

COVID-19 Delays Presentation and Management of Acute Coronary Syndrome

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The COVID-19 pandemic started at the end of 2019 and remains carrying a health threat and significant economic consequences. Over the last two years, COVID-19 has been the main Public Health issue, and has impacted regular healthcare systems, with significant build-up of waiting lists and delay in optimum management of other serious medical conditions including heart diseases and cancer.

For cardiovascular diseases, COVID-19 pandemic had impacted the incidence and treatment of acute coronary syndromes (ACS). A consistent reduction in the rate of ACS presentation to hospitals has been recorded all over the world. Also, a considerable delay in the treatment of patients with ST elevation myocardial infarction (STEMI), compared to the pre-COVID-19 era, has been reported. This is mostly explained by limited access to emergency medical services and the lack of effective clinical management strategies with medical personnel retrained to manage COVID-19 cases. Several studies have shown that during COVID-19 pandemic the time from the onset of symptoms to first medical contact and primary percutaneous coronary intervention (PCI) prolonged significantly [1]. This may be related to the following issues:

1. *Clinical mis-diagnosis:* In the absence of conventional STEMI chest pain, respiratory symptoms may be initially attributed to COVID-19, hence missing the diagnosis of myocardial infarction and delaying its treatment. Also, COVID-19 itself carries a significant short-term risk of myocardial injury and infarction, particularly in patients with existing coronary artery disease and/or pro-inflammatory cardiovascular risk factors (such as diabetes mellitus, hypertension, and obesity [2];

2. *Patients fear to present to emergency department (ED):* The fear of COVID-19 contagion has refrained many patients with unclear symptoms of myocardial infarction to seek hospital care, which resulted in late presentation and treatment of STEMI. This may also lead to the increase in long-term consequences of myocardial infarction, including post-ischemic heart failure, and death [3];

3. *Organization:* While interventional procedures may be more complex in COVID-19 compared to non-COVID patients [1], there have been controversial international opinion on the exact indications for treatment of STEMI.

The above issues led to higher mortality and in-hospital complications in patients with STEMI during the COVID-19 pandemic, as shown in our study [4] when we compared STEMI management and related complications during and before COVID-19 period. We have shown that the number of primary PCI during COVID-19 (year 2020) was reduced by 25.7% compared with previous year, with a longer time from first medical contact to intervention (125.0 ± 53.6 vs. 52.6 ± 22.8 min, $p = 0.001$). Moreover, in-hospital mortality was higher (7.4 vs. 4.6%, $p = 0.036$), as was the incidence of re-infarction (12.2 vs. 7.7%, $p = 0.041$), the need for revascularization (15.9 vs. 10.7%, $p = 0.046$) and length of hospitalization (6.85 ± 4.22 vs. 3.5 ± 2.3 day, $p = 0.0025$) during COVID-19. Whether the adverse events we reported are directly related to COVID is not known. Another study [5] has shown even worse complications. Among 748 COVID-19 patients from 10 centers, 19% had major adverse cardiovascular events: 7% cardiovascular death, 2% acute myocarditis, 4% sustained-supraventricular or ventricular arrhythmias, 2% cardiocirculatory arrest, 1% acute coronary

syndromes, 5% acute heart failure, and 5% pulmonary embolisms.

We believe that the explanation for these results could be multifactorial. Management of ACS during COVID-19 pandemic has been much debated, especially during the first year of the pandemic, when there were many clinical uncertainties and no guidelines. The delay in seeking medical advice during the lockdowns, the time needed for testing and excluding COVID-19 infection, and the fear of SARS-CoV2 infection overwhelmed the health service. The obvious consequence was controversial reperfusion strategies for patients with STEMI. The Chinese Cardiac Society and the Canadian Association of Interventional Cardiology recommended thrombolysis as the preferred reperfusion strategy for patients with STEMI [6,7]. In contrast, the American College of Cardiology (ACC) together with the Society for Cardiovascular Angiography and Interventions (SCAI) and the European Society of Cardiology (ESC) suggested the use of primary PCI, whenever possible [8,9]. Moreover, differential diagnosis between non-COVID ACS and COVID-19 induced myocardial injury, was and remains challenging due to the controversial use of diagnostic tools in these patients [10,11].

A recent meta-analysis [1] has strengthened our findings and showed that COVID-19 patients had lower rate of stent implantation, which may be associated with a higher rate of myocardial infarction with non-obstructive coronary artery disease (MINOCA), hence explaining the dramatically higher mortality in STEMI patients who presented with COVID-19. Longer ischemia time, higher thrombosis burden, and increased rate of adverse cardiovascular events, including cardiogenic shock were also identified as contributors [12,13] to the high mortality. Compared to non-COVID-19, patients with COVID also had significant delays between symptom onset and first medical contact and treatment and rate of stent implantation. They also have higher thrombosis grade, resulting in frequent use of thrombus aspiration and Gp2b3a inhibitors. The meta-analysis also showed higher ICU admission, longer hospital stays, and decreased TIMI flow post-procedure in COVID-19 patients.

In our study all patients were treated with primary PCI without a need for fibrinolytic therapy, even for highly suspected COVID-19 patients. Despite that, the frequency of primary PCI treatment was significantly less and the intervention was delayed during COVID-19 period. This change in practice had significant complications including re-infarction, need for coronary artery bypass surgery, cerebrovascular events and increased in-hospital mortality but the prevalence of new heart failure and bleeding was not affected. In keeping with our study findings, other authors have shown that [14,15] STEMI patients with concomitant COVID-19 had higher intensive care unit (ICU) admission rates and longer lengths of stay.

The reduction in primary PCI during the pandemic is now well

reported worldwide. Kwok et al. reported a clear reduction in primary PCI procedures in the United Kingdom during the lockdown period [16]. Xiang et al. reported a reduction of 62% less primary PCI in China [17], and 73 centers reported 40% reduction in primary PCI in Spain [18]. The Italian Society of Interventional Cardiology (GISE) also reported a decrease in coronary angiography of 48.5% and 45.7% for PCI, during COVID-19 period [19].

Recognition of the above issues about diagnosis and management of ACS during the COVID-19 pandemic and critical analysis of various contributing factors has resulted in better awareness and hence more efficient clinical management planning. Recent data [20] showed that significant changes have occurred in the clinical characteristics, management strategies and outcomes of STEMI patients with COVID-19, mortality reduced by 25 % but still remains high for unvaccinated patients ($p=0.009$). Also, an increased use of invasive angiography for risk stratification and management in 2021 has been observed. A sub-group analysis based on the vaccination status of STEMI patients suggested good protection against severe respiratory illness with its need for intensive care management.

In addition to ACS management changes, evidence exists showing that COVID-19 may predispose to a prothrombotic state, particularly in STEMI patients [21-24]. SARS-CoV-2 causes a systemic inflammatory response, with endothelial and hemostatic activation involving platelets and the coagulation cascade [25]. Ge et al. hypothesized that the delays in STEMI treatment would prolong the time for opening infarct-related vessels which may be associated with higher thrombus burden [26]. Such pathology needs optimum use of the currently available and the development of novel technologies for optimum thrombus aspiration in such patients [27].

Finally, education of general population about early recognition of high-risk ACS symptoms and benefits of timely presentation to ED need to be emphasized [28]. Also, the use of telemedicine and/or telemonitoring in doubtful cases should allow close follow up of patients' symptoms and clinical developments without a need for hospital admission and potential exposure to additional risks.

Conclusions

Management of STEMI patients has significantly changed during the COVID-19 pandemic period, with less primary PCI performed and frequent delay in treatment. This led to longer hospital stay and short- and long-term complication, with consequently significant impact on healthcare systems. New technologies, education of patients and telemedicine should be used to optimize diagnosis and treatment in these patients.

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