

# Specific characteristics of STEMI in COVID-19 patients and their practical implications

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## ABSTRACT

ST-elevation myocardial infarction (STEMI) is one of the cardiac emergencies whose management has been most challenged by the COVID-19 pandemic. Patients presenting with the “lethal combo” of STEMI and concomitant SARS-CoV-2 infection have faced dramatic issues related to the need for self-isolation, systemic inflammation with multi-organ disease and difficulties to obtain timely diagnosis and treatment. The interplay between these and other factors has partly neutralized the major advances in STEMI care achieved in the last decades, significantly impairing prognosis in these patients. In the present review article, we will provide an overview on mechanisms of myocardial injury, specific clinical and angiographic characteristics and contemporary management in different settings of STEMI patients with COVID-19, alongside the inherent implications in terms of in-hospital mortality and short-term clinical outcomes.

**Key words:** STEMI, COVID-19, myocardial injury, in-hospital death, fibrinolysis

## INTRODUCTION

More than two years after it was first described, much remains to be discovered about Coronavirus Disease 19 (COVID-19) caused by Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). While initially identified as atypical pneumonia, it is now evident that COVID-19 is rather a multi-organ disease with a wide variety of clinical presentations. Consistently, several hypotheses on patterns of myocardial injury in patients infected with SARS-CoV-2 have been advanced, including myocarditis, stress cardiomyopathy, and ischemic injury among others [1–4].

ST-elevation myocardial infarction (STEMI) is the most acute manifestation of ischemic heart disease and one of the most life-threatening cardiovascular emergencies [5, 6]. A hypothesis of an association between respiratory diseases and myocardial infarction (MI) had already been proposed during earlier epidemics, such as SARS caused by SARS-CoV-1 and Middle East Respiratory Syndrome, when the

incidence of adverse cardiovascular events, including MI and death, was higher among those infected [7–9]. Also, the recently published IAMI (Influenza Vaccination Against Myocardial Infarction) trial demonstrated that influenza vaccination administered immediately after an acute MI was protective against ischemic events recurrence [10].

Patients presenting with STEMI at the time of the COVID-19 pandemic have been described to present poorer outcomes with higher in-hospital mortality, and multiple factors might contribute to this trend [11–13]. First, logistical challenges related to extensive health systems re-organization and patients’ reluctance to seek medical attention for the fear of catching the infection could have contributed to worse quality of care. Secondly, the presence of symptomatic or asymptomatic SARS-CoV-2 infections might trigger myocardial infarction occurrence and precipitate its course.

Despite the diffusion of various tools for primary prevention and treatment, COVID-19

continues to represent a major health issue worldwide. Therefore, gaining a deep understanding of organ damage associated with COVID-19 is essential to limit its prognostic burden and reach a condition of coexistence with the virus.

This review aims to summarize the current evidence on the “lethal combo” between COVID-19 and STEMI, ranging from pathophysiology of acute myocardial injury associated with SARS-CoV-2 to clinical characteristics, management, and outcomes for patients presenting with STEMI and a SARS-CoV-2 infection.

### MYOCARDIAL INJURY AND COVID-19

Cardiac injury has been shown to be quite common in COVID-19, with up to 40% of hospitalized patients presenting elevated cardiac biomarkers including troponin and brain natriuretic peptides [14, 15]. Myocardial injury associated with COVID-19 has also been described as a determinant of adverse prognosis, and higher troponin levels have been linked to higher rates of in-hospital death [15–17]. The dramatic independent prognostic role of troponin increase is well known. In a recent meta-analysis of 12 262 patients, a rise in troponin was associated with an almost five-fold mortality increase, irrespectively of age, gender, hypertension, diabetes, and coronary artery disease (CAD) [18]. However, whether myocardial injury represents a direct consequence of SARS-CoV-2 infection rather than just a systemic manifestation of the associated acute respiratory distress syndrome (ARDS) is still controversial.

Metkus et al. compared intubated patients with COVID-19 with a historical ARDS cohort, showing that myocardial injury in severe COVID-19 was related to baseline comorbidities and multiorgan failure but was not an independent predictor of mortality at multivariable regression analysis [19]. Most importantly, COVID-19-related ARDS was associated with a lower risk of myocardial injury compared with non-COVID-19-related ARDS [19]. In a similar study of 156 critically ill patients requiring mechanical ventilation in Europe, myocardial injury was more common in non-COVID-19 ARDS, unlike thromboembolic events which were significantly higher in patients with COVID-19 [20].

While such evidence places myocardial injury in COVID-19 in the context that is generally observed in ARDS, several hypotheses of a specific pathogenetic role of SARS-CoV-2 in cardiomyocyte damage have been postulated. These include (1) direct cytotoxic effect by coupling to angiotensin-converting enzyme 2 (ACE-2) receptor expressed in the myocytes [21]; (2) endothelial damage to blood vessels, caused either by a direct link of the virus to the ACE2 receptor or by hypercytokinemia-associated vasculitis, with exposure of tissue factor that promotes a hypercoagulability state [22]; (3) coronary microvascular damage from diffuse thrombogenicity [23, 24]; and (4) coronary atheromas destabilization [25].

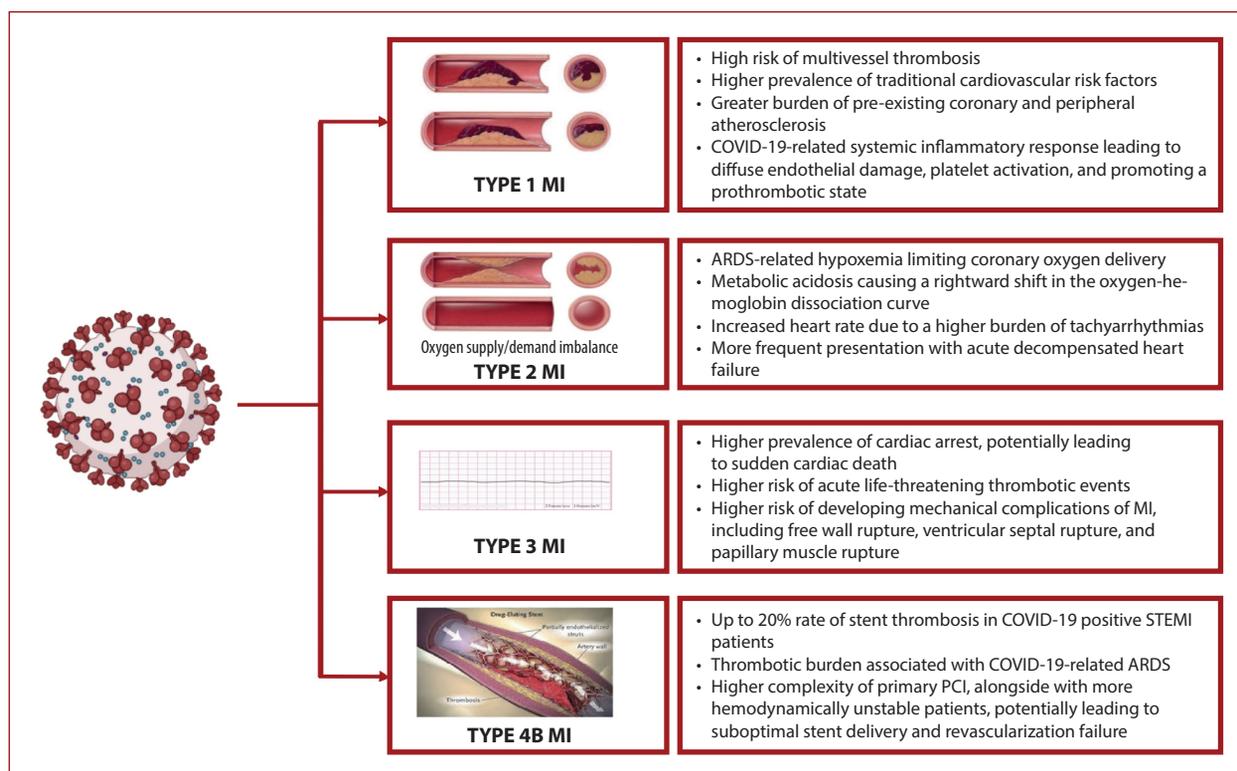
All these mechanisms might explain various manifestations of cardiac damage reported in COVID-19 patients, such as acute MI, myocarditis, arrhythmias, and acute heart

failure [2, 25]. In terms of MI, SARS-CoV-2 infection might most likely trigger three of the types defined by the Fourth Universal Definition: type 1, type 2, and type 4b (Figure 1) [26]. Type 1 MI is caused by atherothrombotic CAD. During COVID-19, systemic vasculitis, microvascular dysfunction, platelets activation and spreading inflammation determine a higher thrombotic burden leading to atherosclerotic plaque instability, as discussed below [27]. Type 2 MI is defined by a mismatch between coronary oxygen supply and demand, which is enhanced by cytokine storm and ARDS-associated hypoxemia. Also, metabolic acidosis is usually observed in severe COVID-19, leading to a rightward shift of oxygen-hemoglobin dissociation curve and worsening of hemoglobin affinity to oxygen [28]. On the other hand, fever and inflammatory states raise the metabolic needs of organs and tissues. Type 4b is a subset of percutaneous coronary intervention (PCI)-related MI characterized by stent/scaffold thrombosis. In COVID-19 positive patients, this event might be triggered by the consistent systemic thrombotic burden, as SARS-CoV-2 infection was independently associated with a 5-times higher risk of in-hospital definite stent thrombosis [27, 29], but a role could also be played by suboptimal stent delivery due to emergency revascularizations in more hemodynamically unstable patients.

### HOSPITAL ADMISSIONS FOR MYOCARDIAL INFARCTION DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has put severe pressure on health systems worldwide. Increasing numbers of patients admitted to emergency departments for COVID-19 resulted in rapid saturation of hospitals and intensive care units (ICU) capacity. New emergency hospitals have been built all over the world to allow prompt treatment of a larger number of critically ill patients. On the other hand, a decreasing rate of hospitalizations from other acute conditions has been described, also including MI [30, 31]. In the United Kingdom, by the end of March 2020, the rate of hospital admissions for acute coronary syndromes fell by 40% compared to the same period in 2019 [32]. Similarly, a 48.8% decrease in acute MI hospitalizations was observed in an Italian nationwide study [33]. This trend becomes even more alarming if we consider the high degree of myocardial injury and MI among patients infected with SARS-CoV-2, as previously described.

Several factors might have contributed to this data. The first and more reasonable hypothesis is the allocation of most healthcare resources, including hospital staff and equipment, to contain the pandemic leading to a lower capacity of dealing with other medical emergencies [34]. Secondly, the pandemic had a psychological impact on patients, generating the fear of in-hospital contagion. This is supported by the observation of a greater reduction in non-ST elevation MI (NSTEMI) admissions compared to STEMI [35]. Moreover, in an observational study con-



**Figure 1.** Patterns of myocardial infarction potentially associated with COVID-19

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 19; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

ducted in Italy in a non-epicenter area with relatively low pressure on the healthcare system, the incidence of STEMI was lower than expected and a U-shaped phenomenon with the nadir of hospital admissions during the first COVID-19 outbreak was observed [36]. Indeed, it should also be noted that infarct-related symptoms such as chest discomfort and dyspnea could be misinterpreted as being related to respiratory infection and targeted as respiratory symptoms in patients with COVID-19. Another interesting hypothesis is the paradoxically beneficial effect of social containment. A more relaxed lifestyle under lockdowns, compared to stressful daily living and sports activities, might have determined a lower incidence of MI, providing short-term protection to those carrying vulnerable coronary plaques [37].

### CLINICAL FEATURES OF STEMI PATIENTS WITH AND WITHOUT COVID-19

Since the first phases of the pandemic, all patients presenting to the emergency department with a STEMI have received a nasopharyngeal swab RT-PCR testing and have subsequently been classified as either COVID-19 positive or negative. In other cases, a STEMI might have occurred in patients who were already hospitalized or quarantined at home with a prior diagnosis of COVID-19. A summary of real-world studies comparing STEMI patients with and without COVID-19, mainly published during the first wave, is reported in Table 1 [27, 29, 38–41].

Two studies conducted in the US demonstrated consistent ethnic disparities, with African American STEMI patients more likely to be COVID-19 positive compared to other ethnicities. While the present pandemic is often regarded as a social equalizer, affecting people from all over the world, ethnic minorities have been reported to suffer disproportionately from COVID-19 [42, 43]. Causes for higher rates of SARS-CoV-2 infection among African Americans might include a limited ability to practice social distancing at home or the higher probability of being part of the “essential workforce” that cannot work from home [44, 45]. The African American ethnicity has also been described as a risk factor for hospitalizations for COVID-19, but it was not related to death rates or the need for invasive ventilation [46]. It is, therefore, presumable that ethnicity itself is not a predisposing factor for worse outcomes and STEMI occurrence and that ethnic disparity is broken down when it comes to receiving hospital care.

STEMI patients with COVID-19 did also more frequently present cardiovascular risk factors, except for smoking, and other relevant comorbidities (chronic kidney disease, prior stroke, prior CAD), compared to their negative counterparts. Arterial hypertension and diabetes have been the two most common comorbidities associated with COVID-19 in the early data from the epicenters [47, 48]. The main point of interaction between SARS-CoV-2 and hypertension is probably the ACE-2 receptor, to which the spike protein (S) of the virion binds to facilitate viral

**Table 1.** Clinical characteristics of STEMI patients with and without COVID-19

	Choudry et al. [27], JACC 2020	Rodriguez-Leor et al. [29], Eurointervention 2021 <sup>b</sup>	Case et al. [38], Am J Cardiol 2021	Kite et al. [39], JACC 2021	NACMI registry [41], JACC 2021	Saad et al. [40], JAMA 2021
Study period	March 2020 – May 2020	March 2020- April 2020	March 2020 – June 2020	March 2020 – July 2020 <sup>c</sup>	January 2020 – December 2020 <sup>e</sup>	January 2019 – December 2020
Country	UK <sup>e</sup>	Spain	US	Global <sup>f</sup>	US and Canada	US
Enrollment strategy	Consecutive patients	Consecutive patients	Consecutive patients	Patients whose data were uploaded on a web-based system	Prospective, investigator-initiated registry	Consecutive patients
Type of MI	STEMI	STEMI	STEMI and NSTEMI	STEMI	STEMI	STEMI (Out-of-hospital)
Prevalence of COVID-19, n (%)	39 (34)	91 (9)	86 (6)	Not assessed (n = 144)	Not assessed (n = 230)	565 (0.7)
Age, years, mean ±SD	61.7 ± 11.0 vs. 61.7 ± 12.6, P = 0.63	64.8 ± 11.8 vs. 62.5 ± 13.1, P = 0.95	70.8 ± 14.7 vs. 66.5 ± 14.6, P = 0.008*	63.1 ± 12.6 vs. 65.6 ± 13.4, P = 0.018*	P > 0.05 for comparison between age groups	P > 0.05 for comparison between age groups
Male gender, %	84.6 vs. 75, P = 0.34	84.4 vs. 78.4, P = 0.18	55.8 vs. 55.1, P = 0.9	77.8 vs. 72.2, P = 0.14	71 vs. 68, P = 0.38	69.9 vs. 70.3, P = 0.85
Afroamerican race, %	56.4 vs. 44.7, P = 0.25	—	64 vs. 48.2, P = 0.005*	—	Not assessed in control group (24% in Covid+ STEMI)	16.8 vs. 11.4, P < 0.001*
Obesity	BMI (kg/m <sup>2</sup> ): 26.7 (24.8–30.7) vs. 26.87 (22.6–29.4), P = 0.36	—	Weight (kg): 80.5 ± 22.7 vs. 86.1 ± 38.2, P = 0.08	BMI (kg/m <sup>2</sup> ): 27.3 ± 4.5 vs. 27.8 ± 5.5, P = 0.18	BMI (kg/m <sup>2</sup> ): 29.3 ± 7.6 vs. 29.5 ± 6.4, P = 0.7	BMI (kg/m <sup>2</sup> ): 25.5 vs. 21.5, SMD = 0.09
Hypertension, %	71.8 vs. 42.1, P = 0.003*	51.7 vs. 53.3, P = 0.28	47.7 vs. 57.8, P = 0.07	64.8 vs. 44.8, P < 0.001*	73 vs. 69, P = 0.16	79.1 vs. 74.8, SMD = 0.1
Dyslipidemia, %	61.6 vs. 36.8, P = 0.02*	48.4 vs. 46.9, P = 0.27	58.1 vs. 59.3, P = 0.83	46 vs. 28.9, P < 0.001*	46 vs. 60, P = 0.001*	66 vs. 67.2, SMD = 0.02
Diabetes mellitus, %	46.2 vs. 26.3, P = 0.04*	23.1 vs. 20.9, P = 0.06	57 vs. 39.7, P = 0.002*	34 vs. 20.9, P < 0.001*	46 vs. 28, P < 0.001*	48 vs. 33.9, SMD = 0.29
Smoking, %	61.6 vs. 46.1, P = 0.17	18.7 vs. 45.5, P < 0.001*	—	31.7 vs. 33.7, P = 0.77	44 vs. 59, P < 0.001*	15.9 vs. 31.6, SMD = 0.38
Chronic kidney disease, %	—	—	44.2 vs. 26.1, P < 0.001*	9.9 vs. 3.6, P < 0.001*	—	20.7 vs. 15.7, SMD = 0.13
Lung disease, %	—	—	Asthma: 3.5 vs. 5.3, P = 0.47	11.8 vs. 13.4, P = 0.78	—	COPD: 11.7 vs. 14.9, SMD = 0.09
Prior stroke, %	—	—	16.3 vs. 8.6, P = 0.02*	7.6 vs. 5.7, P = 0.11	10 vs. 9, P = 0.8	6.7 vs. 6.1, SMD = 0.02
History of CAD, %	Previous PCI: 23.1 vs. 6.6, P = 0.02*	15.6 vs. 13, P = 0.04*	51.2 vs. 65.7, P = 0.006*	Previous PCI: 13.9 vs. 10.2, P = 0.03*	24 vs. 31, P = 0.05*	85.8 vs. 88.8, SMD = 0.09
History of heart failure, %	—	—	44.2 vs. 34.9, P = 0.08	19 vs. 2.8, P < 0.001*	16 vs. 9, P = 0.01*	17.5 vs. 19.7, SMD = 0.06
Troponin T, ng/l, %	1,221 (179–4,143) vs. 369 (78.5–1,109), P = 0.003	—	22.9 ± 52.8 vs. 22.1 ± 43.7, P = 0.91*	2224.0 (58.0–7,449.5) vs. 899.0 (100.0–3,745.0), P = 0.15	—	—

<sup>a</sup>A total of 115 consecutive STEMI patients admitted to Barts Heart Center (London, UK) were included in the analysis. <sup>b</sup>9% of COVID-19 positive and 0.7% of COVID-19 negative STEMI patients in this group were already hospitalized at the time STEMI occurred. <sup>c</sup>Patients in the control group were taken from a pre-COVID-19 (2018–2019) database (n = 24 961). <sup>d</sup>75.3% of the included patients were from Europe, 11.1% from South America, 6.6% from Asia, 4.7% from Africa, and 2.2% from North America. <sup>e</sup>Patients in the control group were taken from a pre-COVID-19 (2015–2019) database and were sex and age matched to the 230 COVID-19 positive STEMI patients (2:1 ratio of control patients to COVID-positive patients) Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus Disease 19; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SMD, standardized mean difference; STEMI, ST-elevation myocardial infarction; UK, United Kingdom; US, United States

entry in the respiratory district, thereby leading to its degradation [49]. ACE-2 downregulation leads to increased angiotensin II levels, which are responsible for enhanced arterial vasoconstriction and increased blood pressure [50–52]. The association between arterial hypertension and inflammation favors microvascular dysfunction and hypertensive end-organ damage, of which MI is one of the manifestations [53, 54]. Similarly, diabetic patients have higher ACE-2 levels than the general population, which predisposes to the infection, as well as lower innate and adaptative immunity activation; also, high blood glucose concentrations directly increase viral replication [55]. Notably, overexpression of reactive oxygen species and some inflammatory cytokines, such as interleukin-6, accelerate MI occurrence and is triggered both by diabetes and SARS-CoV-2 infection [56, 57]. Dyslipidemia has been shown to predict severe COVID-19 development in various studies and meta-analyses [58, 59]. A proposed mechanism involves the high arterial and venous thrombogenicity of COVID-19, which is particularly evident in patients with hypercholesterolemia and seems to be prevented by statin therapy [60]. Conversely, a significantly lower prevalence of smoking habits has been found among SARS-CoV-2 positive STEMI patients, which might seem counterintuitive considering the strong impact of cigarette smoking on both coronary atherosclerosis and respiratory illness. This finding is in line with larger reports on patients diagnosed with COVID-19 [61] but, while a protective immunomodulatory effect of nicotine was initially proposed to justify the reduced risk of SARS-CoV-2 infection, it is now common belief that this result is subject to several biases [62, 63].

Pre-existing coronary or cerebrovascular atherosclerosis was more frequent in COVID-19 STEMI in most of the examined studies. Both a systemic inflammation in response to the virus and the procoagulant and hemodynamic effect of the infection might indeed favor a vulnerable atherosclerotic plaque rupture with subsequent thrombus formation and acute ischemia [22, 64].

Finally, there seemed to be no gender differences between STEMI patients with and without COVID-19, even though women were consistently under-represented. While systemic inflammatory response related to the viral infection might enhance traditional cardiovascular risk factors and trigger coronary atherosclerosis, women often display a different pattern of ischemic heart disease, which might be influenced to a lower degree by SARS-CoV-2 infection [65, 66]. Further studies on COVID-19-related MI in female patients are warranted to help elucidate this point.

### **IN-HOSPITAL PRESENTATION AND ANGIOGRAPHIC CHARACTERISTICS**

Several peculiarities in the spectrum of symptoms and angiographic findings across COVID-19 STEMI patients have been widely reported, and it has been questioned whether this variability only depends on logistic issues or

is rather a consequence of intrinsic characteristics of the viral infection.

In regard to clinical presentation, the NACMI (North American COVID-19 Myocardial Infarction) registry reported a higher prevalence of atypical symptoms, including dyspnea and syncope, rather than chest pain in a cohort of 230 COVID-19 positive STEMI patients compared to a historical control group [41]. Considering the higher frequency of pulmonary infiltrates on chest X-ray observed in patients with COVID-19 in the same study, this suggests respiratory symptoms might mask the classical red flags of STEMI and cause a diagnostic delay. The coexistence of STEMI with SARS-CoV-2 infection might also translate into a higher percentage of heart failure on in-hospital arrival, as observed in a Spanish nationwide registry, in which 31.9% of COVID-19 positive STEMI vs. 18% of negative patients had signs of congestion ( $P = 0.002$ ), with a significant trend towards higher Killip classes in the first group [29].

At coronary angiography, a higher thrombus burden in COVID-19 positive STEMI patients was highlighted by several reports. In the observational study conducted by Choudry et al. [27] at Barts Heart Centre (London, UK), subjects infected with COVID-19 displayed substantially higher rates of stent thrombosis (10.3% vs. 1.2%;  $P = 0.054$ ), greater incidence of multiple thrombotic culprit lesions (17.9% vs. 0%;  $P < 0.001$ ), higher thrombus grade (75% vs. 31.4% with grade 4–5;  $P < 0.001$ ), and more frequent need for glycoprotein IIb/IIIa inhibitors (59% vs. 9.2%;  $P < 0.001$ ) and aspiration thrombectomy (17.9% vs. 1.3%;  $P = 0.002$ ). Interestingly, D-dimer levels correlated with the myocardial blush grade and dosage of heparin required during primary PCI (PPCI) [27]. Similar findings were observed in the registry by Rodriguez-Leor et al. [29] (mechanical thrombectomy was necessary in 44% vs. 33.5% of cases,  $P = 0.05$ , and glycoprotein IIb/IIIa in 20.9% vs. 11.2%,  $P = 0.007$ ), in which there was also a lower usage of P2Y12 inhibitors pretreatment among COVID-19 positive patients. In both these European studies, there were no differences in terms of time to hospital admission, door-to-balloon time, and reperfusion strategy, suggesting that increased thrombogenicity is a direct effect of the SARS-CoV-2 infection. Another small registry ( $n = 78$ ) conducted in 4 hospitals in Italy, Lithuania, Iraq, and Spain reported an alarming 21% prevalence of stent thrombosis [67]. Besides the prothrombotic state induced by COVID-19, which mainly causes venous thromboembolism [68], SARS-CoV-2 infection might trigger arterial thrombosis through platelet activation, vasoconstriction, and endothelial dysfunction [69]. Of note, the influenza virus itself was associated with a higher incidence of MI in a pre-COVID study [70].

Other reports, mainly conducted in the US and China, described a substantial delay in myocardial reperfusion, that did at least in part explain the higher rate of thrombotic complications. In a study by Xiang et al. [11], which collected data on almost 30 000 STEMI registered in China before and after the pandemic, patients admitted for STEMI

during the COVID-19 outbreak presented significantly longer time from symptom onset to first medical contact and from first medical contact to angioplasty/thrombolysis, with these differences being more marked in Hubei province (the epicenter). The NACMI registry observed a significant 13-minute difference in door-to-balloon time (79 vs. 66 min;  $P = 0.008$ ); COVID-19 STEMI patients were also more likely to have a door-to-balloon  $\geq 90$  min (42% vs. 27%;  $P = 0.006$ ), to receive no angiography (22% vs. 0%;  $P < 0.001$ ), and to be treated with fibrinolysis or medical therapy rather than with PCI or coronary artery bypass grafting [41]. In a retrospective cohort study by Saad et al. [40], based on a US STEMI database, patients with COVID-19 did less frequently undergo coronary angiography (81.9% vs. 86.2%) and were more commonly treated with fibrinolytics only (1.9% vs. 0.2%); such gap was even more pronounced among those with in-hospital STEMI, of whom fewer than one third underwent angiography and fewer than one-fourth PPCI. Recommendations from Chinese and American scientific societies, which suggested considering thrombolysis in the first instance during the first outbreak to prevent hospital contagion, might justify the above-mentioned findings [71, 72]. However, even in the international COVID-ACS registry, in which 75% of patients were from European hospitals, significantly longer times from symptom to admission (173 vs. 339 min;  $P < 0.001$ ) and door-to-balloon (83 vs. 37 min;  $P < 0.001$ ) were described, as compared to national pre-COVID-19 databases [39].

In terms of culprit coronary lesions, it has been proposed that COVID-19 patients are more prone to present myocardial infarction with non-obstructive coronary artery disease (MINOCA). The incidence of this condition consistently varied among studies, reaching up to 56% in a case series from New York City [73], 39.3% in a case-series from Lombardy [13], 54.5% in a single-center French prospective study (vs. 6.9% in COVID-negative patients;  $P < 0.001$ ) [74], and 23% in the American NACMI registry (vs. 1% in the control group;  $P < 0.001$ ) [41]. MINOCA is an umbrella for several cardiac conditions, including Takotsubo syndrome, myocarditis, transient thrombosis, and type 2 MI, and this might explain differences in incidence across studies conducted at different times of the pandemic and with heterogeneous inclusion criteria [75]. On the other hand, it can be argued that SARS-CoV-2 potentially associates with several patterns of myocardial injury which mimic STEMI, thus requiring a careful diagnostic assessment in STEMI patients with COVID-19.

### **MORTALITY AND PERI-PROCEDURAL ADVERSE EVENTS**

Historically categorized as a life-threatening cardiovascular emergency, mortality of STEMI has decreased drastically over the last decades, largely due to a substantial reduction in-hospital mortality [76]. The current 30-day mortality rate of patients with STEMI is between 2.5% and 10% according to several observations [77–79]. The association between

STEMI and SARS-CoV-2 infection has led to a tremendous prognostic impact among patients presenting with what has been defined as the “lethal combo”. Table 2 lists the main studies reporting short-term outcomes in STEMI patients with COVID-19. In-hospital mortality ranged from 15% to 40%, with consistent variability across different populations, and subjects who tested positive for SARS-CoV-2 also presented higher rates of cardiogenic shock (CGS), cardiac arrest, prolonged ICU stay, mechanical ventilation, major bleeding and stroke. Several causes, including delay in seeking medical care, longer door-to-balloon time (due to the need of activating specific hospital pathways), higher thrombotic burden, higher rates of baseline comorbidities and coexistence of respiratory distress, systemic inflammation, and multi-organ damage, might lie beyond this trend, and the most suitable etiologic model is likely to be multifactorial. Notably, in the study by Rodriguez-Leor et al. [29], COVID-19 was associated with a significant increase in both cardiovascular and non-cardiovascular mortality among STEMI patients. To assess the effect of different pathogenic factors on in-hospital outcomes, Kite et al. [39] performed a multivariable propensity-based analysis, showing that: (1) SARS-CoV-2 infection was an independent predictor for death (hazard ratio [HR], 3.33; 95% confidence interval [CI], 2.04–5.42) and CS (HR, 1.48; 95% CI, 1.27–1.72); (2) prolonged ischemia times were associated with poorer outcomes, with a 10% increase in mortality for every 10-minute delay; (3) in patients with CGS, CGS rather than COVID-19 was the major determinant of mortality. Even though the direct correlation between longer time to revascularization and occurrence of CGS was not explored, it is evident that patients’ medical education and prompt activation of dedicated cath labs are pivotal to reducing clinical complexity and improving overall survival.

Additionally, patients with MI associated with COVID-19 might be at higher risk of developing mechanical complications, such as free wall rupture, ventricular septal rupture, and papillary muscle rupture [80, 81]. In a recently published large STEMI registry, the occurrence of mechanical complications was independently associated with both SARS-CoV-2 infection and pre-hospital delay, reaching an incidence of 5% in those presenting after 36 hours from symptom onset [82].

### **MANAGEMENT OF STEMI PATIENTS ACCORDING TO DIFFERENT SCIENTIFIC SOCIETIES**

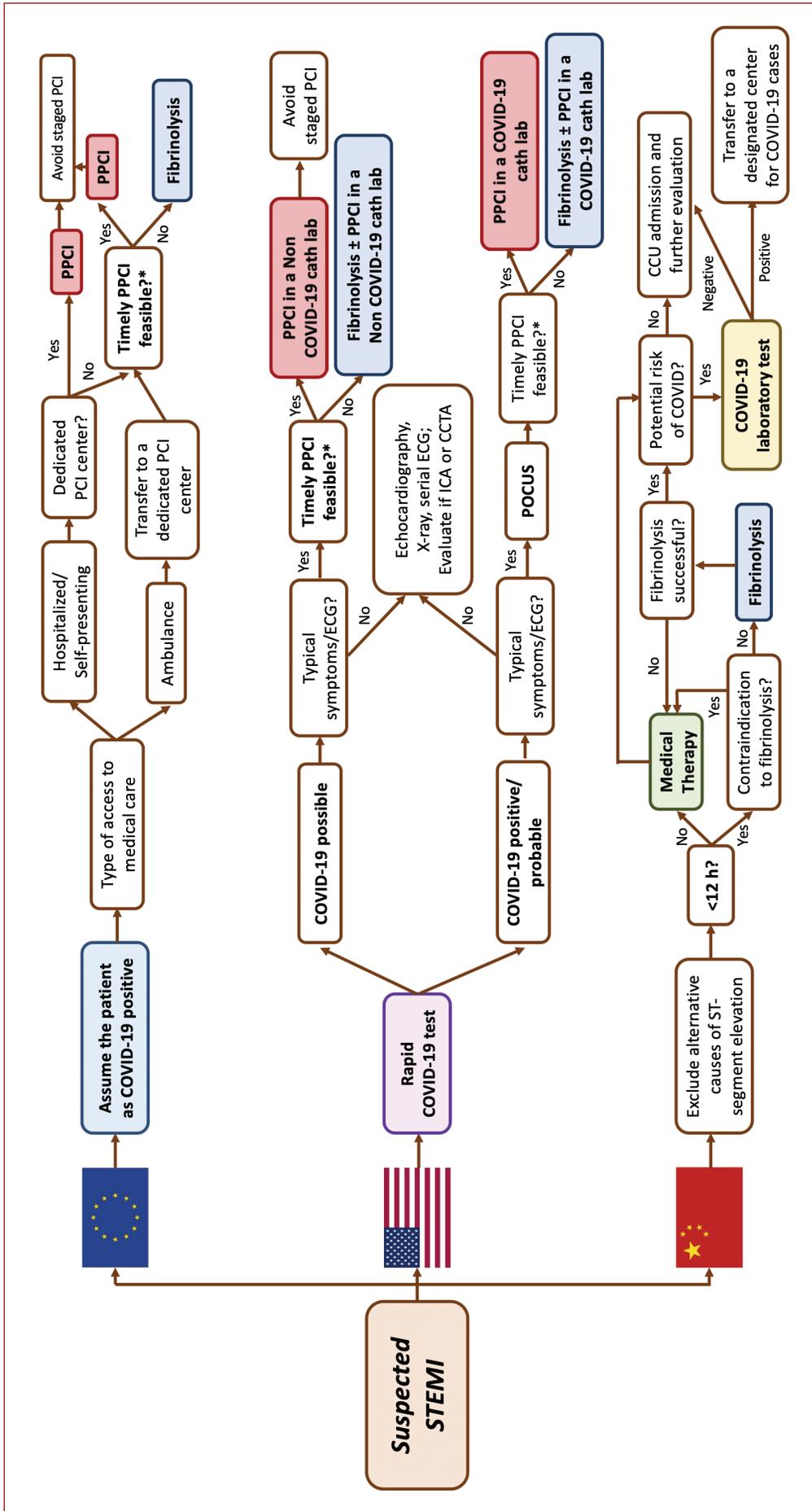
The best way to balance cardiovascular emergencies management — mainly acute MI — and COVID-19 control has been one of the most challenging issues created by the pandemics, especially during its first outbreak. At first, since the majority of patients needing cardiovascular care are not infected, it is essential to maximize their safety and that of medical personnel and at the same time to provide every patient the most advanced available care [83, 84]. The insti-

**Table 2.** Outcomes for STEMI patients with COVID-19

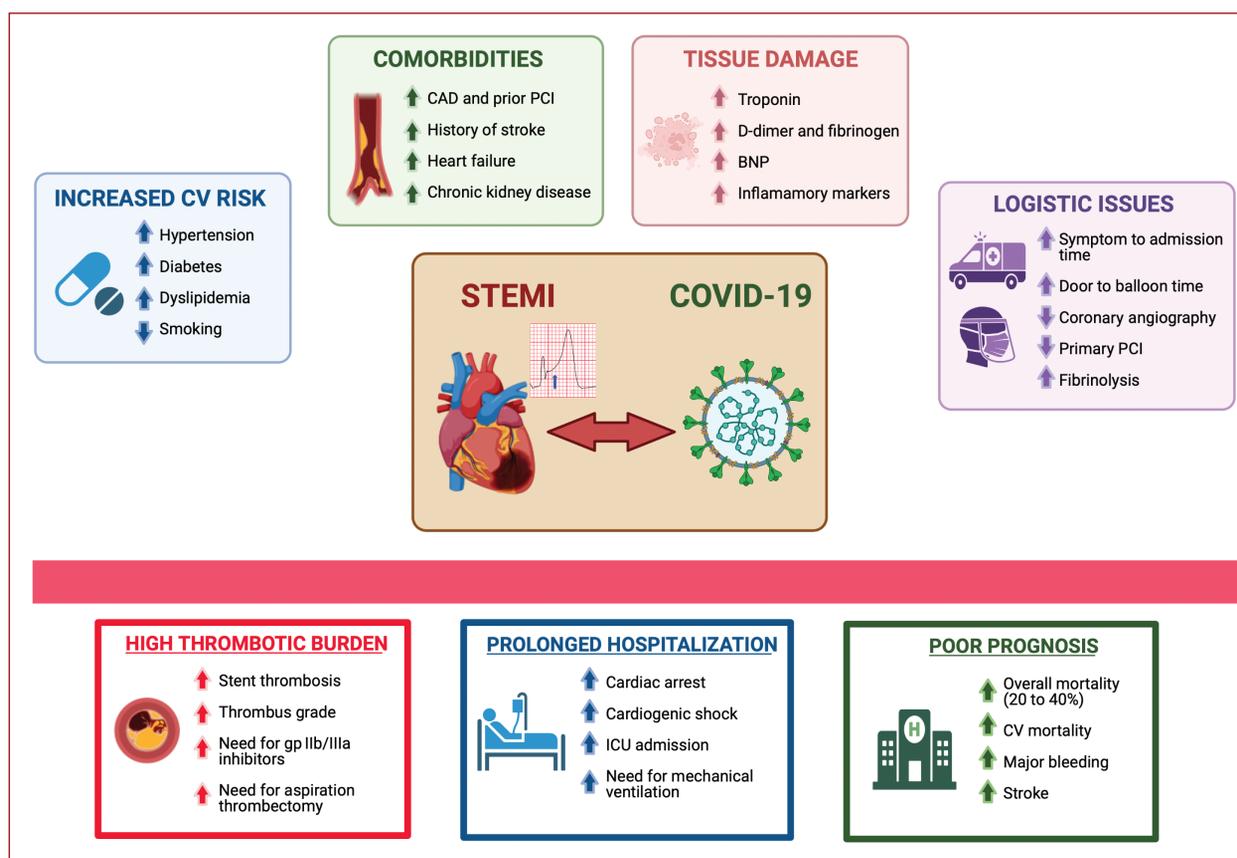
Study	Country	N. of COVID+ STEMI	N. of COVID-STEMI	Mortality, %	ICU admission	Stroke, %	Major bleeding, %	CGS, %	Mechanical ventilation, %
Stefanini et al. [13]	Italy	28	—	39.3	—	—	—	—	—
Choudry et al. [27]	UK	39	76	17.9 vs. 6.5, $P = 0.10$	28% vs. 5%, $P = 0.003^c$	—	—	Cardiac arrest: 28.2 vs. 9.2, $P = 0.01^*$	—
Rodriguez-Leor et al. [29]	Spain	91	919	Overall: 23.1 vs. 5.7, $P < 0.001^*$ CV mortality: 13.2 vs. 5.1, $P = 0.002^*$ Non-CV mortality: 9.9 vs. 0.5, $P < 0.001^*$ 27.9 vs. 3.7, $P < 0.001^*$	—	—	3.3 vs. 1.5, $P = 0.21$	9.9 vs. 3.8, $P = 0.007^*$	4.4 vs. 1.6, $P = 0.06$
Case et al. [38] <sup>b</sup>	US	86	1 447	—	64%	—	—	—	33.7
Hamadeh et al. [67]	Lithuania, Italy, Spain, Iraq	78	—	—	—	Ischemic: 4; hemorrhagic: 6	—	Need for resuscitation: 17	18
Popovic et al. [74]	France	11	72	27.3 vs. 5.6, $P = 0.02^*$	—	—	—	36.4 vs. 4.2, $P = 0.03^*$	—
Kite et al. [39]	Global <sup>b</sup>	144	24 961 <sup>c</sup>	22.9 vs. 5.7, $P < 0.001^*$	33.9%	2.1 vs. 0.14, $P = 0.002^*$	2.8 vs. 0.26, $P < 0.001^*$	20.1 vs. 8.7, $P < 0.001^*$	11.6 vs. 0.4, $P < 0.001^*$
NACMI [41]	US and Canada	230	460 <sup>d</sup>	33 vs. 4, $P < 0.001^*$	Length of stay (days): 3 (1.0–10.0)	3 vs. 0, $P = 0.017^*$	—	18 vs. 10, $P = 0.002^*$	—
Saad et al. — OOH [40]	US	565	75 869	15.4 vs. 9, $P < 0.001^*$	Length of stay (days): 1.0 (0.0; 3.0) vs. 1.0 (0.0–2.0), $P = 0.06$	Death + stroke: 18.2 vs. 10.5, $P < 0.001^*$	9.7 vs. 6.9, $P = 0.007^*$	18.2 vs. 16.8, $P = 0.38$	21.2 vs. 13.9, $P < 0.001^*$
Saad et al. — IH [40]	US	359	3 656	79.9 vs. 38.8, $P < 0.001^*$	Length of stay (days): 7.0 (1.0–15.0) vs. 3.0 (1.0–8.0), $P < 0.001^*$	Death + stroke: 82.5 vs. 44.8, $P < 0.001^*$	27 vs. 25.9, $P = 0.64$	25.3 vs. 27.2, $P = 0.45$	77.7 vs. 46.1, $P < 0.001^*$

<sup>a</sup>This study included both patients with STEMI and with NSTEMI. <sup>b</sup>75.3% of the included patients were from Europe, 11.1% from South America, 6.6% from Asia, 4.7% from Africa, and 2.2% from North America. <sup>c</sup>Patients in the control group were taken from a pre-COVID-19 (2018–2019) database ( $n = 24 961$ ). <sup>d</sup>Patients in the control group were taken from a pre-COVID-19 (2015–2019) database and were sex and age matched to the 230 COVID-19 positive STEMI patients (2:1 ratio of control patients to COVID-positive patients). <sup>e</sup>Crude data were not reported and have been interpolated from a study figure

Abbreviations: CGS, cardiogenic shock; CV, cardiovascular; ICU, intensive care unit; IH, in-hospital; OOH, out-of-hospital; other — see Table 1



**Figure 2.** Recommended management of suspected STEMI during the COVID-19 pandemic according to European, American, and Chinese consensus documents. Main recommendations for the management of patients with suspected STEMI according to the European College of Cardiology (European flag), American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American College of Emergency Physicians (American Flag), and the Peking Union Medical College Hospital (Chinese flag) are summarized. \*If in a PCI center, the ability to perform timely PPCI depends on staff, dedicated cath lab, and personal protective equipment availability. In a non-PCI center, clinical status, transfer time, and team-specific details should be considered  
Abbreviations: CCTA, coronary computed tomography angiography; CCU, coronary care unit; COVID-19, coronavirus disease 19; ICA, invasive coronary angiography; POCUS, point-of-care ultrasound; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction



**Central illustration.** Specific characteristics of STEMI in COVID-19 patients and their practical implications

Abbreviations: BNP, brain natriuretic peptides; CAD, coronary artery disease; COVID-19, Coronavirus Disease 19; CV, cardiovascular; gp IIb/IIIa, glycoprotein IIb/IIIa; ICU, intensive care unit; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

tution of referral centers for PCI and cardiac emergencies has been helpful in terms of limiting overall in-hospital contamination, at the cost of increasing times from symptom onset to coronary revascularization in STEMI patients [11, 39–41].

Several scientific societies have developed an algorithm for suggested management of patients with clinical suspicion of STEMI, which did reflect local epidemiological curves (Figure 2) [72, 85–88]. The Peking Union Medical College Hospital, in China, posed the minimization of total ischemia time as its primary goal. As such, fibrinolysis was recommended as the first-line therapy for almost all patients, while immediate transfer to a cardiac catheterization lab could be considered just in the case of low risk of COVID-19 where a collection of samples for nucleic acids detection was not required [72]. A joint consensus document from the American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI), and the American College of Emergency Physicians (ACEP) advocated to (1) perform ultrarapid COVID-19 testing and, if not available, consider all patients with suspected STEMI as potentially positive; (2) perform additional non-invasive imaging tests before treatment (ultrasound in every patient) to exclude “STEMI mimickers”, thereby taking into account longer door-to-balloon times; (3) regard PPCI as the standard of care as far as it can be timely provided [86].

Similar recommendations have been provided in a recently updated and published guidance from the European Society of Cardiology (ESC), which, however, stressed the goal of a maximum 120 minutes delay from diagnosis to reperfusion allowing PPCI without fibrinolysis [88, 89]. In the case of multivessel CAD on coronary angiography, treatment of non-culprit lesions and complete revascularization at the time of PPCI are also suggested by both the European and American guidelines, to limit further medical staff exposure.

## CONCLUSIONS

STEMI care in the era of COVID-19 has represented a major health issue, with alarming rates of related in-hospital complications and mortality. This is, at least in part, a collateral damage of lockdown and health systems reorganization, which have often not allowed prompt diagnosis and timely reperfusion. However, specific COVID-19 features including increased thrombogenicity, ARDS-related hypoxemia, and the likelihood of affecting patients with more cardiovascular comorbidities, might contribute to further impaired prognosis of STEMI patients with COVID-19. While lessons learned from the first wave will hopefully allow us to better manage these patients in case of future outbreaks, further research elucidating potential mechanisms of interaction between SARS-CoV-2 and coronary atherosclerosis is warranted.

## Article information

**Conflict of interest:** None declared.

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