Angiology
2022, Vol. 0(0) 1–10

DOI: 10.1177/00033197221129351
journals.sagepub.com/home/ang
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SARS-CoV-2 Positivity, Stent Thrombosis, and 30-day Mortality in STEMI Patients Undergoing Mechanical Reperfusion

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Abstract

SARS-Cov-2 has been suggested to promote thrombotic complications and higher mortality. The aim of the present study was to evaluate the impact of SARS-CoV-2 positivity on in-hospital outcome and 30-day mortality in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) enrolled in the International Survey on Acute Coronary Syndromes ST-segment elevation Myocardial Infarction (ISACS-STEMI COVID-19 registry. The 109 SARS-CoV-2 positive patients were compared with 2005 SARS-CoV-2 negative patients. Positive patients were older ($P = .002$), less often active smokers ($P = .002$), and hypercholesterolemic ($P = .006$), they presented more often later than 12 h ($P = .037$), more often to the hub and were more often in cardiogenic shock ($P = .02$), or requiring rescue percutaneous coronary intervention after failed thrombolysis ($P < .0001$). Lower postprocedural Thrombolysis in Myocardial Infarction 3 flow ($P = .029$) and more thrombectomy ($P = .046$) were

observed. SARS-CoV-2 was associated with a significantly higher in-hospital mortality (25.7 vs 7%, adjusted Odds Ratio (OR) [95% Confidence Interval] = 3.2 [1.71-5.99], $P < .001$) in-hospital definite in-stent thrombosis (6.4 vs 1.1%, adjusted Odds Ratio [95% CI] = 6.26 [2.41-16.25], $P < .001$) and 30-day mortality (34.4 vs 8.5%, adjusted Hazard Ratio [95% CI] = 2.16 [1.45-3.23], $P < .001$), confirming that SARS-CoV-2 positivity is associated with impaired reperfusion, with negative prognostic consequences.

Keywords
thrombosis, STEMI, outcome

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Introduction

Coronavirus disease 2019 (COVID-19) has been reported in more than 100 million cases, resulting in several million deaths.[1] An increased cardiovascular (CV) mortality during the COVID pandemic has been described due to direct and indirect effect of SARS-Cov-2 infection.[1,2] Attention has been paid regarding the impact of fear of contagion on the reduced number of ST-segment elevation myocardial infarction (STEMI) patients and their delayed presentation during the COVID pandemic, contributing to the increased mortality observed in this population.[3-7] Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) has also been associated with thrombotic complications, attributed to excessive inflammation, endothelial dysfunction, platelet activation, and coagulation/fibrinolysis disturbances.[2,8] Our and other reports suggested a very high in-hospital mortality rate and in-stent thrombosis among SARS-Cov-2 positive patients with STEMI.[6,9-12]

The aim of the present study was to evaluate the impact of SARS-Cov-2 positivity on in-hospital outcome and 30-day mortality, among patients enrolled with STEMI undergoing mechanical reperfusion in global registry conducted during the COVID-19 pandemic.

Methods

Our study population is represented by patients who underwent SARS-Cov-2 screening, enrolled in the International Study on Acute Coronary Syndromes - ST segment Elevation Myocardial Infarction (ISACS-STEMI) COVID-19, a large-scale retrospective multicenter registry involving primary percutaneous coronary intervention (pPCI) centers from Europe, Latin America, South-East Asia, and North-Africa, including patients treated from March 1 to June 30, 2019 and 2020.[12]

We collected demographic, clinical, procedural data, data on total ischemia time, door-to-balloon time, referral to pPCI facility, PCI procedural data, in-hospital outcomes, including death, Stent Thrombosis (according to ARC definition), and 30-day mortality. We additionally collected detailed information on SARS-Cov-2 positive patients, including the presence of symptoms before or during the intervention, timing of SARS-Cov-2 diagnosis and the specific medications for COVID. The study was approved by the Ethical Committee of AOU Maggiore della Carità, Novara.

Statistics

Data analysis was performed by the use of SPSS Statistics Software 23.0 (IBM SPSS Inc, Chicago, Illinois). Quantitative variables were described using median and interquartile range. Absolute frequencies and percentages were used for qualitative variables. ANOVA or Mann-Whitney and chi-square test were used for continuous and categorical variables, respectively. Normal distribution of continuous variables was tested by the Kolmogorov–Smirnov test. Primary study endpoint was in-hospital mortality. Secondary study endpoints were in-hospital stent thrombosis, heart failure, and major bleeding complications and 30-day mortality.

Multivariable Cox and logistic regression analyses were performed to identify the impact of SARS-Cov-2 positivity on primary and secondary study endpoints after adjustment for baseline confounding factors between the 2 groups. All significant variables (set at a $P < .1$) were entered in block into the model. A 2-sided $P < .05$ was considered statistically significant. The data coordinating center was established at the Eastern Piedmont University.

Results

We included a total of 109 SARS-CoV-2 positive patients who were compared with 2005 SARS-CoV-2 negative STEMI patients. Patient characteristics are described in Table 1. SARS-CoV-2 positive patients were older (67 [58–75] vs 63 [54–72] years, $P = .002$), less often active smokers (25.7 vs 42.1%, $P = .002$), and hypercholesterolemic (29.4 vs 42.6%, $P = .006$), whereas no difference was observed in other major baseline characteristics. A significant difference was observed in geographic areas with most of the patients included in Europe ($P < .001$). SARS-CoV-2 positive patients presented more often later than 12 h (18.3 vs 11.7%, $P = .037$), whereas no difference was observed in door-to-balloon time. Direct presentation to the hub (35.8 vs 25.6%, $P < .001$), cardiogenic shock (16.5 vs 9.6%, $P = .02$), and rescue PCI after failed thrombolysis (14.7 vs 2.6%, $P < .0001$) were more often

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Table 1. Baseline Demographic and Clinical Ccharacteristics.

	SARS-CoV2 Positive (n = 109)	SARS-CoV2 Negative (n = 2005)	*P*
Age (median, IQR)	67 [58–75]	63 [54–72]	.002
Age >75 year – n (%)	28 (25.7)	394 (19.7)	.126
Male gender – n (%)	80 (73.4)	1550 (77.4)	.334
Medical history			
Diabetes mellitus – n (%)	26 (23.9)	458 (22.9)	.811
Hypertension – n (%)	59 (54.1)	1119 (55.9)	.722
Hypercholesterolemia – n (%)	32 (29.4)	854 (42.6)	.006
Active smoker – n (%)	28 (25.7)	844 (42.1)	.002
Family history of CAD – n (%)	15 (13.8)	340 (17.0)	.382
Previous STEMI – n (%)	8 (7.3)	178 (8.9)	.579
Previous PCI – n (%)	12 (11.0)	243 (12.1)	.726
Previous CABG – n (%)	0 (.0)	38 (1.9)	.147
Geographic area			<.001
Europe – n (%)	96 (88.1)	1873 (93.5)	
Latin-America – n (%)	6 (5.5)	34 (1.7)	
South East Asia – n (%)	3 (2.8)	96 (4.8)	
North Africa – n (%)	4 (3.7)	0 (.0)	
Referral to primary PCI hospital			
Type			.039
Ambulance (from community) – n (%)	49 (45.0)	956 (47.7)	
Direct access – n (%)	39 (35.8)	512 (25.6)	
Access to spoke – n (%)	21 (19.3)	535 (26.7)	
Time delays			
Ischemia time, median [25–75th]	210 [100-556]	210 [123-360]	.77
Total ischemia time			
<6 h – n (%)	70 (64.2)	1515 (75.6)	
6–12 h – n (%)	19 (17.4)	256 (12.8)	
12–24 h – n (%)	11 (10.1)	143 (7.1)	
>24 h – n (%)	9 (8.3)	91 (4.5)	
Total ischemia time >12 h – n (%)	20 (18.3)	234 (11.7)	.037
Door-to-balloon time, median [25–75th]	40 [25-97]	35 [22-60]	.27
Door-to-balloon time			
<30 min – n (%)	48 (44)	903 (45)	
30-60 min – n (%)	22 (20.2)	649 (32.4)	
>60 min – n (%)	39 (35.8)	453 (22.6)	
Door-to-balloon time >30 min (%) – n (%)	62 (56.0)	1100 (54.9)	.831
Clinical presentation			
Anterior STEMI – n (%)	47 (43.1)	923 (46.1)	.546
Out-of-hospital cardiac arrest – n (%)	7 (6.4)	174 (8.7)	.411
Cardiogenic shock– n (%)	18 (16.5)	193 (9.6)	.020
Rescue PCI for failed thrombolysis – n (%)	16 (14.7)	53 (2.6)	<.001
Killip class – n (%)			0.7
I	80 (73.4)	1554 (77.5)	
II	10 (9.2)	178 (8.9)	
III	7 (6.4)	93 (4.6)	
IV	12 (11)	180 (9.0)	

Abbreviations: CABG, Coronary Artery Bypass Graft; CAD, Coronary Artery Disease; IQR, interquartile range; PCI, Percutaneous Coronary Intervention; SARS-CoV2, severe acute respiratory syndrome coronavirus-2; STEMI, ST-segment Elevation Myocardial Infarction.
[a]Mann-Whitney test.

observed among SARS-CoV-2 positive patients. Table 1S shows detailed characteristics of SARS-CoV-2 positive, in particular concerning the timing of diagnosis, symptoms, and medical therapy.

Table 2 shows angiographic and procedural characteristics. SARS-CoV-2 positive patients had less often radial access (72.5 vs 83.3%, $P = .004$) and, more importantly, more often impaired postprocedural Thrombolysis in

Table 2. Angiographic and Procedural Characteristics.

	SARS-CoV2 Positive (n = 109)	SARS-CoV2 Negative (n = 2005)	*P*
Radial access (%)	79 (72.5)	1668 (83.3)	.004
Culprit vessel			.380
Left main – n (%)	1 (.9)	37 (1.8)	
Left Anterior descending Artery – n (%)	44 (40.4)	915 (45.7)	
Circumflex – n (%)	16 (14.7)	323 (16.1)	
Right coronary Artery – n (%)	47 (43.1)	710 (35.4)	
Anterolateral branch – n (%)	1 (.9)	5 (.2)	
In-stent thrombosis – n (%)	6 (5.5)	84 (4.2)	.509
Multivessel disease – n (%)	53 (48.6)	1022 (51.0)	.700
Preprocedural TIMI 0 flow – n (%)	70 (64.2)	1336 (66.7)	.593
Thrombectomy– n (%)	31 (28.4)	410 (20.5)	.046
Stenting – n (%)	101 (92.7)	1778 (88.8)	.206
Drug-eluting stent – n (%)	98 (89.9)	1849 (92.3)	.363
Postprocedural TIMI 3 flow – n (%)	94 (86.2)	1845 (92.1)	.029
Gp IIb-IIIa inhibitors/cangrelor – n (%)	31 (28.4)	430 (21.5)	.086
Bivalirudin – n (%)	0 (0)	5 (.2)	1.0
Mechanical support – n (%)	5 (4.6)	100 (5.0)	.850
Additional PCI			.876
During the index procedure – n (%)	11 (10.1)	226 (11.3)	
Staged– n (%)	15 (13.8)	250 (12.5)	
DAPT therapy – n (%)	108 (99.1)	1982 (98.9)	.859
RASI– n (%)	60 (55.0)	1448 (72.3)	<.001

Abbreviations: DAPT, Dual Antiplatelet Therapy; glycoprotein, IIbIIIa; percutaneous, coronary intervention Gp IIb-IIIa; RASI, Renin-Angiotensin System Inhibitors PCI; SARS-CoV2, severe acute respiratory syndrome coronavirus-2; TIMI, Thrombolysis in Myocardial Infarction.

Myocardial Infarction (TIMI) flow (TIMI 3: 86.2 vs 92.1%, $P = .029$), despite no difference in preprocedural recanalization. We observed a trend in greater administration of Gp IIb-IIIa inhibitors (28.5 vs 21.5%, $P = .086$) and a significantly higher use of thrombectomy (28.4 vs 20.5%, $P = .046$) in SARS-CoV-2 positive patients. Furthermore, they received renin–angiotensin system inhibitors (RASI) therapy less often during hospitalization (55 vs 72.3%, $P < .0001$).

Primary and Secondary Study Outcomes

Table 3 shows detailed data on in-hospital outcome. The SARS-CoV-2 positive patients had longer hospitalization (8 [4-16] vs 5 [3-7] days, $P < .001$) and more often needed orotracheal intubation (25.8 vs 5.0%, $P < .001$). SARS-CoV-2 positivity was associated with a remarkably greater in-hospital mortality (25.7 vs 7%, OR [95% CI] = 5.6 [3.54–8.9], $P < .001$) (Figure 1), greater in-hospital definite in-stent thrombosis (6.4 vs 1.1%, OR [95% CI] = 6.2 [2.6–14.2], $P < .001$) (Figure 2), and in-hospital heart failure (22.6 vs 14.6%, OR [95% CI] = 1.65 [1.03–2.64], $P = .035$), without any difference in major bleeding complications (2.7 vs 18%, OR [95% CI] = .67 [.16–2.81], $P = .59$. Among COVID-positive patients, 13 out of 28 deaths were related to COVID. The negative impact on death and stent thrombosis was confirmed after correction for baseline confounding factors (age, smoking, hypercholesterolemia, geographic area, cardiogenic shock, rescue PCI, radial access, postprocedural TIMI 3 flow, thrombectomy, RASI, and in-hospital orotracheal intubation) (Table 3).

No significant impact of chronic therapy with RASI at admission or its administration during hospitalization was observed on mortality among the SARS-CoV-2 positive patients. Figures 1 and 2 show in-hospital mortality and in-stent thrombosis, respectively, according to combined SARS-CoV-2 positivity and use of thrombectomy, suggesting the potential beneficial effects of thrombectomy among SARS-CoV-2 positive patients. The use of Glycoprotein IIb/IIIa (GP IIb/IIIa) did not impact on mortality and stent thrombosis.

Data on 30-day mortality were available in 1871 patients (89%). As shown in Figures 3 and 4 SARS-CoV-2 positivity was associated with a significantly higher mortality (34.4 vs 8.5%, Hazard Ratio [95% Confidence Interval] = 4.24 [2.88–6.24], $P < .001$), that was confirmed after adjustment for baseline confounding factors (adjusted HR [95% CI] = 2.16 [1.45–3.23], $P < .001$). Figure 3 shows 30-day mortality according to the combined SARS-CoV-2 positivity and use of thrombectomy, suggesting the potential beneficial effects of thrombectomy among SARS-CoV-2 positive patients. The use of GP IIb/IIIa did not impact on 30-day mortality.

Table 3. In-Hospital Outcomes.

	SARS-CoV2 Positive (n = 109)	SARS-CoV2 Negative (n = 2005)	Odds ratio	95% CI	*P*	Adjusted* Odds ratio	95% CI	*P*
Death – n (%)	28 (25.7)	141 (7)	5.6	[3.54–8.9]	<.001	3.20	1.71–5.99	<.001
Definite stent thrombosis – n (%)	7 (6.4)	22 (1.1)	6.2	[2.6–14.2]	<.001	6.26	2.41–16.25	<.001
Heart failure – n (%)	24 (22.0)	293 (14.6)	1.65	[1.03–2.64]	.035	1.36	.77–2.38	.29
Major bleeding complications (BARC 3-5) – n (%)	2 (1.8)	54 (2.7)	.67	[.16–2.81]	.59	0.4	.092–1.75	.22

Adjustment for: *Age, Smoking, Hypercholesterolemia, Geographic area, Cardiogenic shock, Rescue PCI, Radial access, Postprocedural TIMI 3 flow, Thrombectomy, RASI, renin–angiotensin system inhibitors, In-hospital orotracheal intubation (p for inclusion in the model <.05); BARC, Bleeding Academic Research Consortium; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

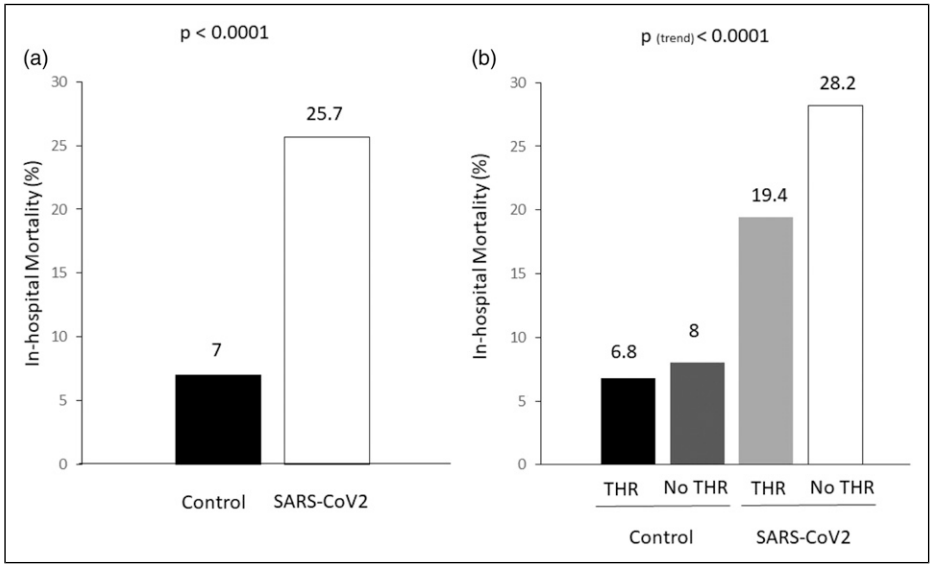

Figure 1. Bar Graph shows the impact of severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) positivity on in-hospital mortality (left panel, A). The right panel (B) shows the outcome of patients according to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) positivity and use of thrombectomy (THR) suggesting potential benefits from THR, especially among SARS-Cov-2 positive patients.

Discussion

The main finding of the present study is that SARS-Cov-2 positivity is associated with a greater use of thrombectomy and impaired procedural reperfusion. Furthermore, it is associated with a higher in-hospital mortality, in-hospital definite stent thrombosis, and 30-day mortality.

COVID-19 has spread across the world with >200 million of people infected and it is still largely affecting our healthcare system.[1] SARS-Cov-2 has been shown to be associated with increased CV mortality due to direct and indirect effects.[1,2] Direct prothrombotic effects have been described, mainly attributed to inflammation, endothelial dysfunction, increased activation of platelets, and coagulation cascade,[2] that may impact on the risk of micro thromboembolism, impaired reperfusion, larger infarct size, and in-stent thrombosis.[11] Moreover, delayed access to medical care and impaired time-to-reperfusion have been largely reported during the COVID-19 pandemic and especially within the first-wave, with a less marked impact in 2021 and 2022, potentially due to the improvements in the management of COVID-19 patients.[10,11]

This is one of the largest reports evaluating the impact of SARS-Cov-2 positivity on in-hospital and 30-day outcome in STEMI patients undergoing mechanical reperfusion. SARS-Cov-2 positive patients were less often smokers and affected by hypercholesterolemia. They frequently had more a delayed presentation, whereas no difference was observed in door-to-balloon time. GP IIb/IIIa inhibitors and thrombectomy were more often used in SARS-Cov-2 positive patients, suggesting a potentially larger thrombus burden as compared with negative patients. In fact, SARS-Cov-2 positivity was associated with impaired epicardial reperfusion.[13]

All these factors contributed to explain the higher in-hospital mortality observed in SARS-Cov-2 positive patients as well as the higher rates of in-hospital definite in-stent

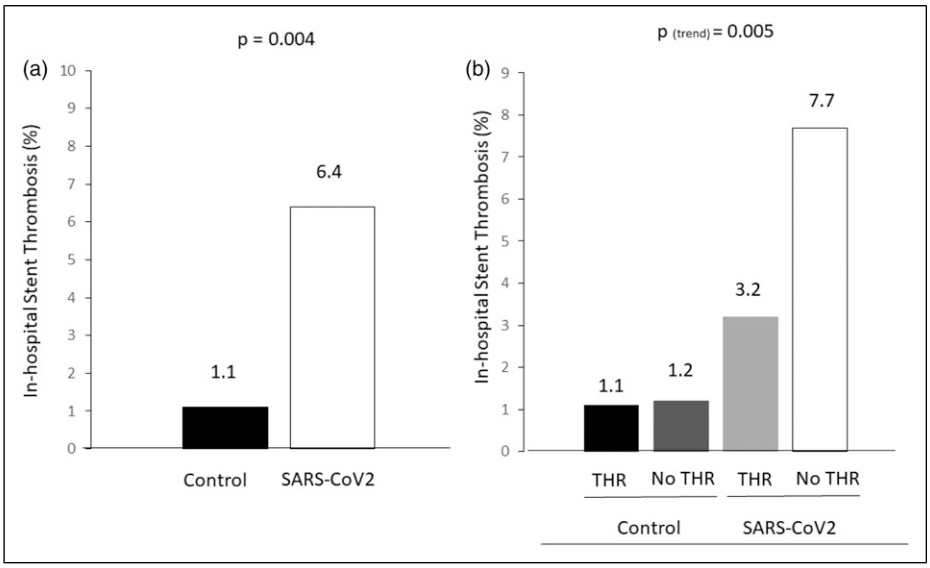

Figure 2. Bar Graph shows the impact of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) positivity on in-hospital definite stent thrombosis (left panel, A). The right panel (B) shows the outcome of patients according to SARS-Cov-2 positivity and use of thrombectomy (THR) suggesting potential benefits from thrombectomy especially among SARS-Cov-2 positive patients.

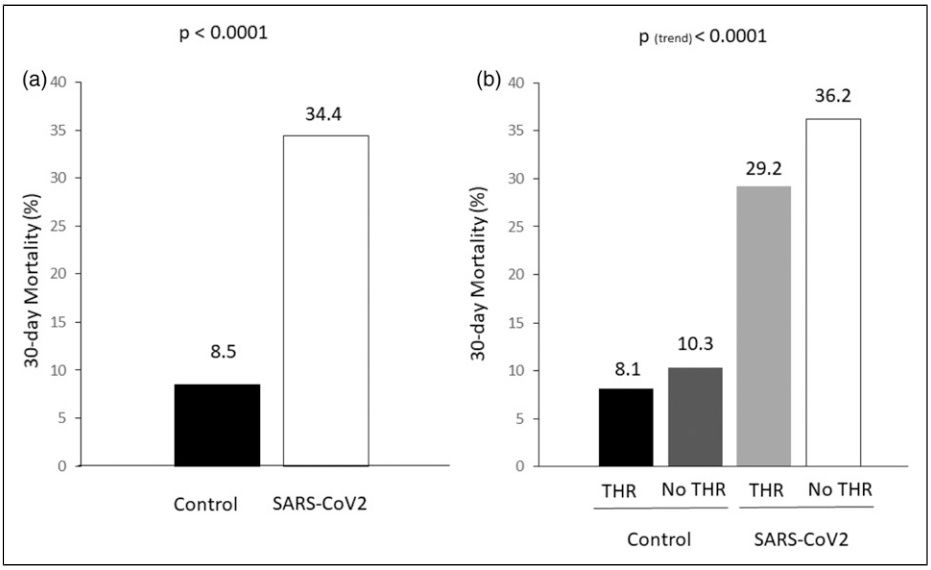

Figure 3. Bar Graph shows the impact of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) positivity on 30-day mortality (left panel, A). The right panel (B) shows 30-day mortality according to SARS-Cov-2 positivity and use of thrombectomy (THR) suggesting potential benefits from THR, especially among severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) positive patients.

thrombosis. These results were confirmed after adjustment for all baseline and procedural confounding factors. The remarkable impact on mortality persisted at 30-day follow-up. Indeed, the long-term prognostic role of COVID pandemic was not assessed in our study, although its negative effects have been documented.[14]

The higher mortality observed in our study is certainly not new[6,9] and it is a consequence of the pulmonary and systemic effects of COVID. In fact, the mortality rate in SARS-Cov-2 positive patients was still remarkably high even after the exclusion of COVID-related deaths (13.7%). In effect, COVID-positive patients displayed longer ischemia time, translating into more advanced conditions at presentation and higher rates of cardiogenic shock, which could account for the worst outcomes and higher use of femoral approach, allowing a quicker access to coronary tree and the use of larger sheets, permitting an eventual shift to a ventricular assistance device if needed. Moreover, hypoxia-induced radial vasospasm and need of mechanical ventilation could have prevented transradial procedures.

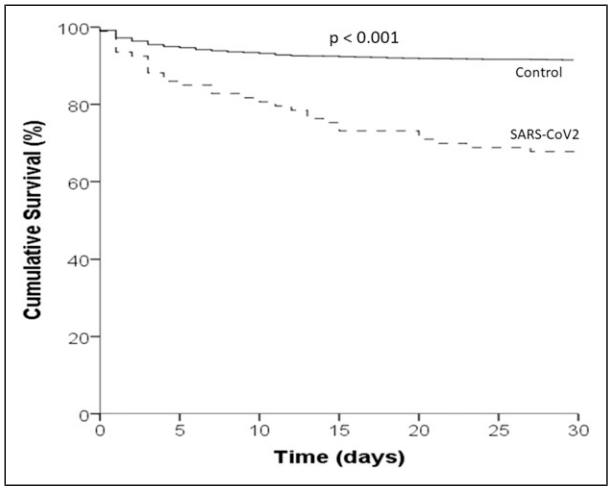

Figure 4. Kaplan–Meier survival curves in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) positive (dashed line) and control patients (solid line).

We confirmed in this large series the higher risk of stent thrombosis associated with SARS-Cov-2 positivity observed in our previous report and anecdotal case reports.[11,15-17] In our study SARS-Cov-2 positivity was independently associated with a 4 times higher risk of in-hospital definite stent thrombosis. A larger thrombus burden, suggested by the higher use of Gp IIb-IIIa inhibitors and thrombectomy and impaired post-procedural epicardial reperfusion, may contribute our findings.[18]

Our data suggest that thrombectomy may play a favorable role in SARS-Cov-2 positive patients. Conflicting results have been observed in randomized trials on the benefits from thrombectomy among STEMI patients.[19-22] However, thrombectomy seems to provide benefits in large thrombus burden and in terms of stent thrombosis,[23-25] being associated with larger implanted stents and a reduced metal burden Application in coronary arteries.[26] These factors may favor SARS-Cov-2 patients, as observed in our study in terms of clinical outcome.

In the last years attention has been focused on the use of GP IIb/IIIa inhibitors in the context of STEMI patients.[27,28] In our study GP IIb/IIIa inhibitors, while more frequently used in the SARS-Cov-2 positive patients, did not favorably impact on outcome.

A major limitation of our study is its study design, being non-randomized and retrospective. We found some differences in baseline characteristics. However, our main results were adjusted for all those baseline and procedural differences. We could not provide data on myocardial blush grade and thrombus score. Moreover, angiographic features, as MBG or TIMI flow, were evaluated by local investigators but not centrally analyzed. Therefore, inter-observer variability in their definition could have occurred.

In addition, a more extensive use of intracoronary imaging could have improved the definition of thrombus burden and the extent of coronary disease. However, the severity of the clinical presentation and the complex management of these patients, especially in COVID-positive patients, prevented its use on a large-scale basis.

Furthermore, we did not collect data about pre-procedural and post-procedural heparin, whose administration has emerged being particularly relevant among patients with COVID-19 infection, although protocols for the use of heparin in these patients were certainly developed in the subsequent waves of the pandemic and were not available in its early phase, when our study was performed.

Our population was enrolled in the initial phase of COVID pandemic, with potential disparities in strategies concerning the use of nasopharyngeal swabs that may have caused a potential selection bias. Furthermore, in our study (ISACS-COVID Registry) we aimed at comparing a non-COVID period (March-June 2019) with the initial worst phase of COVID pandemic (March-June 2020), as previously reported.[11] Unfortunately, we could not provide data on the prognostic impact of SARS-CoV2 positivity during the later phase of the pandemic.

Our population was relatively small, and therefore future larger investigations are certainly needed to further confirm our findings. Finally, despite a relevant heterogeneity in ethnicity, numerical contribution, treatment standards in a study involving so many centers, as reported in the major trial[11] and subsequent subanalyses, results were consistent independently from geographical, clinical or angiographic factors.

In conclusion, the present study showed that among STEMI patients SARS-Cov-2 positivity is associated with a remarkably higher mortality but also higher in-stent thrombosis and heart failure. Moreover, the greater use of thrombectomy and Gp IIb/IIIa in SARS-Cov-2 positive patients may reflect the elevated thrombotic burden and the increased prothrombotic milieu of these patients. Future larger well powered studies are certainly needed to confirm our findings, and to evaluate the potential prognostic benefits from routine adjunctive thrombectomy and Gp IIb/IIIa inhibitors in the SARS-Cov-2 positive patients.

Author Contribution

All authors contributed to: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Author's Note

The study was promoted by the Eastern Piedmont University, Novara, Italy, without any financial support. Clinical Trials.gov Identifier, NCT04412655.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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