sup> A study by Chen et al showed that 2 (2%) were hospitalized for chest pain in 99 patients confirmed COVID-19.<sup>[4]</sup> In a retrospective study of 137 patients confirmed COVID-19 in Hubei province of China, 10 (7.3%) of them presented with the first symptom of palpitations.<sup>[7]</sup> Moreover, according to research of Huang et al reported that 6 (15%) of the first group of patients with pneumonia had heart disease, 23% in intensive care unit, and 11% in non-intensive care unit.<sup>[5]</sup> A study by Zhou et al indicated that 15 (8%) of 191 patients with pneumonia had heart disease, 13 (24%) were non-survivor, and 2 (1%) were survivors.<sup>[6]</sup> All the data support the evidence that basic heart disease is associated with high-risk patients with COVID-19, and myocardial injury is a high-risk factor for death.

Majority of cardiologists have focused on myocarditis or myocardial injury caused by SARS-CoV-2 infection. However,

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The datasets generated during and/or analyzed during the current study are publicly available.

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recent case series indicate similar rates of myocardial infarction and non-coronary myocardial injury in patients with confirmed Covid-19 who had ST-segment elevation on electrocardiography.<sup>[8]</sup> Despite the lack of extensive data both COVID-19 and ACS, it can also be used for reference from past related diseases. A case-control study of 134 patients admitted for acute myocardial infarction during the 2009 H1N1 influenza pandemic found that 13 patients (9.7%) developed influenza-like illness within a month, and respiratory tract infections occurred in 31% of patients between 8 and 14 days before myocardial infarction.<sup>[9]</sup> Compared with the control group, the risk of myocardial infarction events in patients with influenza was 3.17 times higher.<sup>[9]</sup>

Inflammation drives many aspects of the ACS both locally and systemically.<sup>[10]</sup> An increase in the short-term risk of myocardial infarction has been described in association with influenza, pneumonia.<sup>[11]</sup> For type 1 myocardial infarction, which is associated with atherosclerotic plaques and plaque formation requires the involvement of a large number of cytokines, such as interleukin-1, 6, 8 and tumor necrosis factor- $\alpha$ .<sup>[10]</sup> Acute infection can activate the inflammatory activity of atherosclerotic plaque, leading to further plaque development. Meanwhile, the stress of infection can up-regulate the expression of human proteins, such as matrix metalloproteinases and polypeptides, leading to unstable plaques. For type 2 myocardial infarction,<sup>[12]</sup> the infection also increases the risk of the disease, which may be due to the increased demand for energy and oxygen in peripheral tissues and organs caused by inflammation and fever. The fever and infection lead to an increase in heart rate, a relatively short diastolic ventricle, and a decrease in coronary blood supply. For patients with existing vascular plaques, the occurrence of myocardial infarction may be related to plaque progression and the vasoconstriction caused by cytokines. Moreover, the pneumonia caused by infection leads to imbalance of pulmonary perfusion ventilation and decrease of blood oxygen saturation. In view of the fact that patients with COVID-19 combined with critical cardiovascular disease can significantly increase the mortality of patients, it is particularly important to identify and deal with it in time. In the absence of a unified and comprehensive response, this article reviews the diagnosis, management and protection of ACS patients with COVID-19. As this is a review with no recourse to patient identifiable information, ethical approval is not required.

## 2. Identification of ACS under SARS-CoV-2 infection

A series of recently published studies found varying degrees of myocardial injury in patients with COVID-19, which is defined by the presence of cardiac troponin values above the 99th percentile of the upper reference limit. In both mild and severe cases, the serum levels of myocardial necrosis markers were increased to different degrees, but the risk of myocardial injury was higher in the severe cases (about 22.2%–31%)<sup>[5,13,14]</sup> and the risk of myocardial injury was lower in the mild cases (about 2%–4%).<sup>[5,14]</sup> The risk of myocardial injury in non-survivors was significantly higher than that in survivor (46% vs 1%,  $P < .0001$ ).<sup>[6]</sup>

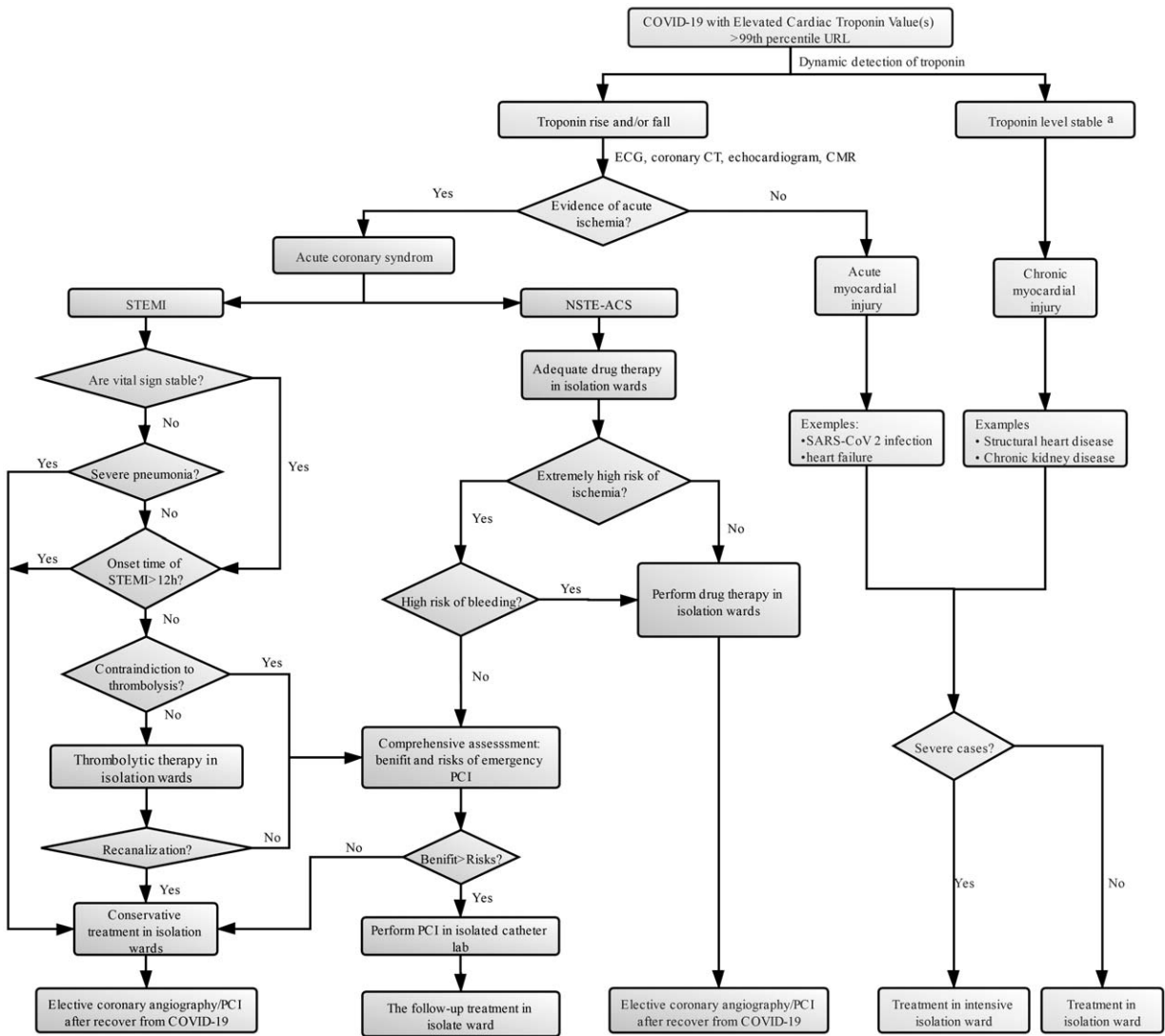
A study from autopsy and histopathological biopsy indicated degeneration and necrosis of cardiomyocytes, and a few monocytes, lymphocytes and/or neutrophils were seen in the interstitium, partial vascular endothelial exfoliation, intimal

inflammation and thrombosis.<sup>[15]</sup> A study by Huang et al exhibited that the cytokine levels of patients admitted to intensive care unit were higher than that of patients admitted to non-intensive care unit,<sup>[5]</sup> and the role of cytokines in plaque formation and rupture was also mentioned many times.<sup>[10]</sup> Furthermore, a case report showed that a patient without history of coronary artery disease developed to complex ACS 2 weeks after diagnosis of Severe Acute Respiratory Syndrome.<sup>[16]</sup> This suggests that acute inflammation and cytokine storms of SARS-CoV-2 infection may play a role in coronary plaque instability. However, the clinical manifestations of ACS patients with COVID-19 may not be accurately identified and found, leading to insufficient diagnosis, especially in patients with severe or critical diseases. Although the fourth Universal Definition of Myocardial Infarction specifically identifies “troponin elevation” as a new concept distinct from myocardial infarction,<sup>[17]</sup> the diagnosis of ACS patients with COVID-19 should be combined with clinical symptoms, physical examination, electrocardiogram and necessary coronary imaging evidence. Patients with atypical symptoms suspected of ACS should be fully inquired about their medical history, which includes predisposing factors, concomitant symptoms, family history and epidemiological history related to other patients or regions with COVID-19. The temperature, electrocardiogram, myocardial enzyme, chest computed tomography and coronary angiograms were asked to examine in time. Although atypical symptoms and possible elevation of cardiac biomarkers are difficult to diagnose ACS in the context of SARS-CoV-2 infection, typical electrocardiogram change and imaging findings of coronary artery stenosis are still necessary for the diagnosis of myocardial infarction.<sup>[18,19]</sup> It is recommended to increase the number of dynamic electrocardiogram monitoring or routine electrocardiogram examination, as well as the monitoring of myocardial enzymes and inflammatory factors. Coronary angiography is performed when necessary to identify the presence of ACS.<sup>[20]</sup> Due to acute myocardial injury may cause by myocardial infarction or SARS-CoV-2 infection. Therefore, the differential diagnosis should be paid attention to. In addition, patients with chronic myocardial injury are more likely to develop into severe cases, which should be focused on and treated actively.

## 3. Management strategies of ACS in the setting of COVID-19

Acute myocardial infarction is urgent, fatal, and the optimal treatment window is short. In addition, respiratory system infection easily leads to respiratory and circulatory failure, which requires active treatment. The management process is proposed for reference to improve the treatment efficiency and reduce the mortality under the background of COVID-19.

Patients with ST-segment elevation myocardial infarction (STEMI) who are suspected or diagnosed with covid-19, if patients with unstable vital signs, which were caused by severe pneumonia should be transferred to the isolation ward for conservative therapy. For patients with unstable vital signs were caused by myocardial infarction or stable vital signs, the onset time of STEMI should be evaluated whether it is more than 12 hours. If the onset time of clinical presentations of myocardial infarction is within 12 hours and without contraindication, thrombolysis therapy in the isolation ward is preferred and the third generation thrombolysis is recommended. After successful thrombolysis, treatment is continued in the isolation ward. After



**Figure 1.** Flow chart of diagnosis and treatment procedures of COVID-19 combined with ACS. CMR = cardiac magnetic resonance, ECG = electrocardiogram, NSTEMI-ACS = Non-ST-segment elevation-acute coronary syndrome, PCI = Percutaneous coronary intervention, STEMI = ST-segment elevation Myocardial Infarction, URL = upper reference limit. <sup>a</sup>Stable denotes  $\leq 20\%$  variation of troponin values in the appropriate clinical context.

the patient has recovered from COVID-19 pneumonia and test of nucleic acid is twice negative, elective percutaneous coronary intervention (PCI) should be considered.<sup>[21]</sup> In the case of contraindications or thrombolytic failure, the risks and benefits of PCI should be assessed. If the benefits outweigh the risks, emergency PCI should be performed in the designated catheter laboratory, if not conservative treatment in the isolation ward.<sup>[22,23]</sup>

Drug therapy should be recommended for non-ST-segment elevation acute coronary syndrome patients with suspected or confirmed COVID-19. If the drug therapy is difficult to stabilize the state of an illness, the risk of ischemia and hemorrhage should be stratified on the basis of adequate drug treatment. If the risk of ischemia is high and the risk of bleeding is not high for patients with non-ST-segment elevation myocardial infarction, emergency PCI should be performed in the designated catheter laboratory after assessing the benefit that meets the prevention and control requirements. Patients undergoing PCI should receive follow-up therapy in the isolation ward of designated hospital. If the patient

does not meet these conditions, the conservative therapy should be performed in the isolation ward. Meanwhile, the cardiologist should provide management advice.<sup>[21-23]</sup> The diagnosis and treatment procedures of COVID-19 patients combined with ACS are shown (Fig. 1).

Even if there is a standardized diagnosis and treatment process, current evidence also suggests that COVID-19 patients with ACS are at a high mortality. The reasons are as following:

1. A series of studies have confirmed thrombocytopenia, elevated level of D-dimer and prolonged prothrombin time in patients with COVID-19.<sup>[4,14,24]</sup>
2. Autopsy also confirmed significant hemorrhagic necrosis in the lung, and histopathological evidence showed major hemorrhage in the alveolar cavity.<sup>[25]</sup>
3. A retrospective cohort study also showed that the D-dimer more than 1  $\mu\text{g/L}$  at admission was associated with increased in-hospital mortality.<sup>[6]</sup>

4. Another study involving 36,182 patients with non-ST-segment elevation acute coronary syndrome denoted that increased risk of death and bleeding in hospital was directly related to the severity of thrombocytopenia.<sup>[26]</sup>

For the above reasons, we consider that the COVID-19 patients with ACS are at high risk of bleeding, which further increases the mortality. Therefore, thrombolysis, PCI, and dual antiplatelet therapy should be performed precisely and individualize.

In addition, ticagrelor should be recommended for COVID-19 coexistence with ACS to improve survival, no matter PCI or drug therapy is given.<sup>[27]</sup> Due to the pleiotropic effects of ticagrelor, it could not only prevent disseminated intravascular coagulation in patients with COVID-19 inhibiting platelet-neutrophil aggregation, neutrophil extracellular traps release,<sup>[28]</sup> and vascular leakage, but also reduce thromboinflammatory markers in patients with pneumonia.<sup>[29]</sup> Meanwhile ticagrelor monotherapy in ACS patients with high bleeding risk was supported by randomized controlled trials.<sup>[30]</sup> In brief, ticagrelor is a good choice in reducing inflammation, preventing disseminated intravascular coagulation and antiplatelet therapy, especially for patients with COVID-19 complicated with ACS.

#### 4. Preparations of the catheter laboratory and protections of the participants

For requiring emergency PCI patients with COVID-19, special passageway and designated catheter laboratory which have been disinfected regularly should be prepared. If possible, the negative pressure catheter laboratory is preferred, otherwise, the conventional catheter laboratory can also be considered. However, the central air conditioner must be turned off in conventional catheter laboratory, including laminar flow and ventilation. With the aim of avoiding infection, instruments used in PCI, such as digital subtraction angiography, need to be protected with a disposable sterile transparent cover, and the catheter bed should be covered with the double disposable sterile sheets. Moreover, the disposable operation kit, disposable surgical instruments and consumables cannot be opened until the patient has arrived and be disinfected. As for trash cans, double medical garbage bags should be used. During the operation of PCI, the door of designated catheter laboratory should hang a warning sign which says “infection operation, unrelated personnel are not allowed to enter”. After the operation, the catheter laboratory should be sterilized with 3% hydrogen peroxide. In addition, instruments, floors, and walls should be wiped with an effective chlorine-containing disinfectant solution of appropriate concentrations (2000–5000 mg/L). Ventilation should be carried out to prevent chlorine poisoning after using chlorine-containing disinfectant. Then, medical waste should be disposed in accordance with relevant regulations and marked with a special label named “COVID-19”. Finally, the catheter laboratory should be ultraviolet disinfection.

Protections of the participants are also very important. The patient and the transporters arrive at the designated catheter laboratory through a special passageway under the condition of secondary or above protective measures. Meanwhile, according to the respiratory symptoms and blood oxygen saturation, the patient shall receive appropriate oxygen therapies and protective measures. During the PCI, the number of surgical personnel should be reduced as far as possible. In addition, medical personnel should comply with the tertiary protection standard.

Frequent access to the catheter laboratory should be avoided. When the operation is finished, the surgical staff shall remove the outermost layer of the operating gowns and transfer the patient to a separate isolation ward under the condition of secondary or above protective measures. The surgical personnel can leave the catheter laboratory after changing the clothes in accordance with the relevant regulations.<sup>[22,23]</sup>

#### 5. Conclusions

The diagnosis of ACS is difficult in the setting of COVID 19, and SARS-CoV-2 infection may cause complex ACS. The disease will be severe and the mortality will be high in this case. Therefore, patients with COVID 19 with suspected ACS should be diagnosed in a timely and personalized approach fully consider the impact of SARS-CoV-2 on the cardiovascular system; adjust the treatment strategy and drug management to avoid a high incidence of severe cases and deaths. In the absence of contraindications, the third generation of thrombolytic drugs should be the first choice for thrombolytic treatment in the isolation ward. For patients who have to receive PCI, this article provides detailed protective measures to avoid nosocomial infection. In addition, due to the increased risk of bleeding, postoperative antiplatelet therapy should be made on the basis of personalized evaluation, and the use of ticagrelor should be highly valued. In the future, the long-term impact of the SARS-CoV-2 on patients with ACS should be pay attention to.

#### Author contributions

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