



# Comparison of long-term outcome of patients with ST-segment elevation myocardial infarction between pre-COVID-19 and COVID-19 era

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## Abstract

**Aims:** To compare major cardiovascular and cerebrovascular events (MACCE) rates between patients in the pre-COVID-19 era and COVID-19 era, and to assess the impact of the presence of COVID-19 (+) on long-term MACCE in ST-segment elevation myocardial infarction (STEMI) in Turkey.

**Methods:** Using the TURSER study (TURKISH ST-segment elevation myocardial infarction registry) data, the current study included 1748 STEMI patients from 15 centres in Turkey. Patients were stratified into COVID-19 era (March 11st–May 15st, 2020;  $n = 723$ ) or pre-COVID-19 era (March 11st–May 15st, 2019;  $n = 1025$ ) cohorts. Long-term MACCE rates were compared between groups. In addition, the effect of COVID-19 positivity on long-term outcomes was evaluated.

The primary outcome was the occurrence of MACCE at long-term follow-up, and the secondary outcome was hospitalization with heart failure.

**Results:** The MACCE and hospitalization with heart failure rates between pre-COVID-19 era and COVID-19 era were 23% versus 22% ( $p = .841$ ), and 12% versus 8% ( $p = .002$ ), respectively. In the COVID-19 era, the rates of MACCE and hospitalization with heart failure COVID-19-positive versus COVID-19-negative patients were 40% versus 20%, ( $p < .001$ ), and 43% versus 11% ( $p < .001$ ), respectively.

**Conclusion:** There was no difference between the pre-COVID-19 era and the COVID-19 era in terms of MACCE in STEMI patients in Turkey. In the COVID-19 era, STEMI patients positive for COVID-19 had a higher rate of MACCE and heart failure hospitalization at the long-term follow-up.

#### KEYWORDS

COVID-19, Mortality, ST-segment elevation myocardial infarction

## 1 | INTRODUCTION

The COVID-19 pandemic, caused by the new SARS-CoV-2, has killed more than 6 million people worldwide as of May 2022. ST-segment elevation myocardial infarction (STEMI) admissions decrease significantly due to the COVID-19 pandemic.<sup>1,2</sup> Also, symptom to first medical contact time has been prolonged during this period. In addition to all this, lower left ventricular ejection fraction (LVEF) values, higher troponin levels and high intracoronary thrombus burden were commonly seen in these patients in the COVID-19 era compared with the pre-COVID-19 era.<sup>3,4</sup>

Although there was no difference between the pre-COVID-19 era and the COVID-19 era regarding in-hospital mortality, COVID-19 (+) STEMI patients had a higher risk of mortality than those without.<sup>1,4</sup> There are limited data with respect to the long-term outcomes of these patients.<sup>5,6</sup> In the presented study, we aimed to assess the effects of both COVID-19 era and the presence of COVID-19 (+) on long-term major cardiovascular and cerebrovascular events (MACCE) in STEMI patients in Turkey.

## 2 | METHODS

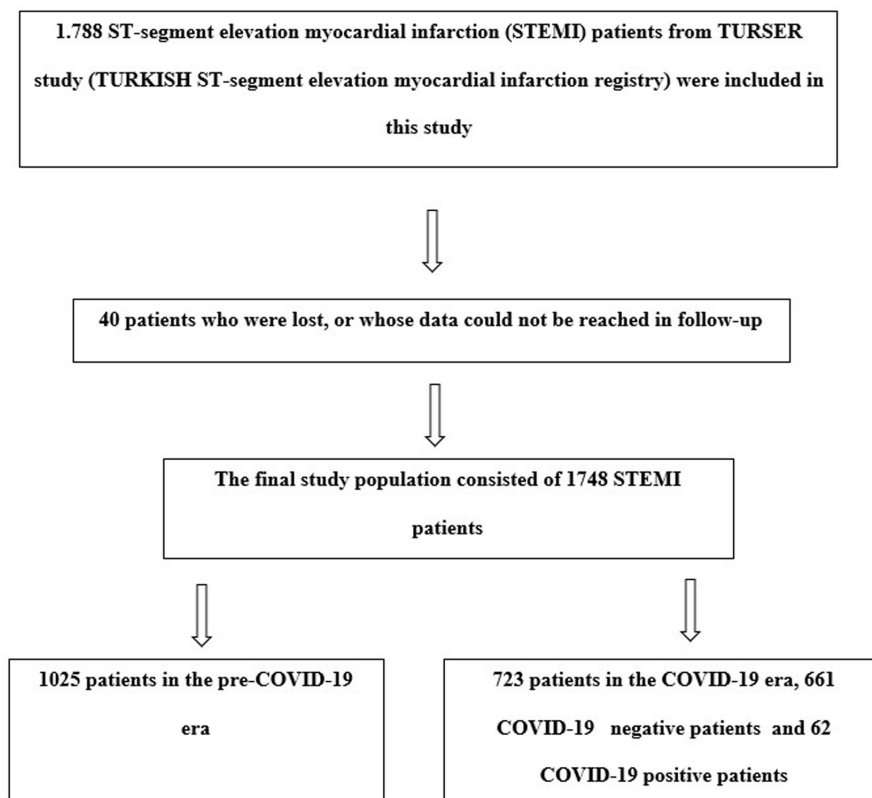
### 2.1 | Study design and patient population

We used data from the TURKISH ST-segment elevation myocardial infarction registry (TURSERT), which is a multicenter, retrospective, observational study that enrolled 1788 patients between 18 and 90 years of age, who were diagnosed with STEMI in 15 centres.<sup>4</sup> Forty patients who were lost, or whose data could not be reached in follow-up,

were not included in this study. The final study population consisted of 1748 STEMI patients (Figure 1). The patients were divided into two groups: COVID-19 era (March 11st–May 15st, 2020;  $n = 723$ ) and pre-COVID-19 era group (March 11st–May 15st, 2019;  $n = 1025$ ). Moreover, the patients in COVID-19 era were grouped as COVID-19 positive ( $n = 62$ ) or negative ( $n = 661$ ). STEMI was defined according to the fourth universal definition of myocardial infarction.<sup>7</sup> Evidence-based optimal medical therapy and coronary revascularization were carried out according to current guidelines and recommendations.<sup>8</sup> All interventional procedures and strategies such as balloon angioplasty, type of stent, aspiration thrombectomy and the usage of intra-aortic balloon pumps were left to the discretion of interventional cardiologists. The thrombolysis in myocardial infarction (TIMI) thrombus grade (TG) was used for the thrombus burden classification.<sup>9</sup> Patients with Grade 5 thrombus burden were reclassified to a thrombus category after flow achievement either with a guidewire or with a small (1.5 mm) balloon.<sup>10</sup> Procedural success was defined as post-PCI TIMI-3 flow. The left ventricle ejection fraction (LVEF) was calculated after measuring the end-diastolic and end-systolic left ventricle (LV) volumes in the apical four-chamber and two-chamber views using the modified Simpson's method. Valve disease was considered as moderate or severe regurgitation in mitral or aortic valves, or severe stenosis for mitral or aortic valves.

The bleeding classification was performed according to the thrombolysis in myocardial infarction (TIMI) bleeding score. Major haemorrhage was defined as 5 gr/dl haemogram, a 15% or greater decline in haematocrit or intracranial haemorrhage. Minor bleeding was defined as 3–5 gr/dl Hb, a 10%–15% gr/dl haematocrit decline or gastrointestinal bleeding. Cardiogenic shock was defined

**FIGURE 1** Flow diagram of patient recruitment



as systolic blood pressure <90 mmHg for at least 30 min with evidence of poor tissue perfusion after correction of nonmyocardial factors.

After the STEMI diagnosis, the patients with no signs of COVID-19 infection were transferred to the routine cardiac catheterization laboratory; however, the patients with symptoms indicating possible COVID-19 were transferred to an allocated cardiac catheterization laboratory.

The COVID-19 diagnosis was made by detecting SARS-CoV-2 on a nasal/pharyngeal swab<sup>11</sup> or by evaluating the symptoms plus radiological imaging.<sup>12</sup> All of these patients were treated as COVID-19 patients in these centres. The study was approved by the ethics committee of the Dokuz Eylul University Faculty of Medicine (2020/10-35) and the Ministry of Health (2020-05-02T23\_17\_42).

## 2.2 | Data collection

The patient's demographic, clinical, laboratory, interventional and long-term outcomes data from each centre were collected by the principal investigator of that centre. Also, the national death registry system data were used to determine long-term mortality. Cineangiographic images of patients were retrospectively analysed by two interventional cardiologists blinded to the patient's COVID-19 status. Data were finally checked for missing or contradictory entries.

## 2.3 | Study outcomes

The primary end-point was the occurrence of MACCE, which included all-cause mortality, hospitalization with heart failure, myocardial reinfarction defined as STEMI or non-ST-segment elevation myocardial infarction, target vessel revascularization defined as any repeat revascularization in the epicardial vessel of the prior stent (main branch or side branches) and cerebrovascular events. The secondary end-point of this study was hospitalization with heart failure in the follow-up.

## 2.4 | Follow-up period

The patients in the COVID-19 period were followed until 22 September 2021, and the patients in the pre-COVID-19 period were followed until 22 September 2020.

## 2.5 | Statistical analysis

Categorical variables are presented as absolute numbers, and percentages, and compared by the  $\chi^2$  test. Continuous variables are shown as mean and standard deviation (SD) and compared by the Student's *t*-test, or Mann-Whitney test as appropriate. Factors entered into the multivariate model comprised those with *p*-values < .1 from the univariate

analysis. Multivariable Cox regression analysis with clinically relevant variables was made to detect independent predictors of long-term MACCE. The cumulative incidence of the primary and secondary end-points was estimated by the Kaplan–Meier method. Two-sided  $p$ -values  $< .05$  were considered statistically significant. All statistical analysis was performed with SPSS version 26 (SPSS Inc.).

## 2.6 | Power analysis

The study needed to recruit 490 participants for each group to have 80% power with 5% type 1 error level when assuming a primary end-point rate of 18% at 1-year follow-up. The power of the study increased to 89.36% with the selection of 1025 patients in the pre-COVID-19 era and

**TABLE 1** Baseline characteristics of the study population

Variables	Pre-COVID-19 era ( $n = 1025$ )	COVID-19 era ( $n = 723$ )	$p$ -Value
Age, years	61.9 ± 12.4	60.6 ± 12.4	.040
Symptoms at admission $n$ (%)			
Chest pain	767 (75)	488 (68)	.005
Dyspnoea	194 (19)	165 (23)	
Arrest	10 (1)	9 (1)	
Other	54 (5)	61 (8)	
Female gender (%)	257 (25)	166 (23)	.310
Hypertension, $n$ (%)	388 (38)	304 (42)	.077
Diabetes mellitus, $n$ (%)	302 (30)	207 (29)	.461
Previous AF, $n$ (%)	43 (4)	39 (5)	.243
Smoking, $n$ (%)	315 (31)	239 (33)	.304
Astma or COPD, $n$ (%)	105 (10)	71 (10)	.772
Previous CAD, $n$ (%)	125 (12)	93 (13)	.677
COVID-19-positive $n$ (%)	-	44 (7)	-
Echocardiographic findings			
LVEF (%)	47.8 ± 9.1	46.7 ± 8.9	.015
LVWM abnormalities $n$ (%)	645 (63)	484 (67)	.084
Valve disease $n$ (%)	104 (10)	66 (9)	.630
Symptom-to-FMC, minutes (median [IQR])	100 (60–180)	120 (75–240)	$< .001$
Symptom-to- (FMC) time			
<2 h, $n$ (%)	542 (53)	312 (43)	$< .001$
2–6 h, $n$ (%)	209 (20)	143 (20)	
6–12 h, $n$ (%)	232 (23)	203 (28)	
12–24 h, $n$ (%)	19 (2)	26 (4)	
More than 24 h, $n$ (%)	23 (2)	39 (5)	
Laboratory findings			
WBC ( $\times 10^3/\mu\text{l}$ )	11.9 ± 3.9	12.1 ± 4.6	.205
Haemoglobin (mg/dl)	13.8 ± 2.1	13.9 ± 2.1	.129
Creatinine <sup>a</sup> (mg/dl)	0.90 (0.74–1.03)	0.90 (0.76–1.10)	.382
Platelet ( $\times 10^9$ /L)	256.5 ± 75.3	251.8 ± 73.3	.185
C-reactive protein <sup>a</sup> (mg/L)	19.2 (2.0–47.6)	23.6 (3.0–53.8)	.128
Troponin <sup>a</sup> (ng/L)	6259 (415–19,176)	9739 (869–24,810)	.099

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; FMC, first medical contact; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVWM, left ventricular wall motion abnormalities; WBC; white blood cell.

<sup>a</sup>Comparison was made using Mann–Whitney  $U$  test at  $p < .05$ , and these values were described by median with interquartile range (25th and 75th percentile).

723 patients during the COVID-19 era with a 5% type 1 error level.

### 3 | RESULTS

#### 3.1 | Patient characteristics

A total of 1748 STEMI patients were examined. The median follow-up time was 524 days (507–541). Patients in pre-COVID-19 era were older than in COVID-19 era ( $61.9 \pm 12.4$  vs.  $60.6 \pm 12.4$ ,  $p = .040$ ). As shown in Table 1, all groups were similar regarding the histories of diabetes mellitus, hypertension, coronary artery disease and atrial fibrillation. Moreover, there was no significant difference between groups with respect to a pre-usage statin, and

ACE-I angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARB) (Table 1). The patients in the COVID-19 era had lower LVEF compared with those in the pre-COVID-19 era ( $46.7 \pm 8.9$  vs.  $47.8 \pm 9.1$ ,  $p = .015$ ).

The time from symptom-to-FMC was significantly longer in COVID-19 group than in pre-COVID-19 group (120 [75–240] vs. 100 [60–180] min  $p < .001$ ). The laboratory values of the groups are illustrated in Table 1. There was no significant difference between groups concerning white blood cell counts (WBC), serum creatinine and troponin levels (each  $p > .05$ ).

Sixteen-two STEMI patients were COVID-19 positive in COVID-19 era. These patients' characteristics are presented in Table 4. There was no significant difference between groups concerning the symptom onset to FMC time, histories of DM, HT, CAD and COPD or asthma

TABLE 2 Angiographic characteristics, interventions and medical treatment

Variables	Pre-COVID-19 era (n = 1025)	COVID-19 era (n = 723)	p-Value
Coronary intervention n (%)	1024 (100)	719 (99)	.079
Infarct-related artery n (%)			
LMCA	15 (2)	17 (2)	.175
LAD	388 (38)	303 (42)	
CX	195 (19)	133 (19)	
RCA	334 (33)	219 (31)	
Other	83 (8)	42 (6)	
Noncritical CAD	9 (1)	5 (1)	
Multi-vessel disease n (%)	412 (40)	292 (41)	.874
Glycoprotein IIb/IIIa inhibitors n (%)	234 (23)	161 (22)	.766
Thrombus aspiration device n (%)	60 (6)	55 (8)	.148
IABP n (%)	29 (3)	12 (2)	.112
Baseline TIMI flow n (%)			
TIMI flow 0–1	932 (91)	642 (89)	.231
Baseline thrombus grade >3	685 (67)	491 (68)	.541
Modified thrombus grade >3	415 (41)	287 (40)	.673
Procedural success:			
Post-PCI TIMI 3 flow n (%)	878 (83)	594 (82)	.319
Multi-vessel PCI during the index procedure n (%)	96 (9)	70 (10)	.824
Complete revascularization during the index hospitalization n (%)	187 (18)	126 (17)	.661
Previous medication			
ACE-I/ARB, n (%)	251 (25)	199 (28)	.153
Statin n (%)	175 (17)	112 (16)	.379
In-hospital or discharge ASA + P2Y12Y inhibitors			
ASA plus Clopidogrel n (%)	754 (73)	498 (69)	.133
ASA plus Ticagrelor n (%)	176 (17)	146 (20)	
ASA plus Prasugrel n (%)	94 (9)	75 (10)	
Pharmaco-invasive treatment n (%)	9 (1)	4 (1)	.438
Patients treated with medical treatment n (%)	4 (0)	7 (1)	.132

Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitors/ angiotensin receptor blocker; ASA, acetylsalicylic acid; CX, circumflex artery; IABP, intra-aortic balloon pump; IQR, interquartile range; LAD, left descending artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

TABLE 3 In-hospital and long-term outcomes of all patients

Variables	Pre-COVID-19 era ( <i>n</i> = 1025)	COVID-19 era ( <i>n</i> = 723)	<i>p</i> -Value
In-hospital outcomes			
Mortality <i>n</i> (%)	71(7)	61 (8)	.239
Shock <i>n</i> (%)	91(9)	62 (9)	.825
Stent thrombosis <i>n</i> (%)	15 (2)	12 (2)	.742
Major bleeding <i>n</i> (%)	0 (0)	3 (0.4)	.039
Minor bleeding <i>n</i> (%)	29 (3)	16 (2)	.426
Long-term outcomes			
MACCE <i>n</i> (%)	231(23)	160 (22)	.841
Mortality <i>n</i> (%)	74 (8)	40 (6)	.186
Myocardial reinfarction <i>n</i> (%)	67 (7)	39 (6)	.329
New revascularization <i>n</i> (%)	88 (9)	62 (9)	.998
Stroke/TIA, <i>n</i> (%)	22 (2)	8 (1)	.100
Hospitalization with HF, <i>n</i> (%)	78 (8)	87 (12)	.002

Abbreviations: HF, heart failure; MACCE, major cardiovascular and cerebrovascular events; TIA, transient ischaemic attack.

TABLE 4 Baseline characteristics of the study population

Variables	COVID-19 (−) ( <i>n</i> = 661)	COVID-19 (+) ( <i>n</i> = 62)	<i>p</i> -Value
Age, years	60.0 ± 12.3	66.9 ± 12.2	<.001
Symptoms at admission <i>n</i> (%)			
Chest pain	454 (69)	34 (55)	.003
Dyspnoea	151 (23)	14 (23)	
Arrest	8 (1)	1 (2)	
Other	48 (7)	13 (21)	
Female gender (%)	146 (22)	20 (33)	.069
Hypertension, <i>n</i> (%)	274 (42)	30 (49)	.290
Diabetes mellitus, <i>n</i> (%)	190 (28)	17 (27)	.930
Previous AF, <i>n</i> (%)	36 (5)	3 (5)	.840
Smoking, <i>n</i> (%)	218 (33)	21 (34)	.887
Asthm or COPD, <i>n</i> (%)	60 (9)	11 (18)	.028
Previous CAD, <i>n</i> (%)	81 (12)	12 (19)	.110
Echocardiographic findings			
LVEF (%)	47.0 ± 8.8	43.6 ± 9.0	.004
LVWM abnormalities <i>n</i> (%)	436 (66)	48 (77)	.067
Valve disease <i>n</i> (%)	53 (9)	13 (25)	<.001
Symptom-to-FMC, minutes (median [IQR])	120 (75–245)	120 (84–240)	.610
Symptom-to- (FMC) time			
Less than 2 h, <i>n</i> (%)	287 (43)	25 (40)	.939
2–6 h, <i>n</i> (%)	129 (20)	14 (23)	
6–12 h, <i>n</i> (%)	185 (28)	18 (29)	
12–24 h, <i>n</i> (%)	24 (4)	2 (3)	
More than 24 h, <i>n</i> (%)	36 (5)	3 (5)	
Laboratory findings			
WBC (×10 <sup>3</sup> /μl)	12.0 ± 4.5	13.5 ± 4.8	.013
Haemoglobin (mg/dl)	14.0 ± 2.0	13.6 ± 2.4	.246
Creatinine <sup>a</sup> (mg/dl)	0.90 (0.70–1.02)	0.91 (0.80–1.21)	.940
Platelet(×10 <sup>9</sup> /L)	252 ± 72	252 ± 83	.975
C-reactive protein <sup>a</sup> (mg/L)	21.0 (2.8–51.3)	55.2 (21.4–147.4)	<.001
Troponin <sup>a</sup> (ng/L)	8170 (789–23,593)	19,254 (6587–26,477)	.005

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; FMC, first medical contact; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVWM, left ventricular wall motion abnormalities; WBC; white blood cell.

<sup>a</sup>Comparison was made using Mann–Whitney *U* test at *p* < .05, and these values were described by median with interquartile range (25th and 75th percentile).

(Table 4). Valve disease was more frequent in COVID-19-positive STEMI patients than those without (25% vs. 9%,  $p < .001$ ). The levels of C-reactive protein (CRP) and troponin were higher in COVID-19 group (55.2 [21.4–147.4] vs. 21.0 [2.8–51.3],  $p < .001$ ; 19,254 [6587–26,477] vs. 8170 [789–26,477],  $p = .005$ , respectively, Table 4) than in non-COVID-19.

### 3.2 | Procedural characteristics

The features of patients regarding procedures are provided in Table 2. Infarct-related artery, multi-vessel disease, glycoprotein IIb/IIIa inhibitors use, IABP, and thrombus aspiration device use, baseline TIMI 0/1 flow, modified

thrombus grade  $>3$ , and post-PCI TIMI -3 flow were similar in both groups.

The patients with COVID-19 (+) had significantly lower rate of coronary intervention than those without (95% vs. 100%,  $p < .001$ ). Baseline modified thrombus grade  $>3$  was higher COVID-19 group than in non-COVID-19 group (59% vs. 38%,  $p = .001$ ). Glycoprotein IIb/IIIa inhibitors use was more common in patients with COVID-19 (34% vs. 20%,  $p = .032$ ). There was no difference between COVID-19 (+) and those without with respect to post-PCI TIMI 3 flow (Table 5). The COVID-19-positive patients had lower LVEF than COVID-19-negative patients ( $43.6 \pm 9.0$  vs.  $47.0 \pm 8.8$ ,  $p = .004$ ). Complete revascularization during the index hospitalization was performed in 29% of COVID-19 (+) patients ( $p = .012$ ).

TABLE 5 Angiographic characteristics, interventions and medical treatment

Variables	COVID-19 (–) ( <i>n</i> = 661)	COVID-19 (+) ( <i>n</i> = 62)	<i>p</i> -Value
Coronary intervention <i>n</i> (%)	660 (100)	59 (95)	<.001
Infarct-related artery <i>n</i> (%)			
LMCA	16 (2)	1 (2)	.285
LAD	278 (42)	25 (42)	
CX	119 (18)	14 (24)	
RCA	207 (31)	12 (20)	
Other	36 (6)	6 (10)	
Noncritical CAD	4 (1)	1 (2)	
Multi-vessel disease <i>n</i> (%)	265 (40)	27 (46)	.400
Glycoprotein IIb/IIIa inhibitors <i>n</i> (%)	126 (20)	15 (34)	.032
Thrombus aspiration device <i>n</i> (%)	46 (7)	9 (15)	.032
IABP <i>n</i> (%)	10 (2)	2 (3)	.313
Baseline TIMI flow <i>n</i> (%)			
TIMI flow 0–1	587 (89)	55 (93)	.308
Baseline thrombus grade $>3$	437 (66)	56 (95)	<.001
Modified thrombus grade $>3$	252 (38)	35 (59)	.001
Procedural success:			
Post-PCI TIMI 3 flow <i>n</i> (%)	538 (82)	48 (81)	.976
Multi-vessel PCI during the index procedure <i>n</i> (%)	65 (10)	5 (8)	.652
Complete revascularization during the index hospitalization <i>n</i> (%)	108 (16)	18 (29)	.012
Previous medication			
ACE-I/ARB, <i>n</i> (%)	181 (27)	18 (29)	.781
Statin <i>n</i> (%)	98 (15)	14 (23)	.107
In-hospital or discharge ASA + P2Y12Y inhibitors			
ASA plus Clopidogrel <i>n</i> (%)	458 (70)	40 (68)	.929
ASA plus Ticagrelor <i>n</i> (%)	134 (20)	12 (20)	
ASA plus Prasugrel <i>n</i> (%)	68 (10)	7 (12)	
Pharmaco-invasive treatment <i>n</i> (%)	1 (0)	3 (5)	.240
Patients treated with medical treatment <i>n</i> (%)	3 (1)	4 (7)	<.001

Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitors/ angiotensin receptor blocker; ASA, acetylsalicylic acid; CX, circumflex artery; IABP, intra-aortic balloon pump; IQR, interquartile range; LAD, left descending artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Variables	COVID-19 (-) (n = 661)	COVID-19 (+) (n = 62)	p-Value
In-hospital outcomes			
Mortality n (%)	43 (7)	18 (29)	<.001
Shock n (%)	49 (7)	13 (21)	<.001
Stent thrombosis n (%)	8 (1)	4 (7)	.002
Major bleeding n (%)	3 (1)	0 (0)	.598
Minor bleeding n (%)	14 (2)	2 (3)	.556
Long-term outcomes			
MACCE	135 (20)	25 (40)	<.001
Mortality n (%)	38 (6)	2 (5)	.666
Myocardial reinfarction n (%)	34 (5)	5 (8)	.326
New revascularization n (%)	56 (9)	6 (10)	.738
Stroke/TIA, n (%)	7 (1)	1 (2)	.687
Hospitalization with HF, n (%)	68 (11)	19 (43)	<.001

Abbreviations: HF, heart failure; MACCE, major cardiovascular and cerebrovascular events; TIA, transient ischaemic attack.

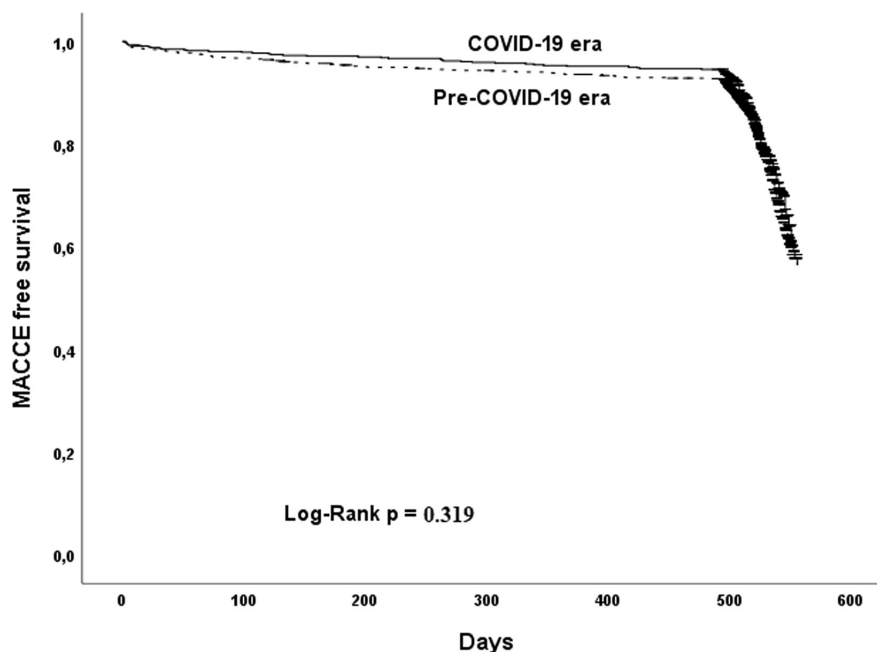


TABLE 6 In-hospital and long-term outcomes of patients during COVID-19 era

FIGURE 2 Kaplan-Meier MACCE-free survival curves of STEMI patients according to two study periods

### 3.3 | In-hospital outcomes

Mortality, shock and stent thrombosis rates was similar between pre-COVID-19 era and COVID-19 era (8% vs. 7%,  $p = .839$ , Table 3) during in-hospital. However, patients who tested positive for COVID-19 among STEMI patients had higher percentage of mortality, shock and stent thrombosis compared with non-COVID-19 patients (29% vs. 7%,  $<0.001$ ; 21% vs. 7%,  $<0.001$ ; 7% vs. 1%,  $p = .002$ , respectively, Table 6).

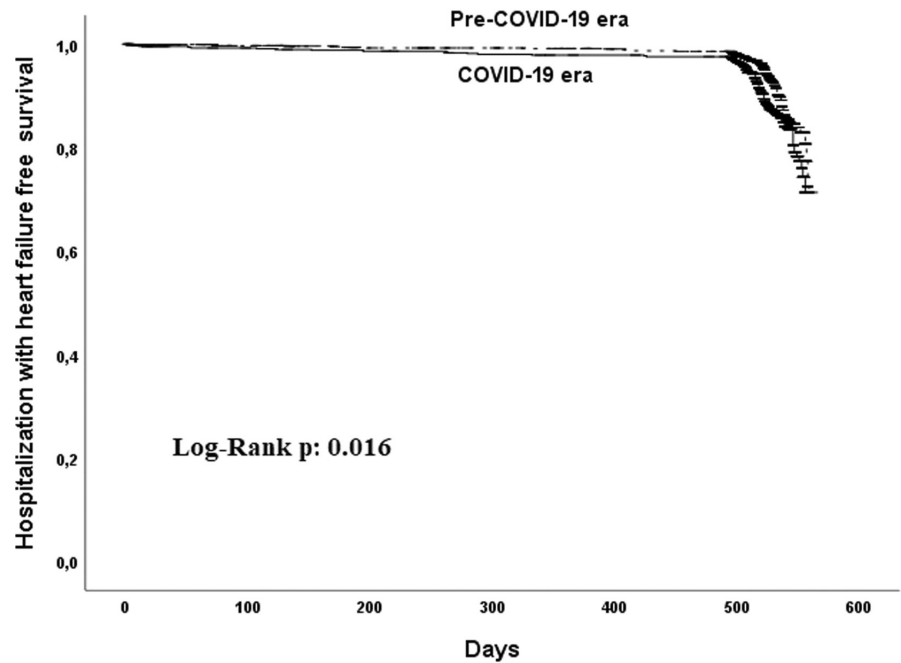
### 3.4 | Long-term outcomes

We observed similar MACCE rates between pre-COVID-19 era and COVID-19 era (23% vs. 22%,  $p = .841$ , Table 3, Figure 2). However, hospitalization with HF was more common in the COVID-19 era compared with COVID-19 era (12% vs. 8%,  $p = .002$ , Table 3, Figure 3).

The presence of COVID-19 (+) in STEMI patients was an independent predictor of MACCE at long-term follow-up (HR: 1.628, 95% CI: 1.042–2.542,  $p = .032$ , Table 7).



**FIGURE 3** Hospitalization with heart failure-free survival analysis of STEMI patients according to two study periods



**TABLE 7** Univariate and multivariate analysis for predictors of MACCE

Variables	Univariate			Multivariate		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Age	1.030	1.021–1.038	<.001	1.016	1.006–1.026	.001
Male gender	0.657	0.529–0.817	<.001	0.750	0.589–0.955	.020
Hypertension	1.736	1.423–2.177	<.001			
Diabetes mellitus	0.999	0.988–1.009	.777			
Symptoms at admission	1.260	1.116–1.422	<.001			
Astm/COPD	1.683	1.253–2.260	.001			
Muti-vessel disease	1.948	1.595–2.380	<.001	1.507	1.216–1.868	<.001
Multi-vessel PCI during index procedure	1.993	1.513–2.626	<.001	1.561	1.167–2.088	.003
IABP	2.320	1.273–4.226	.006	2.657	1.436–4.918	.002
Modified thrombus grade $\geq 4$	1.467	1.202–1.792	<.001	1.413	1.149–1.736	.001
Thrombus aspiration device usage	0.563	0.336–0.944	.029			
In-hospital total bleeding	2.856	1.839–4.435	<.001			
COVID-19 (+)	2.588	1.725–3.882	<.001	1.628	1.042–2.542	.032
Pre-COVID-19 era vs COVID-19 era	0.903	0.738–1.105	.321			
ACE-I/ARB preusage	1.472	1.187–1.826	<.001			
LVEF	0.962	0.952–0.973	<.001	0.975	0.964–0.986	<.001
Haemoglobin	0.900	0.860–0.943	<.001			
Creatinine	1.312	1.197–1.437	<.001	1.206	1.079–1.349	.001
CRP	1.002	1.000–1.003	.060			

Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitors/ angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

The patients with COVID-19 (+) had higher MACCE rates, which were mainly driven by hospitalization with HF, than those with COVID-19 (–) (40% vs. 20%,  $p < .001$ , Table 6, Figures 4–6).

## 4 | DISCUSSION

To our best knowledge, this study may be the first study in terms of being a multicentre study involving a large

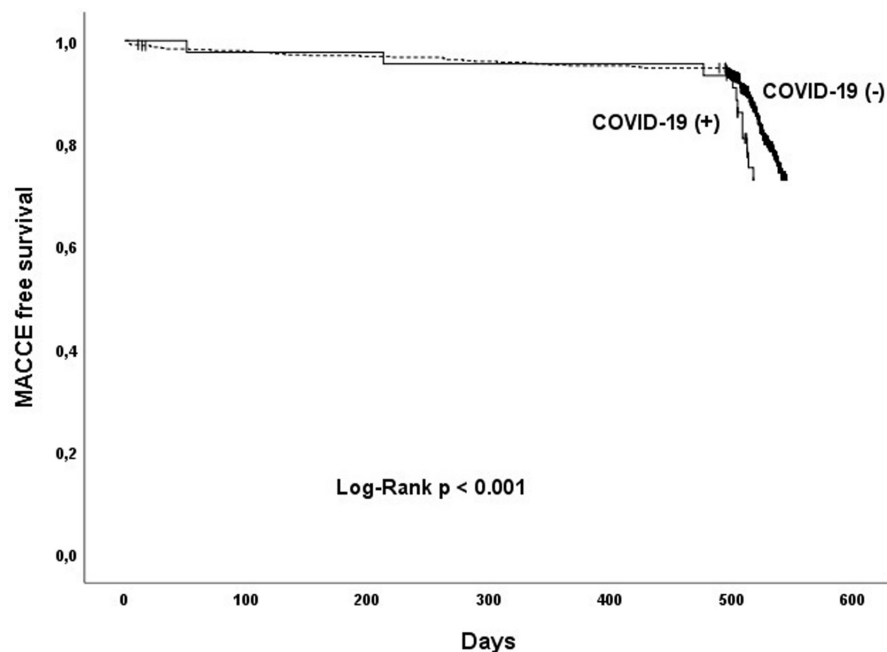


FIGURE 4 Kaplan-Meier MACCE-free survival curves of STEMI patients with COVID-19 (+) and those without during the COVID-19 era

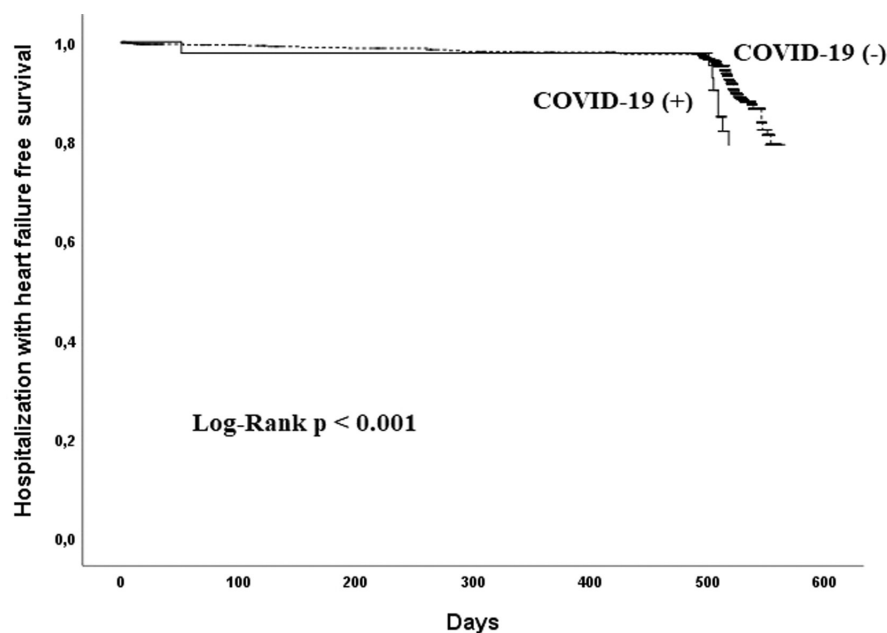


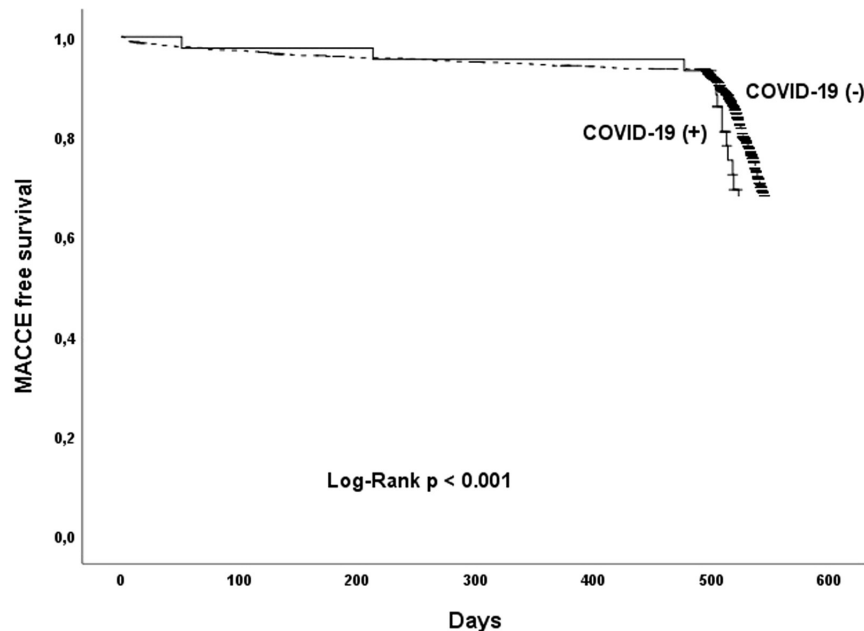
FIGURE 5 Hospitalization with heart failure-free survival analysis of STEMI patients with COVID-19 (+) and those without during COVID-19 era

number of STEMI patients and representing long-term follow-up of STEMI patients in both the COVID-19 era and pre-COVID-19 era. The current retrospective study found that STEMI patients with COVID-19 had a higher rate of MACCE compared with those without COVID-19 at long-term follow-up. Moreover, hospitalization with HF was more frequent during COVID-19 than pre-COVID-19.

Total ischaemic time plays an important role in determining cardiovascular outcomes in STEMI patients.

Mortality rates increase with increasing this time.<sup>13</sup> Both symptom-to-FMC time and door-to-balloon time were prolonged in these patients in the COVID-19 era when compared with the pre-COVID-19 era.<sup>14-17</sup> The presented study showed that symptom-to-FMC time during the COVID-19 era was longer than the pre-COVID-19 era in STEMI as found in previous studies. Prolongation in this time may be due to patient-related delays as we did not have information regarding system-related delays in the presented study.

**FIGURE 6** Kaplan–Meier MACCE-free survival curves of STEMI patients with COVID-19 (+) and those without in two study periods



The data regarding long-term outcomes of STEMI patients in the COVID-19 era and the pre-COVID-19 era were limited. Different results have been reported on this in previous studies.<sup>5,18,19</sup> Recently, a new study published by Phua et al.<sup>5</sup> which included 321 STEMI patients, has shown that there were similar outcomes including all-cause mortality, recurrent coronary event, cardiac-related readmission between the pre-COVID-19 period and COVID-19 period. Unlike that results, a higher mortality rate was seen in acute coronary syndrome patients during the COVID era compared with the pre-COVID-19 era in another study.<sup>19</sup> In a prospective study by Rattka et al.<sup>6</sup> survival was found to be significantly worse in STEMI patients during the COVID-19 pandemic. While the pre-COVID-19 period had a higher HF admission rate, there was no difference between groups in terms of MACCE in the presented study. The patients in the pre-COVID-19 era had higher troponin, and lower LVEF values than those in the pre-COVID-19 era as a reflection of the longer total ischaemic time in our study. These may indicate larger myocardial damage in these patients. All of them may contribute to the development of HF and lead to a higher rate of hospitalization with HF in these patients.

The presence of COVID-19 in STEMI patients was found to be associated with short-term mortality in previous studies.<sup>4-18</sup> The data concerning long-term mortality in these patients were limited. A recently published study showed that acute coronary syndromes patients who were infected with COVID-19 had higher mortality than those without.<sup>19</sup> Contrary to that study, in our study, no difference was demonstrated between STEMI patients with COVID-19 (+) compared to those without in terms of long-term mortality; yet proportions of MACCE

mainly driven by hospitalization with HF were higher in COVID-19 (+) patients.

The high MACCE rates in these patients may be due to many reasons. It has been shown that higher troponin levels were related to poor outcomes in COVID-19 patients.<sup>20</sup> STEMI patients infected with COVID-19 had higher troponin levels and lower LVEF values in the presented study. These may indicate the magnitude of cardiac damage. Furthermore, the presence of a high inflammatory process reflected by increased CRP might be a sign of myocardial destruction by virus. The fact that these patients receiving invasive treatment were less; therefore, this may be a reason for the high rate of MACCE in these patients. The presence of the multi-vessel disease may have contributed to the increased MACCE rates in our study.

There are several limitations of the current study. The nature of observational, retrospective study design might hinder causal inference. As we did not have out-of-hospital mortality data, it was difficult to give information about the effect of this on total mortality. The follow-up time for both pre-COVID and post-COVID periods was relatively short; therefore, to see the effect of COVID-19, these patients may need longer follow-up.

## 5 | CONCLUSION

There was no difference between the pre-COVID-19 era and the COVID-19 era in terms of MACCE in STEMI patients in Turkey. In the COVID-19 era, STEMI patients positive for COVID-19 had a higher rate of MACCE and heart failure hospitalization at the long-term follow-up.

## AUTHOR CONTRIBUTIONS

All authors contributed to the final manuscript.

## CONFLICT OF INTEREST

The author(s) declared no potential conflict of interest concerning the research, authorship and/or publication of this article.

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