Archives of the Balkan Medical Union
vol. 56, no. 1, pp. 88-93
March 2021

MINIREVIEW

CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC AND THE "PARADOX" OF ACUTE CORONARY SYNDROME HOSPITALIZATIONS

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Received 16 Dec 2020, Accepted 01 Febr 2021
https://doi.org/10.31688/ABMU.2021.56.1.11

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a disease affecting mainly the respiratory system, has become the major cause of a worldwide crisis, imposing a real challenge for the healthcare systems. The underlying pathological mechanisms of coronavirus disease 19 (COVID-19), such as increased inflammatory and immune responses, endothelial damage, prothrombotic status, were expected to increase the incidence of acute coronary syndromes (ACS), but observational studies so far indicate an important reduction in ACS admissions and treatment, possibly because of the fear of contagion, reorganization of medical structures and reduction of physical activity. Further work is needed to identify the factors responsible for this situation.

Keywords: COVID-19 pandemic, acute coronary syndrome, hospitalization, coronary intervention.

List of abbreviations:
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

Résumé

La pandémie de COVID-19 et le « paradoxe » des hospitalisations à cause du syndrome coronarien aigu

L'infection par le virus SARS-CoV-2 dans le syndrome respiratoire aigu sévère, une maladie qui affecte surtout le système respiratoire, est devenue la cause majeure d'une crise à l'échelle mondiale, constituant une réelle provocation pour les systèmes de soins de la santé. Les mécanismes pathologiques caractéristiques de SARS-CoV-2, comme les réponses inflammatoires immunes accrues, l'endommagement endothélial, la condition pro-thrombotique, étaient espérés d'augmenter l'incidence de syndromes coronariens aigus (SCA), mais les études observationnelles actuelles indiquent une réduction importante d'hospitalisations et de traitement, probablement à cause d'une peur de contagion, une réorganisation des structures médicales et une diminution de l'activité physique. Une recherche ultérieure s'impose afin d'identifier les facteurs en charge de cette situation.

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COVID-19 – Coronavirus Disease 2019
ACS – Acute Coronary Syndrome
UA – Unstable Angina
STEMI – ST Elevation Myocardial Infarction
NSTEMI – Non-ST Elevation Myocardial Infarction
AMI – Acute Myocardial Infarction
PCI – Percutaneous Coronary Interventions
CTnI – Cardiac Troponin I
CS – Cardiogenic Shock

Mots-clefs: Pandémie de COVID-19, syndrome coronarien aigu, hospitalisation, intervention coronarienne.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a disease affecting mainly the respiratory system, that has become the major cause of a worldwide crisis in 2019, imposing a real challenge for the healthcare systems.

Various measures, consisting in structure and medical personal reorganization and budget reallocations, were taken from governments to manage the overwhelming influx of patients diagnosed or suspected of coronavirus disease 2019 (COVID-19). Meanwhile, containment measures, regional and total national lockdowns were put to limit the spread of the virus, therefore, to reduce the infection rate of the population.

Acute coronary manifestations of COVID 19

The new coronavirus SARS-CoV-2 was identified as the cause of acute respiratory infection with various forms of clinical presentations, ranging from asymptomatic or mild ones to severe pneumonia and acute respiratory distress syndrome (ARDS). SARS-CoV-2 has also cardiovascular clinical manifestations, which are important because they can negatively influence the course of the disease. Many pathways of pathogenesis are now clarified, but others remain unclear. There are different supposed pathways which can explain the forms of acute coronary syndrome during COVID-19.

Increased inflammatory and immune responses, endothelial damage, microvascular dysfunction or thrombosis due to hypercoagulability, and stress cardiomyopathy are possible pathways of acute coronary syndrome. The existence of an inflammatory – cytokine storm can worsen the status of atherosclerotic plaques, inducing destabilization of the plaques and all the thrombotic events presenting with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)[1]. On the other side, inflammation promotes thrombosis, increasing the risk of thrombotic occlusion of arteries, including the coronary arteries. Patients with comorbidities such as diabetes, obesity and probably arterial hypertension may have pro-inflammatory states, which can promote the development of a more serious disease and less favorable outcomes[1].

Different studies assessing the venous and arterial thromboembolism in COVID-19 patients were conducted during this time. Case reports and case series of COVID-19 patients with thromboembolic coronary complications – acute coronary syndromes (acute myocardial infarction (AMI), coronary thrombosis, stent thrombosis – have been reported[2-6]. In April 2019, Lodigiani et al published their study about thromboembolism among patients recovered from COVID-19, and found an incidence of 4.4% of venous thromboembolism, 2.8% of pulmonary embolism, 2.5% of stroke and 1.1% of acute coronary syndrome[7].

Modin et al searched in nationwide registers all patients diagnosed in Danish hospitals with a positive test for COVID-19 infection up to July 16, 2020[8]. They have found 5119 patients diagnosed with COVID-10; from this group of patients, 44 patients have been admitted to the hospital with a diagnosis of first-ever ischemic stroke (44 pts), or first-ever AMI (17 pts) up to 180 days before COVID-19 diagnosis and until the end of available data. The incidence of AMI was approximately 5 times higher during the 14 days after COVID-19 diagnosis, as compared with the control interval[8]. The authors highlighted that these findings provide evidence that COVID-19 may increase the risk of ischemic cardiovascular events. Similar with other acute infections, the underlying mechanisms may include cytokine-mediated plaque destabilization and hypercoagulability[8].

In a recent article, Solano-Lopez et al studied all consecutive patients with AMI who underwent coronary angiography in a 30-day period corresponding chronologically with the COVID-19

outbreak[9]. In total, 187 patients were admitted with AMI, 111 with STEMI and 76 with NSTEMI. Of these, 32 (17%) were diagnosed with COVID-19. Total and cardiovascular mortality were also significantly higher in COVID-19 patients, respectively 25% versus 3.8% ($p < 0.001$) and 15.2% versus 1.8% ($p = 0.001$), and COVID-19 resulted as an independent predictor of in-hospital mortality.

Acute coronary syndrome, admissions, treatment and complications during COVID-19 pandemic

In the light of such clinical presentations, a higher overall incidence of ACS could be expected, yet "paradoxically" cardiologists from all over the world, especially from most affected regions, reported an important drop in the number of patients presented with ACS and related coronary procedures[10-11].

A survey among healthcare professionals conducted by the European Society of Cardiology revealed that fewer patients with heart attacks were admitted to hospitals. On average, the hospitalization rate decreased by 50% and the presentation to hospital was later than usual[10].

The European Association of Percutaneous Cardiovascular Interventions (EAPCI) conducted a survey on the impact of COVID-19 pandemic on interventional cardiology practice. Coronary angiography and percutaneous coronary interventions (PCI) for ACS have been reduced in various extents. The greatest reduction in activity was observed in patients with UA, and 27-31% of respondents stated that the activity was also reduced in STEMI patients[11].

Many studies were conducted to understand what happened with patients with ACS and particularly with AMI in the general population during the COVID-19 pandemic. One of the first publications in the field was that of De Rosa et al, published in April 2020[12], that studied AMI admissions in an Italian multicentre observational survey throughout one-week period during COVID-19 pandemics (319 pts) and compared with the same week in 2019 (618 pts). A reduction of 48.4% in AMI admissions was observed, respectively for STEMI 26.5% reduction and NSTEMI 65.1%. The decline in admissions was seen proportionally in Northern (COVID-19 epicenter), Central and Southern Italy. The STEMI mortality rate was increased in 2020, 13.7% versus 4.1%[12]. Also, an increase in other complications rate and in the time for symptom onset to coronary angiography was observed[12].

De Filippo et al, in a retrospective analysis of 15 hospitals in Northern Italy, found a significant reduction in ACS admissions per day[13]. During COVID-19 period, there were 13.3 compared with 18.9 admissions per day during the same period in 2019.

British investigators[14] demonstrated a significant delay from symptom onset to first medical contact during COVID-19 pandemic (227min (65-790) compared to pre-COVID-19 period 119min (27-203), $p=0.01$). Also, the cardiac troponin I (CTnI) level at admission was significantly higher during COVID-19 pandemic compared to pre-COVID-19 era.

Mafham et al found a substantial reduction in ACS weekly admissions of 40%, by the end of March 2020, which was partly reversed by the end of May 2020 in England[15]. PCI procedures declined for both STEMI (21%) and NSTEMI (37%) patients.

A survey conducted in 73 Spanish centres during a 10-day period of the peak of COVID-19 infections[16] observed an important reduction in the activity of interventional cardiology clinics (diagnostic procedures by 56%, PCI by 48%, structural interventions by 81% and PCI in STEMI 40% reduction).

Moreau et al reported a relative reduction of 73% of ACS admissions and 65% reduction for STEMI admissions compared to 2019[17]. A U-curve revealed a dramatic decline in ACS admissions with the beginning of lockdown and a relative return to normality one month later. Also, the median time from symptom onset to first medical contact was significantly higher in 2020 compared to 2018-2019 (600 versus 121 minutes)[17].

Recently, in a registry study, data from 21 centres participating in the ongoing French Cohort of Myocardial Infarction Evaluation (FRENCHIE) registry were collected[18]. Admissions for AMI decreased between the periods before and after lockdown, from 686 to 481 (30% decrease). Admissions for STEMI decreased from 331 to 252 (24%), and admissions for NSTEMI decreased from 355 to 229 (35%)[18].

In many countries a similar reduction was observed, regardless of the severity of COVID-19 pandemic. In Greece, a country that had low COVID-19 incidence during March-April 2020, but with strict social measures, a study showed an overall reduction of ACS admissions by 28.4% in 2020 compared to 2019[19]. The reduction of hospitalizations was 24.5% for STEMI, 26.5% for NSTEMI and 36.5% for UA.

Also, in USA a study conducted in 49 hospitals across six states with over 15,000 hospitalizations confirmed the reduction of AMI at a rate of 19% less cases per week during the early pandemic period[20]. The observed/expected (O/E) ratio for mortality

related to all AMI (STEMI and NSTEMI) was increased in the period of pandemic, OR 1.27 (95%CI 1.0 to 1.48).

A study from Northern California compared the weekly incidence rates of hospitalization for AMI (STEMI and NSTEMI) before and after March 4th, 2020, when the first death from COVID-19 was reported [21]. These data were also compared with data from the same period of time in 2019. The weekly rates of hospitalization decreased by about 48% during the COVID-19 period. This decrease occurred in patients with NSTEMI [incidence rate ratio 0.51 (95% CI 0.38-0.68)] and probably in patients with STEMI [incidence rate ratio 0.60 (95% CI 0.33-1.08)]. Compared with 2019, the incidence of hospitalization for acute MI was significantly lower in 2020 only after March 4th, demonstrating that the decrease could not be explained by seasonal variation.

As we highlighted before, MI decreased during lockdown due to COVID-19 pandemic, but the complications rate varies from state to state. As mentioned above, we observed an increase in complications in the studies conducted in Italy[12] and USA[20].

Lauridsen et al, using Danish nationwide registries, studied the incidence of AMI-related cardiogenic shock (CS) during the pandemic[22]. They found that the total AMI cases decreased with 15% during the lockdown of 2020 compared with the 2015-2019 period, but the incidence of AMI-CS was similar, 5.9% versus 5.8%, and the adjusted 7-day mortality was similar. Similar results as in Denmark were seen in Hong-Kong, no significant difference in MI-related mortality was observed, 6% vs 12% p=0.24[23].

A reduction in ACS admissions was seen also in other countries, besides Europe and USA. Boukhris et al realized a multinational retrospective survey on the impact of COVID-19 pandemic on ACS volumes in non-Western countries (Russia, Brazil, Kingdom of Saudi Arabia, and Tunisia)[24]. Compared to 2019, STEMI admissions decreased by 17.6% and 39.4% for March and April 2020, respectively, and by 9.6% and 26.4% for NSTEMI, respectively.

In Albania there is an undergoing study evaluating the impact of COVID-19 on ACS admissions from March 9th, 2020 (the first case of COVID-19 in Albania) until April 30th, 2020 (period of total lockdown), compared with the same period in 2019. Preliminary results demonstrate a reduction of ACS in total by 41%, 28% for STEMI, 34% for NSTEMI and 57% for UA (unpublished data).

The main conclusion of all these studies conducted for ACS during COVID-19 pandemic is a reduction of AMI admissions and a delay in hospital presentation or first medical contact. The reasons for this "paradoxical" phenomenon are numerous and probably some of them remain unknown. All authors converge in one point: the fear of possible contagion at the hospital or other medical structures has been one major factor in the reduction of admissions for ACS. This does not necessarily mean that there is a reduced number of AMI, but of patients presenting to the hospital. A considerable number may have remained at home, without seeking medical care.

An important role for the induced fear came from media or lockdown language of self-isolation, which discouraged people to seek medical care, difficulties in consulting family doctors or emergency services. This was presumed in studies in countries with less severe pandemic as Greece[19] or between Northern (more severe) and Southern Italy[12]. A second cause of ACS admissions reduction is probably because of the reorganization of healthcare systems, with Emergency Departments or entire hospital structures in some regions dedicated to affront the pandemic. All this might have postponed less urgent cases. The reduction is higher in UA or NSTEMI than in STEMI[12,17,19-21].

Another possible cause of such reduced numbers is self-isolation of the population, less physical triggers (stress). Fewer activities induced less signs of angina during quarantine periods, converted in less ACS during this time. On the other side, self-isolation, fear, anxiety regarding contracting the SARS-CoV-2, lifestyle changes, unemployment, can induce oxygen supply/demand mismatch, inflammation and prothrombotic status. In this situation, it is unclear which factor is more responsible for inducing most of the ischemic events.

During Ebola pandemic in Africa, in 2013, the same situation was observed regarding delays and reduction in seeking medical care, as it is happening now with COVID-19. In Liberia, in urban areas, only 20–30% of patients seeking care during the epidemic received care, and in rural areas only 70–80% of those seeking care were able to access it[25].

The reduction of AMI admissions does not mean reduction in AMI incidence. AMI recovered late or not recovered at all will impact the cardiovascular morbidity, disability and mortality in the future. The real impact is expected to be observed in months and years after the pandemic.

To minimize the consequences, it is important to reduce the fear of catching the virus, by reassuring that all safety measures for non-COVID patients are taken. All efforts should be done that the population takes all the medical care and urges not to neglect consultations, examinations and hospital recoveries, to prevent any possible cardiac events.

Conclusions

COVID-19 , based on its pathological mechanisms, could be expected to increase ACS incidence, but in reality an important reduction and delay in ACS admissions were observed. Further studies are needed to understand the factors leading to this "paradox".

Author Contributions:

L.S. conceived the original draft preparation. L.S., A.D. and A.G. were responsible for conception and design of the review. L.S., A.D. and A.G. were responsible for the data acquisition. L.S., A.C., E.T. and M.G. were responsible for the collection and assembly of the articles/ published data, and their inclusion and interpretation in this review. A.C., E.T. and M.G. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

Acknowledgements:

None

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