

REVIEW ARTICLE

Practical Approach to Acute Coronary Syndrome in Patients with COVID-19

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Abstract

Acute cardiac injury is associated with higher mortality in patients with the novel coronavirus disease-2019 (COVID-19) and the exact etiology can be challenging to diagnose in the emergency setting during the pandemic. From a pathophysiological perspective, SARS-CoV-2 infection is characterized by an overproduction of inflammatory cytokines (IL-6, TNF-alpha) that leads to systemic inflammation and consequent increased risk of acute myocardial infarction (AMI) caused by atheromatous plaque rupture and significant myocardial oxygen supply-demand imbalance. Moreover, SARS-CoV-2 tropism to the renin-angiotensin-aldosterone system through the ACE2 receptor induces myocarditis that may rapidly progress to left ventricular dysfunction and hemodynamic instability. Myocardial inflammation with pericardial involvement, *i.e.*, myopericarditis, can progress to cardiac tamponade and obstructive shock. These cardiovascular complications, which are associated with a worse prognosis and higher mortality, can be associated with clinical manifestations, electrocardiographic changes, and troponin values similar to AMI. Thus, the diagnosis and treatment of patients with acute chest pain and dyspnea admitted to the emergency department is a significant challenge during the COVID-19 pandemic. Here, we provide a

review of the literature focusing on a practical approach to acute coronary syndrome patients with confirmed or suspected COVID-19.

Introduction

In December 2019, a new positive-strand RNA virus,¹ belonging to the family *Coronaviridae*, began to circulate in Wuhan, China. The new virus shares characteristics with the SARS-CoV and MERS-CoV, both responsible for epidemics in past decades. It was named SARS-CoV-2, which is the cause of the current pandemic announced by the World Health Organization (WHO) in March 2020. In Brazil, at the end of June 2020, the number of confirmed cases had already surpassed 1,5 million, with 65,000 deaths from the disease.² The fatality rate in the country reaches 6.9%, similar to other countries with similar diagnostic approaches.³ Unlike the other six phylogenetically similar viruses, the etiological agent of coronavirus disease-2019 (COVID-19) is highly infectious, with a basic reproduction number (R_0) between 2 and 3.5.⁴⁻⁶ Moreover, some studies have identified high viremias in patients who do not present any symptoms, emphasizing the relevance and the direct impact of this finding on the global spread of the disease.⁷⁻⁹

Acute coronary syndrome is a clinical condition with high prevalence, morbidity, and mortality. Acute chest pain is a usual complaint in the emergency units, with well-defined protocols and differential diagnosis from other (fatal or not) diseases, aiming to establish a rapid and effective treatment. In the current global health crisis, scientific evidence has revealed significant cardiovascular involvement in COVID-19, which makes the management of acute chest pain even more complex

Keywords

Acute Coronary Syndrome; Betacoronavirus; COVID-19; Infection; Pandemics; Troponin; Electrocardiography/methods.

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and challenging in the emergency setting, urging the need for reviewing these protocols. Cardiac involvement in SARS-CoV-2 patients seems to affect mainly those with typical cardiovascular risk factors and to incorporate several pathophysiological mechanisms, such as a direct cardiac injury by the viral cytopathic effect, myocardial injury due to a pro-inflammatory state and systemic inflammation, and decompensation of pre-existing cardiovascular disease.¹⁰⁻¹³

A meta-analysis with 341 patients associated myocardial injury with severe COVID-19 infection since patients with high troponin serum levels required intensive care more often.¹⁴ Myocardial injury is also a predictor of higher mortality in patients with COVID-19. Furthermore, cardiovascular complications such as acute myocardial infarction (AMI) are frequent in these patients and may cause irreversible myocardial damage¹⁵ or even rapidly progress to cardiogenic shock and death.^{16,17}

Therefore, it is imperative to understand the main mechanisms involved in the development of myocardial ischemia in SARS-CoV-2 infection, and its diagnosis, to implement appropriate clinical interventions aiming to prevent unfavorable outcomes and possibly permanent sequelae.

Methodology

This study is an extensive scoping review. The bibliographical survey was performed in the PubMed platform using the descriptors "COVID-19", "2019-nCoV", "Myocardial Infarction", "Acute Coronary Syndrome" and "Echocardiography" in the advanced search function. Articles diverging or not related to the main theme, and articles not written in English were excluded from the review. After exclusions, 59 articles were selected and thoroughly reviewed to compose the present study and were cited either directly or via cross-reference.

Discussion

Cardiovascular Risk Factors

Hypertension and diabetes mellitus has been described as the most prevalent comorbidities among individuals with COVID-19, particularly in the more severe forms of the disease requiring hospitalization. On average, 30% and 10% of severe COVID-19 patients are hypertensive

and diabetics, respectively,¹⁶ and these conditions are also related to higher mortality in these patients, varying amongst different populations.¹⁸ A meta-analysis including 12 studies demonstrated that the prevalence of diabetes and hypertension in patients with severe COVID-19 was significantly higher compared to those with non-severe forms of the disease (OR: 3.52; 95% CI: 2.65-4.67 and OR: 2.69; 95% CI: 2.16-3.34, respectively). Three studies showed that uncontrolled glucose levels are related to higher severity. However, regarding blood pressure control, the results were controversial.¹⁸

In a case study performed in New York City, United States with 5,700 patients (mean age of 63 years; 39.7% female), the most frequent comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes mellitus (33.8%).¹⁹ In a meta-analysis with 419 patients (61.8% male, mean age of 55.6 years), the most prevalent comorbidity was hypertension (24.3%), followed by diabetes mellitus (15.2%) and heart disease (6.2%).²⁰ In general, patients with COVID-19 and hypertension had a higher mortality risk compared to those without hypertension.²¹

It is worth highlighting that patients with hypertension and diabetes, from a pathophysiological perspective, have higher inflammation levels. Therefore, these patients are at higher risk for complications due to immune hyperactivity and severe inflammatory response caused by the SARS-CoV-2 infection, heightening pre-existing endothelial dysfunction and inflammation, leading to more adverse outcomes. It is still unclear if the risk of infection among these patients is greater than in the general population. However, hypertension and diabetes are comorbidities associated with the highest morbidity and mortality among patients with COVID-19.¹⁸ Additionally, chronic cardiovascular disease may become unstable as a consequence of the imbalance between the disease-induced increase of metabolic demand and decrease in cardiac reserve.²²

Yang et al.,²¹ in a retrospective study assessing the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on clinical parameters and inflammatory profile of 126 patients with pre-existing hypertension and COVID-19, reported that hypertensive patients had higher mortality rates (10.3% vs. 6.4%) and higher incidence of critical illness (18.3% vs. 11.2%) when compared to normotensive patients, but without statistical significance. Moreover, hypertensive patients with COVID-19 showed higher plasma concentrations of ultra-sensitive C-reactive protein (25.4

[4.6-100.8] vs. 12.6 [2.6-53.3]; $p=0.024$), procalcitonin (0.092 [0.049-0.223] vs. 0.062 [0.035-0.134]; $p=0.017$), and IL-6 (13.8 [4.8-51.3] vs. 8.2 [1.8-22.8]; $p=0.017$) in comparison to non-hypertensive patients of the control group. It is possible that patients with COVID-19 and pre-existing hypertension experience a greater increase in inflammatory markers when compared to non-hypertensive patients, developing, therefore, a more exacerbated immune hyperactivity and more pronounced systemic inflammation.²¹

In addition to a pro-inflammatory state at baseline, which *per se* is a risk factor for a severe form of COVID-19, it must be noted that older age is associated with a higher prevalence of hypertension and diabetes than the general population.^{22,23} Previous studies revealed that older patients with underlying diseases have a higher likelihood of progressing to a more severe form of the disease. Also, exacerbated immune and inflammatory responses associated with a cytokine storm may have a significant role in the progression of COVID-19 in hypertensive patients since increased IL-6 levels and a higher degree of inflammation were identified in this population.²³⁻²⁵

It is still unclear if individuals with diabetes mellitus are more susceptible to COVID-19, but studies have reported a higher risk of unfavorable progression in this group of patients. Huang et al.,²⁶ in a meta-analysis including 30 retrospective and cohort studies with 6,452 patients, evidenced that diabetes mellitus was associated with unfavorable clinical outcomes (RR 2.38 [1.88,3.03], $p<0.001$; I^2 : 62%), with a subgroup composed of higher mortality (RR 2.12 [1.44, 3.11], $p<0.001$; I^2 : 72%), higher risk of severe COVID-19 (RR 2.45 [1.79, 3.35], $p<0.001$; I^2 : 45%), and higher incidence of ARDS (RR 4.64 [1.86, 11.58], $p=0.001$; I^2 : 9%) in patients with COVID-19. However, diabetes mellitus was not associated with a greater need for hospitalization in intensive care units (RR 1.47 [0.38, 5.67], $p=0.57$; I^2 : 63%, $p=0.07$).²⁶

From a pathophysiological perspective, the relationship between diabetes and higher virulence of SARS-CoV-2 has not been well elucidated in the medical literature. However, authors have postulated that pathophysiological mechanisms, such as: a higher expression of ACE2 favoring viral endocytosis; an increased expression of furin, a type-1 membrane-bound protease belonging to the proprotein convertase subtilisin/kexin class (PCSK), optimizing viral entry and replication; and basal hypercytokinaemia at the expense of IL-6, enhancing the systemic inflammatory state

observed in the severe forms of the disease, are all factors potentially responsible for increased risk, virulence, and severity of SARS-CoV-2 infection among patients with diabetes.²⁷ Moreover, diabetic individuals have a higher risk of respiratory infection due to an impaired immune system response.²⁷ Thus, it is postulated that ACE2 may have an important role in aggravating COVID-19 infection among patients with diabetes.²⁶

Furthermore, it is known that the damage caused by COVID-19 to the cardiovascular system is probably multifactorial, caused by metabolic imbalance, systemic inflammation (cytokine storm), coagulation disorders characterized by a pro-thrombotic state, and direct myocardial injury due to a viral cytopathic effect.²³⁻²⁵ Several studies have shown that patients with cardiovascular risk factors (advanced age, hypertension, and diabetes) and pre-existing cardiovascular disease (coronary arterial disease, cardiomyopathies, and cerebrovascular disease) have a higher risk of progressing to more severe forms of COVID-19, and are consequently more susceptible to cardiac complications.^{10,18,28} Hence, the association between SARS-CoV-2, coronary artery disease, and acute coronary syndromes is most likely related to the ability of these several mechanisms to destabilize previous coronary artery plaques and cause complications.^{29,30} Therefore, patients with heart disease present greater susceptibility to viral infection and cardiac complications related to COVID-19.

Pathophysiology

The fourth definition of AMI published by the American Heart Association (AHA), American College of Cardiology (ACC), and European Society of Cardiology (ESC) is characterized by acute myocardial injury associated with clinical, electrocardiographic, and laboratory findings suggestive of ischemia, being classified in five types according to the underlying pathophysiological mechanism.³¹

Individuals with previous cardiovascular disease and cardiovascular risk factors are at higher risk for type 1 AMI and atherothrombosis when infected by the coronavirus.³² Patients with severe COVID-19 develop cytokine storm with consequent systemic inflammation, which increases the predisposition to thrombosis due to a hypercoagulability state, causing atherosclerotic plaque instability and rupture, coronary thrombosis, and subsequent ischemia and necrosis of the myocardial segment irrigated by the occluded coronary artery.^{31,33}

Previous epidemiological studies about influenza have already demonstrated an association between the viral infection and an increased risk for acute coronary syndrome during the first seven days of the disease.^{31,33}

Type 2 AMI, characterized by an oxygen supply-demand imbalance, has also been described in patients with SARS-CoV-2 infection with or without previous cardiovascular diseases.^{31,32} The pathogenic hypothesis for the correlation between COVID-19 and type 2 AMI derives from the increase of metabolic demand generated by viral infection and the decrease of oxygen supply due to hypoxemia in patients with severe respiratory failure in more advanced stages of the disease.³⁴ Furthermore, a Chinese study suggests that some proteins in the viral structure of SARS-CoV-2 may bind to the hemoglobin beta chain, reducing the oxygen supply to tissues.³⁵

Despite its scarce description in the medical literature, the existence of another type of AMI, the type 4b, should be mentioned. This type is restricted to patients with previous coronary disease who already underwent primary angioplasty, which in the context of SARS-CoV-2 infection, might progress to stent thrombosis and myocardial ischemia.³¹ The pathophysiological correlation between AMI type 4b and COVID-19, as previously mentioned, seems to be associated with a hypercoagulability state due to endothelial dysfunction caused by inflammatory hyperactivity and hypercytokinaemia observed in SARS-CoV-2 infection. Also, it is worth reinforcing the chronic pro-inflammatory state of these patients due to coronary artery disease, which exacerbates the expression of cytokines and contributes to the formation of new thrombus.³⁶

The Role of Troponin and Electrocardiography

Several studies have demonstrated that myocardial injury, diagnosed by the increase in troponin levels, is associated with higher mortality in patients with COVID-19.^{13,37} In a meta-analysis that included 13 studies, patients with acute myocardial injury required more hospitalization in intensive care units (RR 7.945, $p < 0.01$) and presented higher mortality (RR 7.95, $p < 0.001$).³⁸ In a retrospective study which analyzed 187 patients hospitalized with COVID-19, serum troponin levels presented a significant positive linear correlation with C-reactive protein and NT-proBNP levels, evidencing an important association between myocardial injury and ventricular stress with systemic inflammation, which is

mainly present in the more severe stages of the disease.³⁹ Therefore, these findings suggest that troponin is an important prognostic marker in patients infected with SARS-CoV-2.^{13,38,39}

Infection by SARS-CoV-2 increases the risk of AMI particularly because it induces instability and rupture of pre-existing atherosclerotic plaque and causes significant oxygen supply-demand imbalance in the myocardium.³² Moreover, there are case reports describing the development of acute myocarditis, due to a likely viral tropism or association with the hypercytokinaemia and systemic inflammation triggered by viral infection, with clinical and laboratory presentations suggestive of AMI, becoming, therefore, an important differential diagnosis in patients with COVID-19.⁴⁰

Due to the significant clinical similarity between myocarditis and acute coronary syndrome, it is vital to determine the pre-test probability through the elucidation of risk factors, physical examination, and complementary exams such as serum troponin dosage and electrocardiography (ECG). Due to their practicality, these exams are feasible to perform in an adverse hospital environment, where the risk of disease transmission is high and complex logistics for invasive exams would otherwise be required.^{32,41}

The ECG may be a useful tool to elucidate cardiovascular complications related to COVID-19. Electrocardiographic changes such as convex ST-segment elevation or depression and ischemic T-wave, respecting the anatomic topography of the culprit coronary artery, especially when associated with mirrored reciprocal images in anatomically opposed electrocardiographic leads, corroborate the diagnosis of AMI. However, it does not completely exclude the possibility of a myopericarditis,⁴¹ which usually presents with diffuse ST-segment changes not anatomically correlated with a certain coronary bed, absence of mirrored reciprocal images, and concave morphology.^{42,43} Furthermore, there are reports of myocarditis associated with pericardial inflammation with unspecific ECG repolarization abnormalities, presence of alternating QRS amplitude and low voltage, accentuating the importance to investigate concomitant pericardial effusion in these patients.⁴⁰

The fourth global definition of AMI postulates that the diagnosis of atherothrombotic type 1 AMI is established based on the increase or decrease of troponin serum levels, with at least one measurement above the 99th percentile of the upper reference limit in a healthy

population, in association with a compatible clinical state.³¹ Nevertheless, it is worth noting that patients with acute myocarditis may also present increased troponin levels besides similar clinical manifestations during hospital admission. Thus, although increased troponin values reflect myocardial injury, it does not indicate the etiology and the underlying pathophysiological mechanism.³¹ On the other hand, troponin curve and delta may help to diagnose patients with precordial pain and suspected COVID-19, since myocardial injury associated with ischemia usually reaches its peak in 12-24 hours, while non-ischemic etiologies such as myocarditis present a late peak and a longer plateau.^{14,32}

A retrospective study including 6,557 patients assessed ultrasensitive troponin variability in emergency rooms and reported that an absolute delta of 16 ng/L presented a specificity and sensitivity of 94.2% and 83.2% for AMI, respectively, being a significant AMI predictor in patients with basal troponin between 14 and 50 ng/L.⁴⁴ This result reinforces that, although the analysis of troponin curve and absolute delta may be useful for the differential diagnosis between AMI and myocarditis in patients with acute precordial pain and suspected COVID-19 in the emergency setting, it does not have the capacity for diagnostic exclusion.

The European Society of Cardiology⁴⁵ guidance advocates that mild elevations in troponin serum levels in patients with suspected COVID-19, 2-3 times higher than the upper limit, particularly in older patients with pre-existing cardiovascular disease, do not require a more profound investigation for type I AMI unless the patient has suggestive clinical manifestations or electrocardiographic changes. However, a significant increase (*i.e.* five times the upper limit) indicates a more severe myocardial injury in patients with COVID-19, potentially reflecting cardiac complications such as Takotsubo syndrome, myocarditis, or COVID-19-induced type I AMI. It is noteworthy that due to its prognostic value in patients with COVID-19, major centers have recommended the measurement of serum troponin levels in every patient, with suspected or confirmed COVID-19, with cardiovascular risk factors, established cardiovascular disease, or symptoms indicating a more severe form of the disease.²⁸

Nonetheless, in emergency rooms, diagnostic uncertainty may persist even after performing ECG and measurement of serum troponin levels in patients with precordial pain and suspected SARS-CoV-2 infection. In these cases, point-of-care echocardiography may be

a useful tool to clarify the diagnosis. Moreover, in the absence of symptoms or electrocardiographic findings suggestive of type I AMI with a significant increase in troponin, an echocardiographic evaluation may be also beneficial to define the underlying cause of cardiac injury.

Role of Echocardiography

Echocardiographic assessment may also help in the differential diagnosis between myocarditis and acute coronary syndrome in COVID-19. Transthoracic echocardiography is more likely to detect contractility changes in the ventricular segment perfused by the culprit coronary artery of patients with acute coronary syndrome. On the other hand, the usual finding in myocarditis is diffuse hypokinesia with a reduction in the ejection fraction, maybe associated with a discrete pericardial effusion, although segmental dyskinesia and even a hyperdynamic state may also occur. However, acute myocarditis may also occur with preserved ventricular function without any segmental ventricular contractility changes evidenced by echocardiography. Thus, abnormal electrocardiographic and echocardiographic findings, combined with the patient's clinical manifestations may guide the differential diagnosis and outcome of COVID-19 patients.³³

The main echocardiographic findings described in the more severe forms of COVID-19 are: (1) hyperdynamic state, represented by an increase in cardiac output and left ventricular ejection fraction with reduced peripheral vascular resistance; (2) stress-induced acute cardiomyopathy, characterized by abnormalities in segmental contraction and left ventricular apical ballooning (Takotsubo cardiomyopathy); (3) right ventricular hypertrophy and acute pulmonary hypertension; and (4) global systolic and/or diastolic dysfunction, caused by severe hypoxia, long-term anoxia and/or systemic inflammation. It is worth noting that circulatory failure in these patients is usually associated with a state of significant ventricular dysfunction and reduced peripheral vascular resistance secondary to concomitant lactic acidosis.⁴⁶

Another significant aspect of the echocardiographic evaluation of these patients is the assessment of pulmonary vascular resistance and the presence of right ventricular dysfunction due to hypoxia, vasospasm of the pulmonary arteries, hypercapnia, and inflammation.⁴⁶ This finding may point to the presence of pulmonary thromboembolism (PTE), which is often described in patients with more severe SARS-CoV-2 infection. The presence of echocardiographic findings such as interventricular septum protrusion

towards the left ventricle, right ventricular systolic and/or diastolic dysfunction, changes in pulmonary artery flow, and acute tricuspid valve regurgitation indicate the presence of pulmonary hypertension and right ventricular dysfunction in patients with COVID-19.⁴⁶ The association between pneumonia caused by COVID-19 and pulmonary embolism is a challenge for frontline intensive care physicians since the symptoms overlap. Bedside echocardiography may be a useful tool to early detect PTE.⁴⁷

In a study evaluating 120 patients with COVID-19, right ventricular global longitudinal strain (RVGLS) was shown to be a significant predictor of mortality in these patients. Lower RVGLS values were associated with higher serum levels of D-dimer and C-reactive protein, in addition to a higher incidence of ARDS and greater need for mechanical ventilation.⁴⁸ It is worth noting that the severe forms of COVID-19 associated with cytokine storm result in systemic inflammation and hypercoagulability. Thus, acute right ventricular dysfunction in patients with COVID-19 may be secondary to an abrupt right ventricular pressure overload caused by increased pulmonary vascular resistance in PTE and/or pulmonary artery vasospasm resulting from severe hypercapnia and/or hypoxemia in patients with severe respiratory failure.⁴⁶ Clinically, a suddenly increased dyspnea associated with pleuritic chest pain requires PTE investigation in patients with COVID-19.^{46,48}

It is noteworthy that coronary computed tomography angiography and cardiac magnetic resonance imaging (CMR) may be useful to clarify the diagnosis. Regarding magnetic resonance imaging, the presence of interstitial myocardial edema without anatomical correlation, early myocardial gadolinium enhancement (EGE), and multifocal late myocardial enhancement with subepicardial or mesocardial distribution suggest myocarditis. On the other hand, myocardial ischemia presents a subendocardial or transmural distribution, respecting the anatomical topography of the obstructed coronary artery.⁴⁹ Furthermore, coronary computed tomography angiography can assess the presence or absence of coronary obstruction in a non-invasive manner, having, however, limitations due to the need for heart rate control and coronary vasodilation during the exam. Thus, since neither CMR nor coronary computed tomography angiography is not very feasible due to the high transmission rate of COVID-19, increased risk of health-care personnel contamination during patient transportation, and prolonged-time of these exams,

these tests should be considered in stable patients, as additional diagnostic methods when the diagnosis cannot be established by echocardiography.³⁷

Transthoracic echocardiography should ideally be performed in an emergency setting, by point-of-care or dynamic method, as an early assessment method of patients with COVID-19. The method provides hemodynamic evidence to guide clinical management. In critically ill patients, it is recommended a daily echocardiographic evaluation for a strict assessment of the ventricular function and hemodynamic parameters, and guidance of treatment with inotropic and/or circulatory support.²⁸

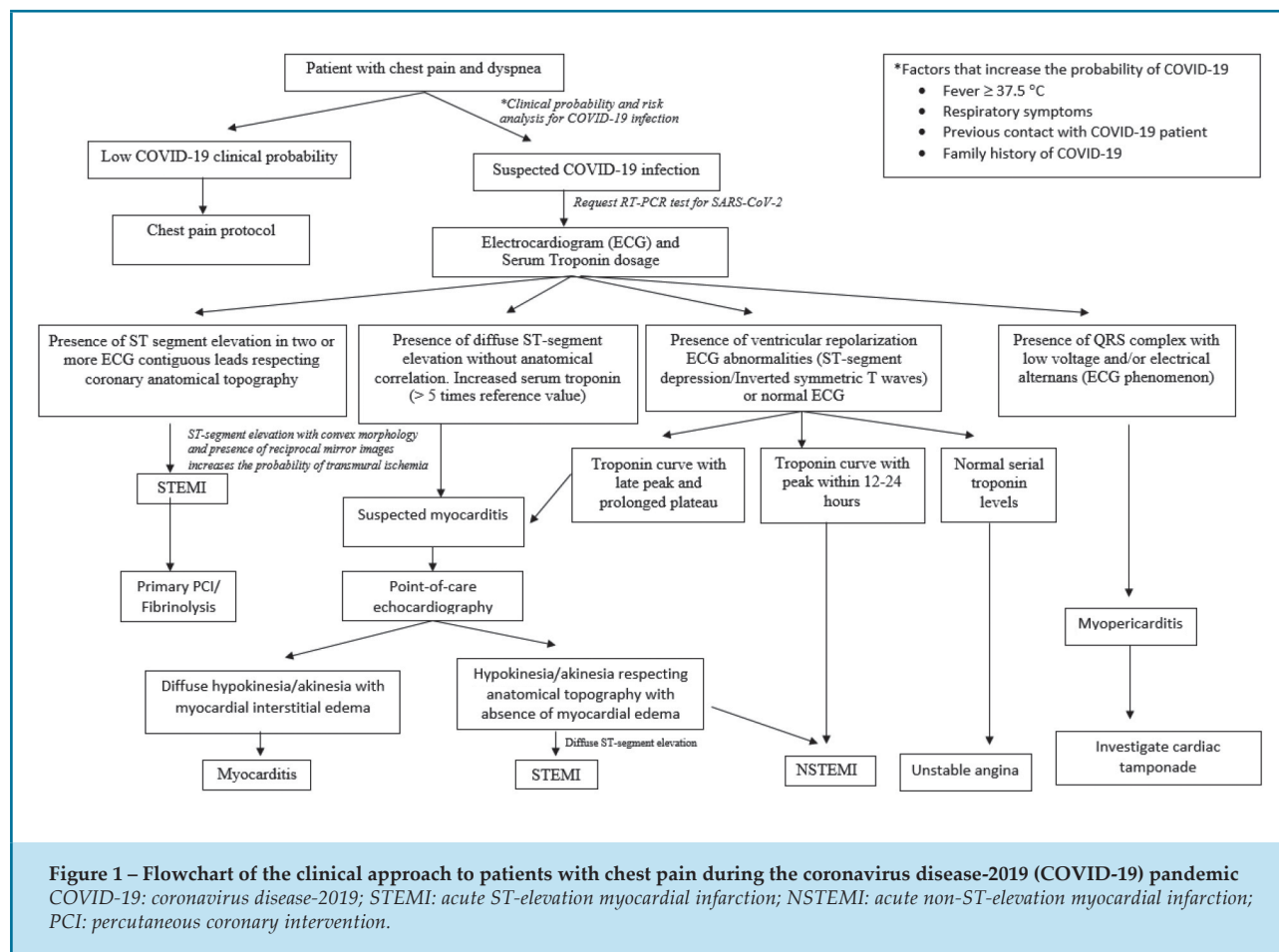
Clinical Approach

During the current pandemic, patients presenting to the emergency department with chest pain, dyspnea, and hyperdynamic state, are highly suspected cases of COVID-19. However, due to its high prevalence, acute coronary syndrome must also be considered as a differential diagnosis.⁵⁰ Moreover, in the most severe forms of COVID-19, there are cardiovascular complications such as myocarditis, acute myocardial infarction, and right ventricular overload due to severe pulmonary involvement.^{33,41,51}

Thus, clinical reasoning is based on clinical assessment, appropriate propaedeutic, risk stratification, and complementary diagnostic exams (ECG, cardiac enzymes, and bedside echocardiography) (Figure 1), taking into consideration that a diagnostic error in this context has a strong iatrogenic effect regarding the patient – due to the risks of an unnecessary procedure – and the healthcare team – due to the exposure to a potential infection without the appropriate protection and caution.³⁷

Several scientific societies and institutions have positioned themselves on the relocation of the scarce medical supplies in face of the increased demand for hospital care and adjustments in the management of acute coronary syndrome during the COVID-19 pandemic.^{37,52}

An initial guidance – Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI⁵² – proposed the first hospital protocols for the management of AMI in the COVID-19 pandemic. The paper suggests a preference for fibrinolysis over primary percutaneous intervention (PCI) aiming to avoid contamination of healthcare professionals. However, this strategy has generated undesirable results.⁵³



A second guidance – Management of Acute Myocardial Infarction During the COVID-19 Pandemic – published by the Society for Cardiovascular Angiography and Interventions (SCAI), American College of Cardiology (ACC), and American College of Emergency Physicians (ACEP) has been used as a foundation for most of the new current protocols. The document proposes that patients should be classified into five distinct groups: definitive diagnosis of acute ST-elevation myocardial infarction (STEMI), possible diagnosis of STEMI, acute non-ST-elevation myocardial infarction (NSTEMI) and unstable angina, patients out of the therapeutic window, and patients in cardiogenic shock/out-of-hospital cardiac arrest.³⁷ Regardless of the category to which the patient is assigned, a COVID-19 rapid test must be performed if available, to define the patient's infectious state.³⁷ Furthermore, the adoption of individual protection procedures while providing care to any patient with suggestive symptoms of COVID-19 is imperative, including hemodynamic and other invasive procedures. The guidance on the diagnosis and management of acute coronary syndrome proposed for the COVID-19 pandemic is summarized on Table 1.

It is worth mentioning that this guidance³⁷ and several other similar institutional protocols,⁵⁴ published based on a smaller set of evidence, contrast with those that recommend performing fibrinolysis as a preferable therapeutic strategy to STEMI with primary angioplasty reserved only for patients with contraindications to this pharmacological procedure,^{55,56} patients without a confirmed SARS-CoV-2 infection,⁵⁷ and AMI patients with hemodynamic and/or electrical instability.⁵⁸

Nevertheless, the request for cardiac catheterization (38% in the United States) during the SARS-CoV-2 pandemic has decreased. This fact may be explained by: 1) reluctance of patients with symptomatic AMI to seek health care due to fear of contracting COVID-19, resulting in a longer therapeutic window; 2) higher frequency of diagnostic errors due to the burden of healthcare logistics; 3) increased use of fibrinolytic therapy as the main therapeutic intervention, due to its presumed safety regarding the risk of SARS-CoV-2 transmission.⁵⁹

Table 1 – Clinical approach to patients with acute coronary syndrome during the coronavirus disease-2019 (COVID-19) pandemic

Category	Diagnosis	Conduct
STEMI	Definitive diagnosis (suggestive ECG + common AMI symptoms)	Primary PCI (if available) or Fibrinolysis and referral to a COVID-19 dedicated cardiac catheterization laboratory Performance of SARS-CoV-2 rapid testing Appropriate individual protection procedures must be rigorously adopted during PCI
STEMI	Possible diagnosis (differential diagnosis: myocarditis)	“Point-of-care” echocardiography If needed: chest X-ray, serial ECG, enzymatic curve, and echocardiography and, in the last instance, coronary computed tomography angiography (inconclusive echocardiography, myocarditis excluded) Confirmed PCI (if available) or Fibrinolysis and referral to a COVID-19 dedicated cardiac catheterization laboratory after a COVID-19 rapid test (absence of a catheterization lab with appropriate door-to-balloon time)
NSTEMI	Differential diagnosis of myocarditis (ECG and enzymes of myocardial necrosis)	GRACE score ≥ 140 or hemodynamic instability: Urgent invasive coronary angiography Confirmed NSTEMI: PCI – percutaneous coronary intervention
UA/ low risk NSTEMI	ECG and enzymes of myocardial necrosis	Clinical management and drug treatment following ACS guidelines. Invasive coronary angiography after controlling the infectious state considering the initial risk stratification
Cardiogenic shock/out-of-hospital CA	a) ECG with ST-elevation + echocardiographic segmental changes	a) Primary PCI
	b) Without ST-elevation + hemodynamic instability	b) Primary PCI
	c) Without ST-elevation in stable patient	c) Supportive treatment: analgesia, oxygen therapy, nitrate, antiplatelet therapy etc.
Out of therapeutic window	ECG changes + markers of myocardial necrosis	Supportive treatment: analgesia, oxygen therapy, nitrate, antiplatelet therapy etc.

STEMI: acute ST-elevation myocardial infarction; NSTEMI: acute non-ST-elevation myocardial infarction; UA: Unstable Angina; AMI: acute myocardial infarction; ECG: electrocardiography; PCI: percutaneous coronary intervention; GRACE (Global Registry of Acute Coronary Events); CA: cardiac arrest

Conclusion

Acute myocardial injury is significantly associated with in-hospital mortality, and a marker of worse prognosis in patients infected with SARS-CoV-2. Risk stratification and assessment of the pre-test probability are essential to improve the diagnostic accuracy of cardiovascular complications of COVID-19, with as accurate as possible differentiation of myocarditis from acute coronary syndrome, careful indication of invasive

diagnostic tests, and consequent implementation of appropriate therapies.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Author Contributions

Conception and design of the research: Azevedo RB, Muxfeldt ES; Acquisition of data: Azevedo RB, Botelho BG, Hollanda JVG, Ferreira LVL, Andrade LZJ,

Lilienwald Oei SSM, Mello TS, Muxfeldt ES; Analysis and interpretation of the data: Azevedo RB, Botelho BG, Hollanda JVG, Ferreira LVL, Andrade LZJ, Lilienwald Oei SSM, Mello TS, Muxfeldt ES; Statistical analysis: none; Obtaining financing: none; Writing of the manuscript: Azevedo RB, Botelho BG, Hollanda JVG, Ferreira LVL, Andrade LZJ, Lilienwald Oei SSM, Mello TS, Muxfeldt ES; Critical revision of the manuscript for intellectual content: Azevedo RB, Muxfeldt ES.

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