Original Article

The Pragmatic Role of COVID-19 on the Thrombus Grade of Patients with Contemporary ST-Segment-Elevation Myocardial Infarction

Ata Firouzi, MD[1], Zahra Hosseini, MD[1], Zeinab Norouzi, MD[1], Zohre Hosseini, MD[1], Afshin Amirpour, MD[2], Hamed Talakoob, MD[3], Arash Amin, MD[4], Abbas Soleimani, MD[5], Nasrolah Moradifar, MD[4], Shahrokh Karbalai, MD[5], Mohammadhossein Mozafarybazargani, MD[3], Hamidreza Hekmat, MD[6], Majid Maleki, MD[1], Parham Sadeghipour, MD[1], Seyedeh Mahnaz Mirbod, MD[2], Mina Ghorbanpoor Kohnaki, MD[1], Hooman Bakhshandeh, MD, PhD[1], Masoomeh Kalaei Nia, MD[1], Fatemeh Sadate Habibizade, BSc[1], Sara Iraninejad, BSc[1], Mohammadreza Baay, MD[1], Ehsan Khalilipur, MD[1*]

[1]Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.
[2]Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.
[3]Cardiovascular Research Center, Alborz University of Medical Sciences, Karaj, Iran.
[4]Lorestan Heart Center, Madani Hospital, Lorestan University of Medical Sciences, Khorram Abad, Lorestan, Iran.
[5]Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.
[6]Ziaeian Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Received 02 December 2021; Accepted 24 May 2022

Abstract

Background: *Limited data exist on the clinical outcomes of patients with coronavirus disease 2019 (COVID-19) presenting with ST-segment-elevation myocardial infarction (STEMI).*

Methods: *This multicenter study, conducted in 6 centers in Iran, aimed to compare baseline clinical and procedural data between a case group, comprising STEMI patients with COVID-19, and a control group, comprising STEMI patients before the COVID-19 pandemic, and to determine in-hospital infarct-related artery thrombus grades and major adverse cardio-cerebrovascular events (MACCEs), defined as a composite of deaths from any cause (cardiovascular and noncardiovascular), nonfatal strokes, and stent thrombosis.*

Results: *No significant differences were observed between the 2 groups regarding baseline characteristics. Primary percutaneous coronary intervention (PPCI) was performed in 72.9% of the cases and 98.5% of the controls (P=0.043), and primary coronary artery bypass grafting was performed in 6.2% of the cases and 1.4% of the controls (P=0.048). Successful PPCI procedures (final TIMI flow grade III) were significantly fewer in the case group (66.5% vs 93.5%; P=0.001). The baseline thrombus grade before wire crossing was not statistically significantly different between the 2 groups. The summation of thrombus grades IV and V was 75% in the case group and 82% in the control group (P=0.432). The rate of MACCEs was 14.5% and 2.1% in the case and control groups, respectively (P=0.002).*

Conclusion: *In our study, the thrombus grade had no significant differences between the case and control groups; however, the in-hospital rates of the no-reflow phenomenon, periprocedural MI, mechanical complications, and MACCEs were statistically significantly higher in the case group.*

[*]**Corresponding Author:** ***Ehsan Khalilipur,*** *Assistant Professor of Interventional Cardiology, Iran University of Medical Sciences, Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Vali-Asr Ave, Tehran, Iran. 1996911101. Tel: +98 21 23922028. Fax: +98 21 23922340. E-mail: ehsankhalilipur@gmail.com.*

J Teh Univ Heart Ctr 2022;17(3):103-111

This paper should be cited as: Firouzi A, Hosseini Z, Norouzi Z, Hosseini Z, Amirpour A, Talakoob H, et al. The Pragmatic Role of COVID-19 on the Thrombus Grade of Patients with Contemporary ST-Segment-Elevation Myocardial Infarction. J Teh Univ Heart Ctr 2022;17(3):103-111.

Keywords: *ST-segment-elevation myocardial infarction (STEMI); COVID-19; Thrombus burden; Primary PCI*

Introduction

The World Health Organization declared coronavirus disease 2019 (COVID-19) a global pandemic on March 11 in the wake of a cluster of pneumonia cases of unknown etiology in Wuhan, China. Now, over 12 months since the onset of the pandemic, the virus continues to spread inexorably despite exhaustive research on its characteristics, pathophysiology, and treatment options in tandem with intensive efforts to curb its dissemination. Indeed, a consensus has yet to emerge as to what constitutes a dedicated therapy for this viral infection. COVID-19 infection can induce a cytokine storm by increasing the secretion of proinflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6, triggered by the high binding affinity and entrance of the viral spike (S) protein into angiotensin-converting enzyme 2 (ACE2) on the surface of human cells.[1] The respiratory tract is the organ that becomes involved the most, and it may eventually result in the development of acute respiratory distress syndrome.

The cardiovascular system can also be afflicted by the virus. The relationship between this virus and cardiovascular diseases (CVDs) is bidirectional: as myocardial injury and cardiovascular complications are not uncommon in infected patients, the most advanced cases of COVID-19 are those with preexisting CVDs. The most frequent predisposing CVD risk factors, according to multiple recent trials, are aging, hypertension, diabetes mellitus, smoking, cerebral events, chronic renal failure, chronic obstructive pulmonary disease, obesity (probably), and a history of coronary artery disease.[2] Thus, the prevalence of CVDs may be a marker of accelerated immunologic dysregulation and may relate indirectly to COVID-19 prognosis.

Acute myocardial injury, which leads to elevated troponin levels, is the most common presentation of cardiac injury and has been reported in 8% to 12% of patients. The possible mechanisms for troponin release in these patients include demand-supply mismatch (myocardial infarction [MI] type II), coronary thrombotic occlusion (either by plaque erosion or by rupture [MI type I]), coronary spasm, stress cardiomyopathy, microvascular thrombosis, and the secondary effects of systemic inflammation and hemodynamic disturbances associated with severe disease. Patients with elevated cardiac troponin levels have a worse prognosis.

ST-segment-elevation myocardial infarction (STEMI) has been reported in several studies as the first manifestation of COVID-19 among infected patients. Additionally, increased release of pro-thromboembolic agents, such as tissue factor, fibrinogen, factor VIII, D-dimer (a D-dimer level exceeding twice the upper limit of normal seems to be an independent risk factor for in-hospital mortality in patients with COVID-19), and von Willebrand factor, in conjunction with increased platelet activation, may eventually induce arterial or even venous thrombosis (the clinical manifestations of an inflammation-thrombosis-hypercoagulability cascade).[3] As STEMI is an emergent condition in CVDs, immediate percutaneous reperfusion is the preferred option in patients with possible, probable, or definite COVID-19 based on various studies in different countries. Further, it appears that the mortality rate of patients with STEMI in the COVID-19 era is dramatically higher than that before this devastating pandemic. Recent trials have posited several speculations as regards this topic.

In the present retrospective cohort study, we assessed STEMI patients with or without COVID-19 who underwent primary percutaneous coronary intervention (PPCI). Our objective was to determine in-hospital infarct-related artery thrombus grades; any-cause deaths (cardiovascular and noncardiovascular); nonfatal strokes; and major adverse cardio-cerebrovascular events (MACCEs), defined as a composite of deaths from any cause (cardiovascular and noncardiovascular), nonfatal strokes, and stent thrombosis.

Methods

The current multicenter retrospective case-control study consecutively recruited 188 patients. The control group consisted of 140 patients with STEMI who underwent PPCI in 1 center prior to the COVID-19 pandemic (before December 2019). The case group comprised 48 patients with STEMI as the first presenting symptom and with confirmed COVID-19 infection who underwent PPCI.

The confirmation of COVID-19 was based on SARS-CoV-2 on nasal/pharyngeal swabs for the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test, conducted immediately after angiography irrespective of the presence or absence of infection symptoms and diagnostic radiological chest imaging.

A questionnaire was filled out for the entire study population. Two blinded expert interventional cardiologists reviewed the angiographic findings of all the patients. The trial was arranged to compare baseline characteristics, angiographic findings, procedural data, and clinical outcomes between the case group, comprising STEMI patients with COVID-19, and the control group, comprising STEMI patients before the COVID-19 pandemic. The study protocol was approved by the institutional ethics committee.

All the contributing centers provided data, and the Kolmogorov–Smirnov test was used to examine normal distributions. Continuous variables were compared using the Student t test between the study groups and were presented as the mean and the standard deviation (SD). Categorical variables were compared using the χ^2 or the Fisher exact test, and percentages as absolute frequencies were provided. The Statistical Package SPSS, version 26.0, for Windows (IBM Corp, Armonk, NY, USA) was utilized for all the analyses. A P value below 0.05 was considered significant. The Medical Ethics Committee of Iran University of Medical Sciences approved all the phases of the current study.

The primary outcomes were composed of angiographic findings concerning culprit lesions before and after wiring the vessel (the number of coronary artery diseases, the status of culprit lesions and infarct-related arteries, and the thrombus grade based on the Mehta classification), the baseline and final thrombolysis in myocardial infarction (TIMI) flow grades, the absence or presence of the no-reflow phenomenon, and the rate of successful PCI or primary coronary artery bypass grafting (CABG).

The secondary outcomes encompassed the in-hospital rates of any-cause deaths (cardiovascular and noncardiovascular), nonfatal strokes, MACCEs (a composite of deaths from any cause [cardiovascular and noncardiovascular], nonfatal strokes, and stent thrombosis), periprocedural MI, acute and subacute stent thrombosis, mechanical complications, major vascular complications, complete revascularization (at the index session or during the hospitalization or in another hospitalization), major bleeding based on the *Bleeding* Academic Research Consortium (BARK) classification, the baseline left ventricular ejection fraction, hospitalization duration, contrast-induced nephropathy, and clinical findings (Killip class, out-of-the-hospital cardiac arrest, and cardiogenic shocks).

The exclusion criteria consisted of non–STEMI, age over 85 years, thrombolytic therapy, rescue PPCI, pharmacomechanical PCI, post-CABG status, and critical illness.

Results

The study population comprised 188 patients with STEMI criteria in electrocardiography. The control group consisted of 140 patients who underwent PPCI prior to the COVID-19 pandemic (before December 2019) in 1 center. The case group contained 48 patients with confirmed COVID-19 infection who underwent PPCI between April 2020 and December 2020 in 4 other centers. COVID-19 was confirmed based on SARS-CoV-2 on nasal/pharyngeal swabs for the RT-PCR test, performed immediately after angiography notwithstanding the presence or absence of infection symptoms and diagnostic radiological chest imaging.

No significant differences were observed between the 2 groups of COVID-19–positive patients (the case group) and the control group regarding age (59.31±7.82 y in the case group vs 61.17±6.67 y in the control group) and sex (79.1% male in the case group vs 79.4% in the control group). Hypertension was reported in 31.2% of the case group and 32.8% of the control group (P=0.194), although more patients in the control group suffered from hypertension. The incidence rate of diabetes mellitus was 27.0% and 30.7% in the case and control groups, respectively (P=0.990). Dyslipidemia was found in 39.5% of the COVID-19–positive patients and 24.2% of the control group (P=0.087), albeit more patients in the case group had dyslipidemia. The prevalence rates of the other baseline characteristics in the groups are presented in Table 1. Apropos of the presenting Killip class, 81.2% of the COVID-19–positive patients and 90.7% of those in the control group were in class I (P=0.180), even though more patients in the control group were in Killip class I. The rate of out-of-the-hospital cardiac arrest was almost similar in the 2 groups (2.0% in the case group vs 1.2% in the control group; P=0.782). The rate of cardiogenic shock was statistically significantly higher in the COVID-19–positive group (14.5% vs 3.6%; P=0.003).

Primary angiography was performed for all the patients after they had taken clopidogrel (600 mg) or ticagrelor (180 mg) in the absence of contraindications. All the patients had culprit lesions. The decision regarding the time of PCI (ad hoc or deferred procedures), the access site, the type of revascularization, the use of manual thrombectomy, glycoprotein IIb/IIIa inhibitor administration, intracoronary thrombolytic or vasodilator injection, and PCI on non-culprit lesions in the index procedure was dependent on the operator's judgment and the patient's condition. Symptom onset to first medical contact (FMC) and FMC to wire crossing were expectedly longer in the COVID-19–positive group than in the control group (Table 2). The rate of significant coronary artery stenosis (>50% stenosis) was different between the 2 groups. In the COVID-19–positive patients, single-vessel disease was more pronounced (62.5% vs 60.7%; P=0.153), whereas the summation of double and triple-vessel diseases was lower in the case group than in the control group (22.9% vs 39.3%;

Table 1. Baseline demographic data of the study population*

	Case Group	Control Group	P
Mean age (y)	59.31±7.82	61.17±6.67	0.534
Sex (male)	38 (79.1)	111(79.4)	0.952
Hypertension	15 (31.2)	46 (32.8)	0.194
Diabetes mellitus	13 (27.0)	43(30.7)	0.990
Dyslipidemia	19 (39.5)	34 (24.2)	0.087
Smoking	16 (33.3)	51 (36.4)	0.913
Previous cerebrovascular accidents	1 (2.0)	4 (2.8)	0.861
Previous myocardial infarction	2 (4.2)	10 (7.1)	0.556
Previous revascularization	6 (12.5)	26 (18.5)	0.537
Chronic kidney disease	2 (4.2)	6 (4.2)	0.893
Presenting Killip class I	39 (81.2)	127 (90.7)	0.188
Out-of-the-hospital cardiac arrest	1 (2.0)	3 (1.2)	0.782
Cardiogenic shock	7 (14.5)	5 (3.6)	0.003

*Data are presented as mean±SD or n (%).

P=0.15). The distribution of culprit lesions was similar in the 2 groups (the left main: 5.1% in the case group vs 3.3% in the control group; P=0.812, the left anterior descending: 30.7% vs 53.6%; P=0.456, the left circumflex artery: 20.5% vs 15.4%; P=0.853, and the right coronary artery: 43.5% vs 28.1%; P=0.559). The location of culprit lesions in infarct-related arteries was not statistically significantly different between the COVID-19–positive group and the control group. Nonetheless, the proximal segment was more frequently involved in the case group (56.4% vs 42.7%; P=0.093), while mid-part vessel involvement was less common in the case group (30.7% vs 53.6%; P=0.093). The incidence of more than 1 culprit lesion/concomitant multi-vessel thrombosis (7.6% in the case group vs 8.5% in the control group; P=0.682) and acute or subacute stent thrombosis during hospitalization (2.4% in the case group vs 2.1% in the control group; P=0.969) was similar in the 2 groups. PPCI was performed in 72.9% of the case group and 98.5% of the control group (P=0.043), and primary CABG was performed in 6.2% of the case group and 1.4% of the control group (P=0.048). The number of successful PCI procedures (final TIMI flow grade III) was significantly lower in the COVID-19–positive group (66.5% vs 93.5%; P=0.001), and this group had a significantly higher number of primary CABG procedures owing to failed PCI (10.4% vs 0.7%; P=0.001). The rates of cardiac arrest and resuscitation during PPCI were significantly higher in the case group (12.5% vs 2.1%; P=0.002), as was the incidence of severe left ventricular systolic dysfunction (30.8% vs 23.7%; P=0.052). The incidence of periprocedural MI (high-sensitivity troponin I elevation>5 times or >20% elevation in troponin after PCI in those who had positive troponin at baseline) was remarkably higher in the COVID-19–positive patients than in the control group (14.5% vs 0%; P=0.001) (Table 2).

The baseline thrombus grade before wire crossing according to the Mehta classification myocardial blush was not statistically significantly different between the 2 groups (Table 2). The baseline summation of thrombus grades 0 to III was 25.0% in the COVID-19–positive patients and 17.5% in the control group (P=0.432), and the summation of thrombus grades IV and V was 75.0% in the case group and 82.1% in the control group (P=0.432). The difference between the 2 groups in terms of the thrombus grade after wiring the vessel was also nonsignificant. The summation of thrombus grades 0 to III was 31.3% in the case group and 28.5% in the control group (P=0.497), and the summation of thrombus grades IV and V was 68.7% in the case group and 71.5% in the control group (P=0.497). Unexpectedly, the rate of the administration of glycoprotein IIb/IIIa was significantly lower in the case group (17.6% vs 52.8%; P=0.005) (Table 2).

The rate of TIMI flow grades 0 and I before wire crossing was 73.7% in the COVID-19–positive group and 72.8% in the control group (P=0.812), and the final TIMI flow III was considerably lower in the COVID-19–positive group than in the control group (71.1% vs 81.4%; P=0.031) (Table 2).

The no-reflow phenomenon was significantly more frequent in the case group than in the control group (14.5% vs 0.7%; P<0.001). The need for vasodilators and mechanical circulatory support devices during PPCI was notably higher in the COVID-19–positive patients than in the patients in the control group (12.5% vs 3.5%; P=0.035).

The rate of complete revascularization in the index hospitalization was statistically meaningfully lower in the case group than in the control group (61.8% vs 84.7%; P=0.004).

The occurrence of in-hospital mechanical complications was infrequent. Our findings revealed 1 case of post-MI ventricular septal rupture and 3 cases of acute mitral regurgitation in the COVID-19 positive patients and 1 case of acute mitral regurgitation in the control group (8.3% vs 0.7%; P=0.022). The incidence of contrast-induced nephropathy (creatinine level elevation>0.3 mg/dL or glomerular filtration rate reduction>25% within 48 h) was markedly higher in

Table 2. Angiographic and procedural data of the study population

	Case Group	Control Group	P
FMC-to-wire passage <90 min	15 (31.2)	115 (82.1)	0.001
Single-vessel disease	30 (62.5)	85 (60.7)	0.153
Summation of double and triple-vessel diseases	11 (22.9)	55 (39.3)	
Culprit lesion distribution			
LM	2 (5.1)	5 (3.3)	0.812
LAD	12 (30.7)	80 (53.6)	0.456
LCX	8 (20.5)	23 (15.4)	0.853
RCA	17 (43.5)	42 (28.1)	0.559
Location of the culprit lesion in the IRA			
Proximal	22 (56.4)	59 (42.7)	0.093
Mid-part	12 (30.7)	74 (53.6)	
Distal	5 (12.8)	5 (3.6)	
More than 1 culprit lesion/concomitant multi-vessel thrombosis	3 (7.6)	12 (8.5)	0.682
Acute or subacute stent thrombosis	1 (2.4)	3 (2.1)	0.969
PPCI	35 (72.9)	138 (98.5)	0.043
Primary CABG	3 (6.2)	2 (1.4)	0.048
Successful PCI	26 (66.5)	131 (93.5)	0.001
Primary CABG owing to failed PCI	5 (10.4)	1 (0.7)	0.001
Cardiac arrest and resuscitation during PCI	6 (12.5)	3 (2.1)	0.002
Severe LV dysfunction	12 (30.8)	54 (23.7)	0.052
Periprocedural MI	7 (14.5)	0 (0)	0.001
Summation of thrombus grades 0 to III (before wire crossing)	12 (25.0)	25 (17.5)	0.432
Summation of thrombus grades IV and V (before wire passing)	36 (75.0)	115 (82.1)	
Summation of thrombus grades 0 to III (after wiring)	15 (31.3)	40 (28.5)	0.497
Summation of thrombus grades IV and V (after wiring)	33 (68.7)	100 (71.5)	
Administration of glycoprotein IIb/IIIa inhibitors	3 (17.6)	74 (52.8)	0.005
TIMI flow grade 0 and I (before wire crossing)	28 (73.7)	102 (72.8)	0.812
TIMI flow grade III (after revascularization)	27 (71.1)	114 (81.4)	0.031
No-reflow phenomenon	7 (14.5)	1 (0.7)	<0.001
Need for MCS	6 (12.5)	5 (3.5)	0.035
Complete revascularization in the index hospitalization	21 (61.8)	105 (84.7)	0.004

CABG, Coronary artery bypass grafting; FMC, first medical contact; IRA, Infarct-related artery; LM, left main, LAD, Left anterior descending; LCX, Left circumflex; RCA, MCS, Mechanical circulatory support; Right coronary artery; PCI, Percutaneous coronary intervention; LV, Left ventricle; MI, Myocardial infarction; TIMI, Thrombolysis in myocardial infarction

Table 3. In-hospital outcomes of the study population

	Case Group	Control Group	P
Mechanical complications	4 (8.3)	1 (0.7)	0.022
CIN	7 (14.5)	5 (3.5)	0.017
Hospitalization duration (<7 d)	27 (56.2)	123 (87.8)	0.006
In-hospital cardiovascular deaths	5 (10.4)	0 (0.0)	0.001
Noncardiovascular deaths	0	0	0.037
Nonfatal strokes	2 (4.1)	0 (0)	0.052
Rate of deaths from any cause	5 (10.4)	0 (0)	0.001
MACCE	7 (14.5)	3 (2.1)	0.002
Major vascular complication	0 (0)	1 (0.7)	0.526
Major bleeding	2 (4.1)	2 (1.4)	0.218

CIN, Contrast-induced nephropathy; MACCE, Major adverse cardio-cerebrovascular events

the case group than in the control group (14.5% vs 3.5%; P=0.017). Hospitalization duration was significantly longer in the COVID-19–positive group (<7 d: 67.5% vs 87.8%; P=0.006). The rate of in-hospital cardiovascular deaths was statistically significantly higher in the case group than in the control group (10.4% vs 0.0%; P=0.001), while the rate of noncardiovascular deaths was 0 in both groups. Nonfatal strokes were statistically meaningfully more frequent in the COVID-19–positive group (4.1% vs 0.0%; P=0.052). The rate of any-cause deaths was also significantly higher in the case group than in the control group (10.4% vs 0.0%; P=0.001). The rate of MACCEs was 14.5% and 2.1% in the case and control groups, respectively (P=0.002). The 2 study groups were similar in terms of major vascular complications (P=0.526) and total major bleeding based on the BARK classification (P=0.218) (Table 3).

Discussion

STEMI has been reported as a rare presenting feature of the COVID-19 pandemic. Several theories have been propounded in multiple trials and registries with regard to the etiologies of this manifestation. Almost all studies and registries during this pandemic have demonstrated that the incidence and prevalence of STEMI patients either in PCI-capable centers or in non–PCI-capable centers have fallen significantly by between 30% and 50%.[4] Additionally, the mean symptom-to-device time and the mean FMC-to-device time have risen dramatically by comparison with the same time frame in the previous year (delays in treatment timelines).[5] In the early days of the pandemic, the focal point of the research was on the kind of revascularization (PPCI or thrombolytic injection) in patients with COVID-19 infection to reduce the chance of virus spreading. Gradually, a consensus emerged that each center should consider its local facilities in the formulation of its dedicated protocols to enhance patient care during the pandemic. Significance was also attached to PPCI in settings with dedicated cardiac catheterization laboratories, cardiac care units, and personal protective equipment (PPE).

Multiple small non-randomized trials have compared the outcomes of STEMI patients between 2 groups of COVID-19–positive and COVID-19–negative in minimum follow-up periods of 30 days. Four major registries in Hong Kong (125 patients),[5] the United States (18 patients),[6] Italy (28 patients),[7] and England (115 patients)[8] have published their data. The Hong Kong registry failed to report the rate of in-hospital mortality. In the United States registry, the total in-hospital mortality rate was 72%, of which 50% were related to MI. The total in-hospital mortality rate was 32% in the Italy registry, where culprit lesions were detected only in 35% of the patients. In the England registry, the rate of in-hospital mortality in STEMI patients was 17.9% in the COVID-19–positive group and 6.5% in the COVID-19–negative group. In the registries of the United States and Italy, respectively, more than 50% and about 40% of the patients assessed had no culprit lesions. However, the mortality rates were significantly higher among STEMI patients with COVID-19: 72% in the United States and 39% in Italy. A key finding in the England registry was a high thrombus burden in COVID-19–positive patients by comparison with COVID-19–negative patients (75% vs 31.4%). Moreover, in STEMI patients, multi-vessel thrombosis was seen in 17.9% of the COVID-19–positive patients as opposed to none of the COVID-19–negative patients. Additionally, according to the England registry, stent thrombosis as the initial presentation was 10 times more likely in patients with COVID-19, among whom angiographic complexity and the use of glycoprotein IIb/IIIa inhibitors or thrombectomy were more frequent as well. The in-hospital mortality rate in the England registry was much lower than that in the registries of the United States and Italy. A large observational study in China showed a rise in the rates of in-hospital mortality and in-hospital heart failure from 4.6% to 7.3% and from 14.2% to 18.4%, respectively, in STEMI patients during the COVID-19 outbreak.[9] Another large retrospective multicenter and observational registry of STEMI patients in Spain reported an all-cause mortality rate of 7.5% during the COVID-19 era as opposed to 5.1% in the pre–COVID-19 era.[10]

In our previous cohort study, conducted on 48 patients with STEMI in the early phase of the pandemic, all the cases had culprit lesions, and about 18% of them were suspected with COVID-19 infection based on chest computed tomography scan findings or PCR. The total mortality rate was 6.25% during a follow-up period of 35.9±12.7 days. In that study, we recommended PPCI as the default revascularization strategy even in confirmed cases of COVID-19 in dedicated cardiac catheterization laboratories with appropriate PPE.[11]

The relationship between a high thrombus burden in the culprit vessel and a poor prognosis in STEMI patients has been confirmed in previous trials. The Rotterdam Study, which excluded totally thrombotic occluded vessels, reported significantly higher rates of death, repeat MI, and infarct-related artery revascularization in the group with a high thrombus burden (24.9% vs 15.3%; P<0.001).[12] The sensitivity of the angiographic-guided estimation of small or moderate-sized thrombi is not more than 50% to 60%. Additionally, interobserver discrepancies are relatively high, and the best way for the accurate assessment of thrombus burden is imaging modalities such as intravascular ultrasonography and optical coherence tomography.[12] Still, in most trials, including the present study, the thrombus burden is approximated subjectively by at least 2 expert interventionalists.

The setting of COVID-19 is concomitant with cytokine storms, highly activated inflammatory parameters (elevated acute-phase reactant factors), and extreme prothrombotic

states (eg, elevated levels of D-dimer, fibrinogen, ferritin, and lactate dehydrogenase). In this setting, the probable associations between the clot burden of culprit lesions in patients with COVID-19 infection presenting with STEMI and in-hospital and at least 30 days' follow-up MACCE rates have yet to be evaluated adequately. Multiple case reports and case series have demonstrated that patients with COVID-19 infection have a higher trend toward the incidence of thrombosis in the arterial (coronary, cerebral, and peripheral arteries) and venous (deep vein thrombosis and pulmonary emboli) systems.

In the current historical randomized single-blind 2-arm study on STEMI patients divided into the COVID-19–positive group and the control group, the study population's mean age was 59.31±7.82 years, 79% were male in both groups, and there were no statistically significant differences in the baseline characteristics and comorbidities between the groups (Table 1). In earlier studies and registries, the rates of cardiovascular comorbidities, such as hypertension and diabetes mellitus, were markedly higher in patients with COVID-19 infection (especially critically ill patients), those admitted to the intensive care unit, and those who died. In our study, emergent angiography was performed for all the patients; nonetheless, the FMC-to-wiring time was significantly prolonged in the case group. By comparison with previous studies, all the patients with STEMI had culprit lesions. The distribution of culprit lesions, the number of infarct-related arteries, the rate of stent thrombosis, and the presenting Killip class were similar between our 2 groups. PPCI and primary CABG were performed in 98.5% and 1.4% of the control group, respectively, and 72.9% and 6.2% of the COVID-19–positive patients, respectively (P=0.043 and P=0.048, respectively). The thrombus grades of culprit lesions at baseline and after wiring were not statistically significantly different between our 2 groups of STEMI patients, who underwent PPCI: those who underwent the procedure before the pandemic and those who underwent the procedure with a positive COVID-19 test (P=0.432 and P=0.497, respectively). While the baseline TIMI flow grade of infarct-related arteries was similar in the 2 groups, the final TIMI flow grade III and the rate of successful PCI were statistically meaningfully higher in the control group. The rates of the no-reflow phenomenon, periprocedural MI, failed PCI, cardiogenic shocks, cardiac arrest during PCI, the need for mechanical circulatory support, and emergent CABG were significantly higher in the COVID-19–positive group (Table 2). In our study on patients with STEMI undergoing PPCI, the results demonstrated drastic increases in the short-term (in-hospital) clinical outcomes (MACCEs), mechanical complications, and hospitalization duration in the COVID-19–positive patients in comparison with the control group (Table 3). Additionally, more patients in the case group had lower ejection fractions at baseline (Figure 1).

Recent studies have shown that similar to other viral infections, such as SARS-CoV, MERS-CoV, and influenza, COVID-19 can lead to a rise in systemic inflammatory markers, including C-reactive protein, ferritin, D-dimer, fibrinogen, factor VIII, von Willebrand factor, and troponin (suggestive of myocardial injury). According to a study by Cui et al,[13] a D-dimer level above 3 times the upper limit of normal can predict mortality with a sensitivity of more than 90% and a specificity of more than 80%. COVID-19 can induce proinflammatory and procoagulative states

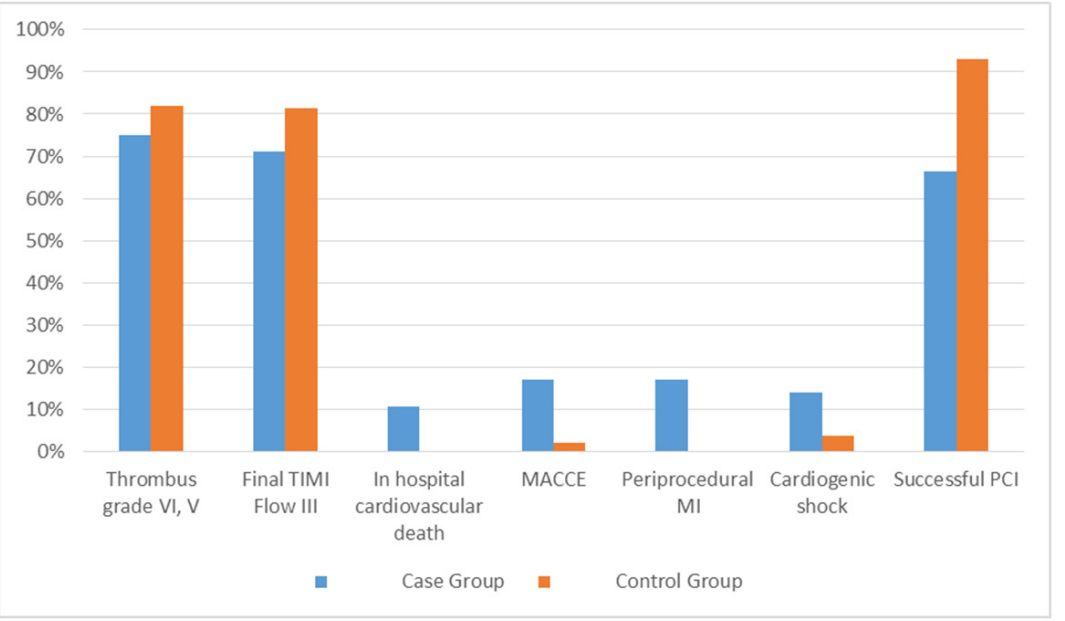

Figure 1. The image shows the effects of COVID-19 on the outcomes of patients with STEMI.
MI, Myocardial infarction; TIMI, MACCE, Major adverse cardio-cerebrovascular events, Thrombolysis in myocardial infarction

by systemic endothelial injury and increased secretion of proinflammatory cytokines and chemokines, such as TNF-α, IL-1β, and IL-6, leading to cytokine storms and microthrombus formation in venous and arterial beds. In an earlier study, the rate of venous and arterial thromboembolic complications in hospitalized patients with COVID-19 infection was remarkable (≈8%).[14] Activated macrophages secrete collagenases, which degrade collagen, a major constituent of the fibrous cap on atherosclerotic plaques; this process can lead to plaque rupture. Activated macrophages are also known to secrete tissue factor, a potent procoagulant, enhancing platelet activation. Increased platelet activation triggers more fibrin production and thrombus formation when plaques rupture. A single-center report from Italy described 20 patients with COVID-19 and acute limb ischemia. The incidence rate of critical limb ischemia at this center was high compared with that in the previous year (16.3% vs 1.8%; P<0.001).[15] Direct vascular injury caused by SARS-CoV-2 infection might also increase the risk of thrombus formation and acute coronary syndromes (clinical manifestations of an inflammation-thrombosis-hypercoagulability cascade). We did not check inflammatory markers in our study; nevertheless, recent trials have shown that the inflammatory storm in infected patients might present itself with acute coronary syndromes. Nevertheless, in contrast to recent studies, we found a similar thrombus grade in our 2 study groups, although the rates of the no-reflow phenomenon, microvascular obstruction, and failed PCI were higher, and infarct size was larger in our COVID-19–infected group significantly. On the other hand, as the FMC-to-wire time was significantly longer in this group, the total ischemic time was more prolonged, and the rates of mechanical complications, cardiogenic shocks, and cardiac arrest during PCI were higher. Finally, as a consequence of larger infarction size, the rates of cardiovascular deaths and total morbidity and mortality were statistically meaningfully higher in our case group.

Given the retrospective and multicenter nature of our study, we have some missed data. Another salient drawback is that we did not check inflammatory markers to establish their correlation with angiographic and clinical outcomes; we merely relied on multiple recent trials, which confirmed this relationship. Another weakness is inter and intraobserver variations in the estimation of the thrombus burden grade by visual assessment and not by dedicated intracoronary imaging tools. That our follow-up duration was limited to in-hospital admissions can be deemed another shortcoming.

Conclusion

The outbreak of COVID-19, which is a multisystemic disorder, has led to a substantial drop in the number of admitted STEMI cases and delays in patients' access to care. In our study, performed on STEMI patients, baseline demographic characteristics and thrombus grades had no significant differences between the case group, comprising COVID-19–positive patients undergoing PPCI, and the control group, encompassing patients undergoing PPCI before the COVID-19 era. However, the in-hospital rates of the no-reflow phenomenon, periprocedural MI, mechanical complications, and MACCEs (a composite of any-cause deaths [cardiovascular and noncardiovascular], nonfatal strokes, and stent thrombosis) were statistically significantly higher in the case group. It, therefore, appears that the most important factor that led to the increased rate of MACCEs in this group may be prolonged symptom onset to FMC and FMC to wiring.

To improve the clinical outcomes of STEMI patients with concurrent COVID-19 infection, we recommend that the FMC-to-wiring time be lessened as much as possible. Moreover, centers should accelerate the reperfusion of infarct-related arteries, which requires dedicated cardiac catheterization laboratories, cardiac care units, and PPE. Further comprehensive investigations on the pathophysiology of this virulent virus and its effect on the cardiovascular system are needed to optimize the short and long-term cardiovascular outcomes of these patients.

Acknowledgments

This study was approved and supported by the Medical Ethics committee and the Cardiovascular Intervention Research Center of Rajaie Cardiovascular Medical and Research Center. We thank all the patients who participated in this study and granted us permission to analyze their data to reduce the cardiovascular burden of the COVID-19 pandemic.

References

1. Meduri GU, Kohler G, Headley S, Tolley E, Stentz F, Postlethwaite A. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. Chest 1995;108:1303-1314.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-1242.
3. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18:1738-1742.
4. Abdi S, Salarifar M, Mortazavi SH, Sadeghipour P, Geraiely B. COVID-19 sends STEMI to quarantine!? Clin Res Cardiol 2020;109:1567-1568.
5. Tam CF, Cheung KS, Lam S, Wong A, Yung A, Sze M, Lam YM, Chan C, Tsang TC, Tsui M, Tse HF, Siu CW. Impact

of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment-Elevation Myocardial Infarction Care in Hong Kong, China. Circ Cardiovasc Qual Outcomes 2020;13:e006631.
6. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-Segment Elevation in Patients with Covid-19 - A Case Series. N Engl J Med 2020;382:2478-2480.
7. Stefanini GG, Montorfano M, Trabattoni D, Andreini D, Ferrante G, Ancona M, Metra M, Curello S, Maffeo D, Pero G, Cacucci M, Assanelli E, Bellini B, Russo F, Ielasi A, Tespili M, Danzi GB, Vandoni P, Bollati M, Barbieri L, Oreglia J, Lettieri C, Cremonesi A, Carugo S, Reimers B, Condorelli G, Chieffo A. ST-Elevation Myocardial Infarction in Patients With COVID-19: Clinical and Angiographic Outcomes. Circulation 2020;141:2113-2116.
8. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, Woldman S, Jain AK, Knight CJ, Baumbach A, Mathur A, Jones DA. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol 2020;76:1168-1176.
9. Xiang D, Xiang X, Zhang W, Yi S, Zhang J, Gu X, Xu Y, Huang K, Su X, Yu B, Wang Y, Fang W, Huo Y, Ge J. Management and Outcomes of Patients With STEMI During the COVID-19 Pandemic in China. J Am Coll Cardiol 2020;76:1318-1324.
10. Rodríguez-Leor O, Cid-Álvarez B, Pérez de Prado A, Rossello X, Ojeda S, Serrador A, López-Palop R, Martín-Moreiras J, Rumoroso JR, Cequier Á, Ibáñez B, Cruz-González I, Romaguera R, Moreno R; Working Group on the Infarct Code of the Interventional Cardiology Association of the Spanish Society of Cardiology Investigators, Villa M, Ruíz-Salmerón R, Molano F, Sánchez C, Muñoz-García E, Íñigo L, Herrador J, Gómez-Menchero A, Gómez-Menchero A, Caballero J, Ojeda S, Cárdenas M, Gheorghe L, Oneto J, Morales F, Valencia F, Ruíz JR, Diarte JA, Avanzas P, Rondán J, Peral V, Pernasetti LV, Hernández J, Bosa F, Lorenzo PLM, Jiménez F, Hernández JMT, Jiménez-Mazuecos J, Lozano F, Moreu J, Novo E, Robles J, Moreiras JM, Fernández-Vázquez F, Amat-Santos IJ, Gómez-Hospital JA, García-Picart J, Blanco BGD, Regueiro A, Carrillo-Suárez X, Tizón H, Mohandes M, Casanova J, Agudelo-Montañez V, Muñoz JF, Franco J, Del Castillo R, Salinas P, Elizaga J, Sarnago F, Jiménez-Valero S, Rivero F, Oteo JF, Alegría-Barrero E, Sánchez-Recalde Á, Ruíz V, Pinar E, Pinar E, Planas A, Ledesma BL, Berenguer A, Fernández-Cisnal A, Aguar P, Pomar F, Jerez M, Torres F, García R, Frutos A, Nodar JMR, García K, Sáez R, Torres A, Tellería M, Sadaba M, Mínguez JRL, Merchán JCR, Portales J, Trillo R, Aldama G, Fernández S, Santás M, Pérez MPP. Impact of COVID-19 on ST-segment elevation myocardial infarction care. The Spanish experience. Rev Esp Cardiol (Engl Ed) 2020;73:994-1002.
11. Firouzi A, Baay M, Mazayanimonfared A, Pouraliakbar H, Sadeghipour P, Noohi F, Maleki M, Peighambari MM, Kiavar M, Abdi S, Maadani M, Shakerian F, Zahedmehr A, Kiani R, Alemzadeh-Ansari MJ, Rashidinejad A, Hosseini Z. Effects of the COVID-19 Pandemic on the Management of Patients With ST-elevation Myocardial Infarction in a Tertiary Cardiovascular Center. Crit Pathw Cardiol 2021;20:53-55.
12. Sianos G, Papafaklis MI, Serruys PW. Angiographic thrombus burden classification in patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. J Invasive Cardiol 2010;22(10 Suppl B):6B-14B.
13. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020;18:1421-1424.
14. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094-1099.
15. Bellosta R, Luzzani L, Natalini G, Pegorer MA, Attisani L, Cossu LG, Ferrandina C, Fossati A, Conti E, Bush RL, Piffaretti G. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020;72:1864-1872.