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Systematic Review

COVID-19 Outcomes in Patients Hospitalised with Acute Myocardial Infarction (AMI): A Protocol for Systematic Review and Meta-Analysis

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Abstract: Background: Patients with cardiovascular disease and risk factors for cardiovascular illness are more likely to acquire severe 2019 novel coronavirus (2019-nCoV) infection (COVID-19). COVID-19 infection is more common in patients with cardiovascular illness, and they are more likely to develop severe symptoms. Nevertheless, whether COVID-19 patients are more likely to develop cardiovascular disorders such as acute myocardial infarction (AMI) is still up for debate. Methods: We will follow the preferred reporting items for systematic review and meta-analysis (PRISMA) to report our final study, including a systematic search of the bibliographic database using the appropriate combination of search terms or keywords. The choice of search terms is discussed in more detail later in this paper. The obtained results will be screened, and the data extracted from the studies selected for systematic review will be based on the predefined inclusion and exclusion criteria. Using the obtained data, we will then perform the associated Meta-analysis to generate the forest plot (pooled estimated effect size Hazard Ratio (HR) and 95% Confidence Intervals (CI) values) using the random-effects model. Any publication bias will be assessed using the funnel plot symmetry, Orwin and Classic Fail-Safe N Test and Begg and Mazumdar Rank Correlation Test and Egger's Test of the intercept. In cases where insufficient data occur, we will also perform a qualitative review. Discussion: This systematic review will explore COVID-19 clinical outcomes, especially survival in patients hospitalised with Acute Myocardial Infarction, by utilising a collection of previously published data on hospitalised COVID-19 patients and Myocardial Infarction. Highlighting these prognostic survival analyses of COVID-19 patients with AMI will have significant clinical implications by allowing for better overall treatment strategies and patient survival estimates by offering clinicians a method of quantitatively analysing the pattern of COVID-19 cardiac complications.

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1. Introduction

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a type of coronavirus. Since the first case was reported in December 2019 in Wuhan, Hubei Province, China, the aggregate number of reported COVID-19 cases has increased and still being unpredictable despite significantly large vaccination policies. Millions of individuals were impacted worldwide quickly, prompting the World Health Organization to designate it a pandemic in March 2020 [1–3]. Although the majority of the focus is currently on pulmonary consequences, clinicians must be mindful of cardiovascular issues, which can contribute considerably to the disease's mortality [4–7].

Following transmembrane protease serine 2 activations of the viral surface spike protein, infection with SARS-CoV-2 is activated by binding the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor [8]. ACE2 is strongly expressed in type-II alveolar cells and the intestine's mucosa, the heart, the kidney, and the endothelium [9]. Patients with severe COVID-19 have been shown to suffer various consequences, including MI, heart failure, myocarditis, and arterial and venous thromboembolic phenomena [10].

The current COVID-19 outbreak has turned into a global public health crisis [11]. As of 28 April 2021, infected patients were found in 185 countries, with more than 3,000,000 cases reported worldwide and more than 210,000 deaths [12,13]. SARS-CoV-2, similar to many other coronaviruses, is assumed to have originated in bats, as it has 89 to 96% nucleotide identity with bat coronaviruses [14]. SARS-CoV-2, such as SARS and MERS, is assumed to have spread from bats to an intermediate host (likely a Malayan pangolin with which it shares 91 percent nucleotide identity) and finally to humans [15].

COVID-19 interacts with the cardiovascular system on multiple levels, causing complications such as myocardial injury and dysfunction in patients with primary cardiovascular disease (CVD) [12]. CVD was prevalent in 8% of SARS patients and over 30% of MERS patients [16,17]. According to China's National Health Commission statistics, 35% of COVID-19 identified patients had hypertension, 17% had coronary heart disease, and 12% had elevated troponin levels and/or cardiac arrest without known CVD. CVD presence in COVID-19 patients with SARS and MERS increases the death rate by 12-fold, most notably in those with severe diseases. The aged patients have impaired immune responses or elevated human angiotensin-converting enzyme 2 (ACE2). The COVID-19 patients with CVD had increased troponin levels or cardiac arrest. Increased hs-cTnl tracks with inflammatory biomarkers, namely Lactate dehydrogenase, IL-6, ferrine, and more, leads to reflect cytokines storm Intravenous immunoglobulin and steroids, cardiac biomarkers are the therapeutic approaches used to treat COVID-19 patients with CVD, which normalizes within three weeks of duration. Involving ACE2 directs myocardial injury; however, the exact mechanism behind the CVD in COVID-19 patients is unclear and still under investigation. Other proposed mechanisms includes cytokines storm in response to immune dysregulation. Hypoxia triggers extra calcium, leading to cardiac myocyte apoptosis [18].

Acute myocardial infarction is caused by total obstruction of a coronary artery, which results in an abrupt lack of blood supply and oxygen to the heart muscle. The risk factors of AMI, electrocardiographic changes and cardiac bio-markers elevation associated with AMI are well established.

COVID-19 may have a correlation with the prognosis of other diseases as well. For instance, even though the specific pathophysiology of involvement of kidney in COVID-19 infection is unknown, it has been observed that Acute Kidney Injury (AKI) during COVID-19 is associated with septic shock, multi -organ failure indicating that acute tubular necrosis is the aetiology of AKI [19]. Conversely, ACE2 receptor expression was found in

kidney cells in a research based on single-cell transcriptome analysis [20], implying the possibility of acute kidney cellular injury following SARS-CoV-2. During the stroke alerts examination, COVID-19 was found to be an independent risk factor for imaging-confirmed acute ischemic stroke. This data implies that COVID-19 infection is linked with elevated cause of death and disability that extends beyond the virus's primary cardiopulmonary consequences [21].

Extensive research has suggested a clear link between COVID-19 and cardiovascular diseases. Several earlier or pre-existing cardiac problems can result in severe problems in the presence of COVID. In contrast, COVID-19 itself has been reported to be the sole reason for several cardiac problems such as inducing myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism. The potential drug-disease interactions have badly affected the patients suffering from COVID-19 and comorbid cardiovascular diseases and have worsened the situation. Some asymptomatic patients suffering from COVID-19 have been found to display typical cardiac abnormality symptoms. Cardiovascular comorbidities, mainly coronary heart disease and hypertension, exhibit the highest mortality in patients suffering from COVID-19. Research demonstrates that the drugs commonly used to decrease cardiovascular risk may influence the severity of the disease. Several studies have conveyed enhanced levels of cardiac biomarkers in COVID-19 patients in China. A study with 41 COVID-19 positive patients in Wuhan reported 5 with myocardial injury and enhanced levels of high-sensitivity cardiac troponin I (>28 pg/mL), out of which 4 were in severe condition. Another similar study with 191 COVID-19 positive patients reported 17% acute cardiac injury [22].

A study by Katsoularis et al. demonstrates a considerable risk of patients becoming affected with AMI and ischaemic stroke due to COVID-19. This study included around 86,742 patients with COVID-19. This study indicates that COVID-19 is a risk factor for acute myocardial infarction and ischaemic stroke. It, in turn, gives a clear indication that acute myocardial infarction stroke represents a vast clinical picture of COVID-19 and explains the great need to become vaccinated against COVID-19. This research demonstrates that the risk of incidence of AMI in patients with COVID-19 is between 1.1% to 8.9%. In addition, there is a substantial amount of risk of the incidence of ischaemic stroke, which has been reported to be between 0.9% to 4.6%. This study has reported COVID-19 as an independent factor for AMI, and ischaemic stroke as the risk of acquiring these is much higher in COVID-19 than other bacterial or viral infections because of COVID's unique pathophysiological conditions. The embellished inflammatory response and the virus's direct effect on the endothelial cells result in ACE 2 receptor downregulation [23].

Through this manuscript, we have tried to design a protocol for systematic review and meta-analysis to demonstrate the link between COVID-19 and acute myocardial infarction (AMI) and to obtain a clear idea about COVID-19 outcomes in hospitalised AMI patients. By performing an extensive meta-analysis, this review aims to establish the mortality rate of COVID-19 with AMI and how pragmatic approaches can be taken to find a powerful solution for the same. This work thus aims to provide a complete insight into survival outcomes of COVID-19 patients hospitalised with AMI.

1.1. Rationale

1.1.1. The Importance of the Issue

According to Wu et al., 2020, severe COVID-19 patients suffer from respiratory and cardiac failure. COVID-19 presents various clinical manifestations, from asymptomatic clinical presentation to fatal multi-organ failure, with mortality rates ranging from 0.7% to 67% [20,24,25]. Compared to the liver and kidney, Momtazmanesh et al. suggested that COVID-19 affects the heart as the second most frequently affected organ after the lungs [20,26].

The exact mechanisms of cardiac injury in COVID-19 individuals have not been validated. Nonetheless, direct viral invasion, indirect damage caused by systemic inflammatory syndrome and cytokine storm, renin-angiotensin-aldosterone system dysregulation, car-

diac injury induced by hypoxia, cardiac microvasculature damage, cardiac damage, and stress-induced cardiomyopathy subordinate to multi-organ failure are all hypothesized to cause cardiac injury [25,27,28]. Thus, the purpose of this study is to use meta-analysis to better understand the impact of myocardial infarctions in COVID-19 patients.

1.1.2. How Will the Study Address the Issue?

The current study focuses on the COVID-19 outcomes in hospitalised acute myocardial infarction (AMI). In this systematic review and meta-analysis, data from previously published research will be pooled and analysed. We believe that this study will contribute in the following way:

a. This body of research will help us comprehend the increased incidence of COVID-19 and related mortality among COVID-19 patients who have pre-existing or newly acquired cardiovascular diseases.
b. This study intends to provide more knowledge on the patients hospitalised with COVID-19 and acute myocardial infarction using pooled Hazard Ratio (HR) and 95% Confidence Interval (CI).
c. Regardless of aetiology, it becomes pivotal for the clinicians to understand the standard protocol and other clinical interventions for the treating COVID-19 patients with cardiac complications. Therefore, our systematic review and meta-analysis could provide a better insight into survival outcomes of COVID-19 patients hospitalised with AMI.
d. The combined information and data from different studies to be used in our analysis may provide a complete picture of how COVID-19 patients' prognosis connects with cardio-vascular comorbidities, particularly AMI. This will aid scientists, healthcare workers, and other concerned professionals to acquire a deeper understanding on this subject.

2. Materials and Methods

The study aims to deduce the clinical outcome of patients who tested positive for COVID-19 and have a medical history of cardiovascular diseases, specifically acute myocardial infarction. The protocol for this study is being framed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

2.1. Search Methods

Studies that evaluate the outcomes of hospitalised COVID-19 patients who have an underlying heart disease will be considered by the authors and relevant studies will be collected for data extraction. A detailed search strategy will be undertaken to collect the published studies. Bibliographic databases including SCOPUS, EMBASE, Science Direct, Medline, PubMed and Google scholar databases will be used to find relevant studies. The search will be carried out based on subject applicable search terms or keywords included in Table 1. The data collection for this study will not be restricted to any particular study location or ethnicity of the patients. All the data from relevant original studies will be collected irrespective of the studies' countries. The initial screening will be based on the examination of title and abstract of the published articles. There will be no limits on the study participants such as age, sex, country of origin and ethnicity. The next screening stages will involve a thorough, manual search of individual studies to find if each study has the required data. Only the full-text articles that fall under the inclusion criteria will be considered. The studies used will be collected from a reference list of screened articles to avoid missing any eligible studies. Any dispute between the reviewers will be resolved through a discussion or an unbiased third viewer inspection.

Table 1. A list of the search terms used by the search strategy.

S No.	Search Terms
1.	"Acute myocardial infarction" AND "2019-nCov" OR "SARS-CoV-2"
2.	"Acute myocardial infarctio" OR "AMI" AND "COVID-19"
3.	"Severe acute respiratory syndrome coronavirus 2" OR "COVID-19" AND "Cardiovascular disease"
4.	"2019-nCov" OR "SARS-CoV-2" AND "Cardiovascular disease" OR "CVD"
5.	"COVID-19" OR "SARS-CoV-2" AND "Heart" OR "CVD"
6.	"COVID-19" AND "Cardiovascular risk factors"
7.	"2019-nCoV" OR "COVID-19" AND "STEMI"
8.	"2019-nCoV" OR "COVID-19" AND "Cardiac outcome"
9.	"2019-nCoV" OR "COVID-19" AND "Coronary artery disease"

2.2. Search Terms

A well-designed search strategy/method, which will be discussed in the methodology part of the article, is the backbone of any systematic review. To discover suitable studies for data extraction, the above-mentioned search terms will be employed in bibliographic databases such as SCOPUS, EMBASE, Science Direct, Medline, PubMed, and Google Scholar. The search terms are used to find the majority of the investigations that will be examined for selection and inclusion.

2.3. Study Selection

To uphold the quality of the study and to prevent collection of unnecessary data, a inclusion and exclusion criteria will be developed. This will ensure that only relevant papers containing the required information are included in the study. After screening the relevant studies, the full-text articles will be subjected to the inclusion and exclusion criteria for the selection process. The studies fulfilling the criteria will be included in the final quantitative data analysis of the systematic review.

2.3.1. Inclusion Criteria

Primary inclusion criteria will be studies analysing the COVID-19 outcome and hospitalised patients with AMI.

Other inclusion criteria include:

(1) Studies reporting patients with COVID-19 and other cardiac complications.
(2) Studies reporting cardiovascular comorbidities.
(3) Outcomes of patients with STEMI.
(4) Clinical data of patients with COVID-19 and AMI.
(5) Studies that complied with the PRISMA guidelines for systematic review and meta-analysis.

2.3.2. Exclusion Criteria

(1) Studies published in languages other than English.
(2) Letter to the editor, case studies, review articles, fact sheets and non-human studies.
(3) Unpublished studies, uninterpretable data, conference proceedings or thesis.
(4) Studies using patient's Information from datasets.
(5) Duplicates will be removed, and the study will be excluded if it falls within the exclusion criteria.

Data will be collected by independent authors separately. Any disagreement between the reviewers will be resolved by discussion. Any inclusion or exclusion criteria will be added after the agreement of all the authors.

2.4. Data Collection and Management

Initially, the data collected by the authors will be stored in individual Microsoft excel sheets. After completing the data extraction, the excel sheets will be collated, and any repetitions excluded. After the assortment of collected data, all the identified citations will be uploaded in EndNote (Clarivate Analytics, 20.2 (MacOS)/20.2.1 (Windows), PA, USA), and the duplicates will be removed. These search results will be reported in full in the final report and presented in a PRISMA flow diagram, including the model from the PRISMA guidelines as attached as Figure 1.

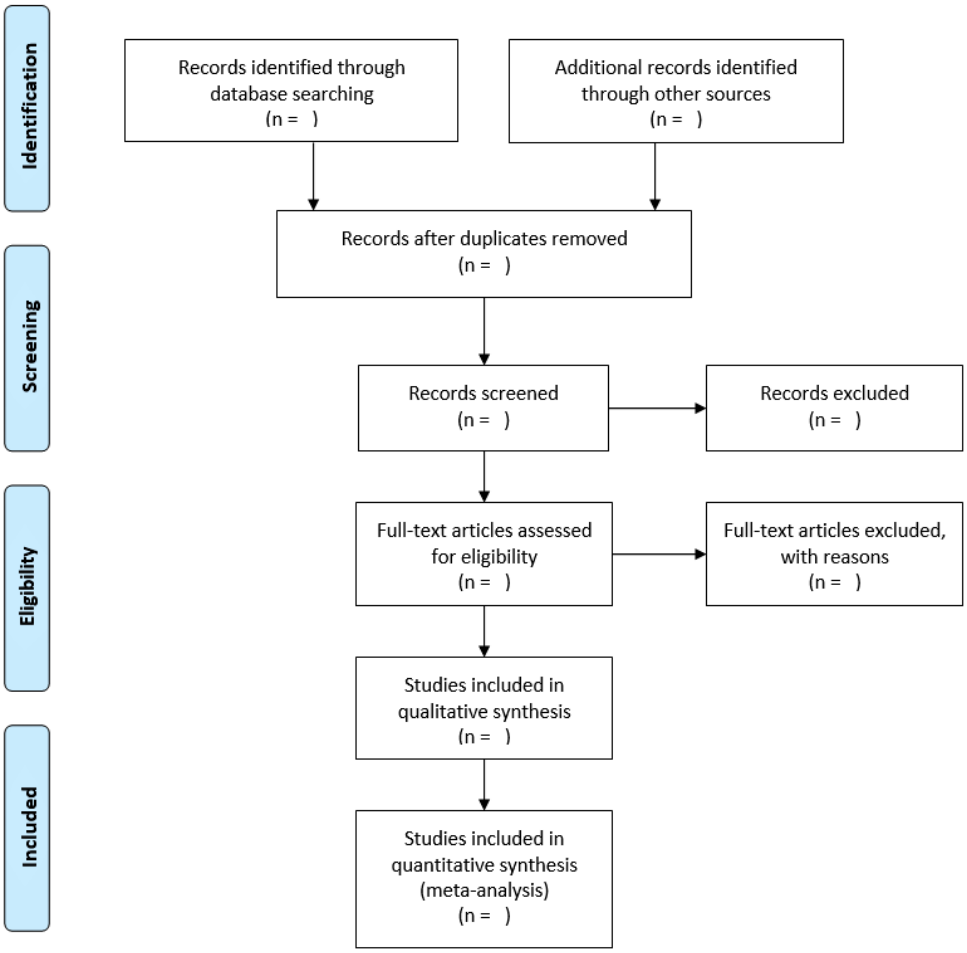

Figure 1. Schematic representation of articles to be included in the meta-analysis.

The full-text articles will then be analyzed, and the following data will be collected:

(1) Authors details
(2) Year of publication
(3) Study location
(4) Patients' details (Age, Gender, Ethnicity)
(5) Cardiovascular risk profile (Diabetes, Smoking history, Hypertension, Percutaneous coronary intervention (PCI), Dyslipidemia, Coronary heart disease (CAD), Chronic obstructive pulmonary disease (COPD))
(6) In the case of MI, it will be categorised into ST-elevation MI (STEMI) or Non-STEMI
(7) Troponin level
(8) Left ventricle function
(9) Cardiogenic shock status
(10) Mortality

2.5. Publication Bias

Publication bias will be evaluated by visually analysing the funnel plot generated with HR and 95% CI values. The symmetry of the funnel plot is inversely associated with the degree of publication bias in the study. The Classic fail-safe N and Orwin fail-safe N tests can be used to impute and adjust the funnel plot for any small missing studies [29]. The Begg and Mazumdar rank correlation test will be used to analyze the correlation between ranks of effect size and their respective variances [30]. Egger's Test of the intercept and Duval and Tweedie's trim and fill method will be used to predict the standardized effects and to recompute the effect size to acquire a symmetrical funnel plot [31,32].

2.6. Heterogeneity Assessment

Cochran's Q and Higgins' (I^2) tests will be applied to assess the heterogeneity of the combined HR [33,34]. The I^2 statistics will be used to determine heterogeneity, where an I^2 value of above 50% is a typical indication for heterogeneity. For the Q test, a p value of <0.01% is suitable. If heterogeneity is observed, a random effect model will be developed and applied, and tau-squared statistics will be used to estimate the variation of heterogeneity between the test accuracy seen in different studies. The Q statistics will be used to study the null hypothesis, with the tau squared test applied to locate depression. Forest plots will be generated and will then be used for detailed analysis.

2.7. Reporting of the Review and Ethics

The systematic review and comprehensive meta-analysis findings will be encapsulated in a flow diagram that summarizes the selection process as per PRISMA guidelines (2020 Statement). In-text descriptions will be utilized to explain the qualitative data in the studies. This systematic review and meta-analysis protocol is based on various previously published studies conglomerated in databases. Therefore, no formal Human Research Ethics Committee (HREC)'s approval is required.

3. Discussion

The systematic review on outcomes of patients with COVID-19 who were hospitalized with Acute Myocardial Infarction (AMI) aims to estimate the impact of the cardiovascular associated disease with COVID-19 and their relations with COVID-19 across the included studies. Elderly patients are more prone to have COVID-19 infections, especially severe forms of the disease. Similarly, elderly patients are prone to cardiovascular diseases (CVD). The severity of COVID-19 disease and death rates seem to be higher in older people, especially patients with hypertension and cardiovascular diseases [35]. Does the presence of CVD or the associated risks factors of CAD-like diabetes, hypertension, obesity, smoking, and dyslipidaemia propose any increased risk of a poor prognosis? What happens to those patients who develop MI while infected with COVID-19? Can we identify patients with COVID-19 who are at risk of developing a coronary event? Can we better predict a person's prognosis who has both MI and COVID-19, so that escalation of appropriate therapy could be accomplished early?

Various cardiac complications associated with COVID-19 medications need to be studied extensively. A study has reported that COVID-19 primarily causes myocarditis infecting the myocardium of the patients. An autopsy specimen taken from the patient's heart revealed interstitial mononuclear inflammatory infiltrates [36]. It has also been reported that after infection of COVID-19, the patients with myocarditis had developed reduced systolic function [37]. Cardiac injury could be due to ischemia and infection-related myocarditis, and maybe an important prognostic factor in patients with COVID-19 infection. The systematic review for this protocol and the statistical report from the meta-analysis may aid the clinicians in appropriate prioritizing and monitoring the outcomes of patients hospitalized with AMI patients with COVID-19.

Real time monitoring sensors are gaining popularity in recent times. When implanted or adhered to the human skin, the small sensors in a wireless body area sensor network

(WBASN) might be invasive or non-invasive. WBASNs are used in healthcare for a variety of purposes, including early illness identification, surveillance, post-surgery monitoring, and support. In reality, WBASN applications cover a wide range of topics, including omnipresent healthcare, defence, athletics, entertainment, and a variety of other fields involving humans.

These sensors do not interfere with the person's activities, yet they may capture vital signs throughout any activity. During his or her everyday routine, a patient's blood pressure, pulse, or temperature, for example, might be monitored [38]. The most lethal kind is myocardial infarction (MI), which is commonly referred to as a heart attack amongst most individuals [39]. The effect of MI can be decreased utilising WBASN technology if aberrant situations are checked on a frequent basis. Early identification of medical anomalies and discomfort is one of the key uses of WBASNs [40]. A portable ECG monitor called a Holter monitor is also used to diagnose heart patients over a period of 24–48 h [41].

According to [42] Delano and Sodini, a wearable ECG monitor was designed to offer long-term collection and analysis of the data. Gravina and Fortino [43] proposed automated methods for detecting the accelerative cardiac defence response (CDR). Surgically implanted devices with wireless communication abilities can be used to assess and provide alerts to help people live longer. Pacemakers, neurostimulators, implanted cardiac defibrillators (ICD), medication pumps, and baclofen pumps are examples of devices that have been employed in the human body [44]. Hussain et al., 2021 [45] designed an ECG-based health monitoring and illness prediction software that may be used in real-time or near-real-time. A wearable ECG patch for cardiac signal capture, a big data platform for real-time data storage and processing, and a healthcare advisory panel for post-stroke management services are the three essential elements.

HealthSOS is a compact, portable and low-cost EEG device based on an eye mask that may be utilised for prognostics of ischemic stroke and changes in functional outcome owing to stroke. The delta-alpha ratio, the delta-theta ratio, and the rsBSI (revised brain symmetry index) were revealed to be statistically relevant indicators for the prognosis of ischemic stroke. Outside of the clinical setting, the HealthSOS system is intended to be a viable healthcare aid system for prognostics of ischemic stroke [46].

This is an active field of COVID-19 cardiac research, and as the published literature expands, our clinical team will further validate our systematic review and comprehensive meta-analysis with recent outcomes by reciting searches and enhancing the review. Therefore, it would be ideal to set forth this protocol to disseminate our systematic review process, preserving transparency and providing a guideline to future researchers endeavouring a similar line of investigation for their reviews and analyses. Quantitative evaluation of the risk variables related with this condition can only be determined by analysing additional research related with COVID-19 clinical outcomes in patients hospitalised with AMI. The research findings analysed using this approach may aid in determining the link between COVID-19 and AMI patient survival. Clinical studies are generally performed on a small number of people for a short time period. As a result, our protocol for systematic review and meta-analysis might give a well-organized picture of the involvement of COVID-19 in patients with AMI. The data gained through this approach will enable clinicians in making educated decisions and therefore will improve the conditions for COVID-19 patients with Acute myocardial infarction.

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