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Comparison of the Effects of Recent Coronavirus 2019 Infection and Vaccination on the Prognosis of Acute Coronary Syndrome: A Retrospective Study Conducted in a Single Center in Türkiye

ABSTRACT

Background: We aimed to examine the effects of COVID-19 infection versus vaccination within the month prior to acute coronary syndrome (ACS) diagnosis with respect to their impact on the development of mortality or major adverse cardiovascular events (MACE).

Methods: This retrospective cohort study included patients hospitalized with a diagnosis of ACS between June 2020 and December 2022. Patients diagnosed with ACS were grouped according to the presence of COVID-19 infection (post-COVID), vaccination (post-vaccine), or non-exposure during the month prior to ACS diagnosis. Patients with and without MACE were also compared separately.

Results: We analyzed 1890 ACS patients (mean age 57.43 ± 11.53 years, 79.15% males). Of these, 319 (16.88%) were in the post-vaccine group, and 334 (17.67%) were in the post-COVID group. Major adverse cardiovascular events occurred in 569 (30.11%) patients. Mortality was recorded in 271 (14.34%) patients. In the post-COVID group, the frequencies of MACE and mortality and length of stay in hospital were significantly higher (vs. post-vaccine and vs. non-exposure groups; both $P < .001$). High age, ST-elevation myocardial infarction, having suffered from Post-COVID ACS, and high glucose were independently associated with increased MACE risk; whereas, hyperlipidemia, 3 or more COVID vaccinations, receipt of the Biontech vaccine, and high estimated glomerular filtration rate were independently associated with decreased MACE risk.

Conclusion: Acute coronary syndrome patients who have recently had COVID-19 infection may have a worse prognostic course compared to those with recent vaccination, necessitating continuing care for pandemic-related risk factors as well as previously known factors impacting MACE and prognosis.

Keywords: Acute coronary syndrome, COVID-19, vaccine, mortality, major adverse cardiovascular events

ORIGINAL INVESTIGATION

INTRODUCTION

Acute coronary syndrome (ACS), encompassing unstable angina pectoris (USAP), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), has remained a leading cause of hospital admissions and mortality even throughout the pandemic.[1,2] Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[3] is continuing to impact the world. The effects of this pandemic, which has caused almost 7 million deaths as of January 2024,[4] are numerous and multifaceted.[5-7]

The medical picture is primarily respiratory dysfunction, but the clinical impacts include multisystem damage[6,8] and the effects on the cardiovascular system are among the most important secondary impacts of COVID-19.[9,10] Since the early days of the pandemic, studies from many countries around the world have reported a decrease in ACS-related hospital admissions,[11-13] potentially explained by lockdowns and fear of spread.[2] However, differences in health policies of countries and behavioral differences in races cannot be ignored in the frequency of hospital admissions of patients with ACS.[14,15] Moreover, these effects are multifaceted, and

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different factors are at play, causing unexpected effects on patient management. For instance, in patients with STEMI, there are data showing increases in revascularization percentage (in ACS) and percutaneous coronary intervention (PCI) within 24 hours during the COVID-19 pandemic.[16] These results suggest a greater severity profile among patients who seek care[17] and also demonstrate the insufficient or imperfect elucidation of factors that could impact cardiovascular outcomes.

Data on the prognostic impact of ACS and concomitant or recent COVID-19 infection are based on the results of a small number of studies, which have shown poor clinical outcomes.[18,19] On the other hand, although adverse cardiac effects have been reported after COVID-19 vaccination, the effects of vaccination on ACS prognosis remains unclear.[20-22] To our knowledge, the effects of recent COVID-19 infection and COVID-19 vaccines on ACS prognosis have not been assessed. Therefore, the primary aim of this study was to examine the effects of recent COVID-19 infection or vaccination (within the prior month) on mortality and major adverse cardiovascular events (MACE) in patients hospitalized with a diagnosis of ACS during the COVID-19 pandemic. Secondly, we sought to investigate the effects of various demographic and clinical parameters on ACS prognosis.

METHODS

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee.

Setting and Population

This retrospective study was carried out in our hospital. Patients who had been hospitalized with a diagnosis of USAP, STEMI, or NSTEMI in the coronary intensive care unit of our hospital between June 2020 and December 2022 were included. The study excluded patients with incomplete data, individuals whose primary hospitalization cause was not ACS (i.e., those who experienced ACS while hospitalized for a different reason), and subjects who underwent both vaccination and contracted COVID-19 infection within the evaluation period.

Examined Parameters

During the study period, comprehensive patient data, including age, sex, race, body mass index (BMI) in kilograms per square meter (kg/m^2), smoking status, comorbidities, medical history, COVID-19 disease, vaccination details, event classification (USAP, STEMI, or NSTEMI), MACE during hospitalization, medication usage, selected laboratory results, length of hospital stay, and mortality statistics, were systematically recorded. The information was recorded retrospectively from the hospital's computerized database, patients' charts, and the national database registration system administered by the Ministry of Health of the Republic of Türkiye (e-Nabız). Length of hospital stay was considered as the time interval between presentation with ACS and discharge or hospital mortality. Mortality, the primary endpoint of the study, included both in-hospital deaths and deaths between discharge and the time study data were collected. In-hospital mortality information was obtained from hospital records, post-discharge mortality information was obtained from e-Nabız.

Grouping, Endpoints, and Secondary Definitions

Patients were primarily grouped based on COVID-19 and vaccine receipt within the prior month before ACS diagnosis: those who received a COVID-19 vaccine (post-vaccine), those who contracted COVID-19 (post-COVID), and those who were not exposed to either of these (non-exposure) in the last 1 month before the diagnosis of ACS. Comparisons were made between these groups in terms of variables. Patients were also grouped as those who had MACE (MACE group) and those who did not (non-MACE group) during hospitalization. Comparisons were made between these groups in terms of variables, and independent risk factors for MACE were also investigated.

"Active smokers" were defined as patients who had consumed a minimum of 100 cigarettes throughout their lifetime and currently smoked at least one cigarette per day. "Ex-smokers" comprised individuals who had smoked a minimum of 100 cigarettes in their lifetime but had ceased smoking at least 30 days prior to study inclusion. "Non-smokers" included those who had smoked fewer than 100 cigarettes in their lifetime and had not smoked in the last 30 days, as well as individuals who had never smoked. Patients classified as "passive smokers" were non-smokers who were exposed to smoking (presence at time of smoking).[23]

ACS Management and Related Variables

The diagnosis, classification, and treatment management of ACS were performed in line with the current ESC guidelines.[24-26] ST-elevation myocardial infarction and NSTEMI diagnosis were based on the electrocardiography findings and the level of cardiac biomarkers. ST-elevation myocardial infarction was considered as the presence of characteristic symptoms of myocardial ischemia related to persistent electrocardiographic ST elevation and the increase of cardiac enzyme levels. ST elevation at the J point in at least 2 adjacent leads of 2 mm (0.2 mv) in men or 1.5 mm (0.15 mv) in women in leads V2–V3 and/or of 1 mm (0.1 mv) in other adjacent chest leads or the limb lead was considered as positive ST elevation.[26,27] Electrocardiographic ST depression or prominent T-wave inversion and/or positive cardiac enzymes in the absence of ST elevation and in a proper clinical setting for ACS were considered NSTEMI.[28] After ACS diagnosis, coronary angiography was performed on the same day using

HIGHLIGHTS

- Having COVID-19 before ACS increases the risk of mortality and major adverse cardiovascular events.
- Having received 3 or more COVID-19 vaccines or the Biontech vaccine before ACS reduces the risk of major adverse cardiovascular events.
- Older age and ST elevation myocardial infarction increase the risk of major adverse cardiovascular events.

standard Judkins techniques or radial approach.[29] Major adverse cardiovascular events consist of all cardiac deaths or any cardiac or vascular problem requiring intervention during hospitalization. The time of MACE was measured as the day on which MACE occurred after hospitalization for ACS.

COVID-19-related Variables

The diagnosis, treatment, and follow-up of COVID-19 disease were based on the local protocol, which adheredto Ministry of Health guidelines and WHO recommendations on COVID-19.[30-32] The data on COVID-19 infection history (never, one time, twice or more), COVID-19 vaccination status (none, 1 time, 2 times, 3 times, 4 times, or 5 times), and COVID-19 vaccine brands (none, only Sinovac, only Biontech, only Turkovac, Sinovac + Biontech, Sinovac + Turkovac, Biontech + Turkovac, Sinovac + Biontech + Turkovac) were obtained through the e-Nabiz system. Of note, Sinovac was the first vaccine available in Türkiye, and Biontech was the second (around 6-8 months later). Turkovac became available much later (10-12 months after Biontech). All were administered at a dosage of 2 vaccine shots, 2-4 weeks apart.

Laboratory Analyses

All blood analyses were performed in our certified local laboratory with routine devices that were maintained and calibrated in accordance with the manufacturer's recommendations. The first venous blood taken after the patients were hospitalized for ACS (before intervention) was used for the quantification of urea, creatinine, and platelet count. Additionally, the estimated glomerular filtration rate (eGFR; in mL/min per 1.73 m^2) was calculated using the Modification of Diet in Renal Disease study equation.[33,34] Creatinine clearance was calculated using the Cockcroft–Gault equation.[35]

Statistical Analysis

We used the SPSS software (v25.0, IBM; Armonk, NY, USA), and "significant" results were based on a *P*-value threshold of <.05. The normal distribution of variables was assessed through histograms and Q–Q plots. Descriptive statistics for numerical data were reported as mean ± standard deviation (normal distribution) or median (25^{th}-75^{th} percentile) (non-normal). Frequency (percentage) was used for categorical variables. Between-group comparisons for normally distributed continuous variables employed either the student *t*-test or one-way analysis of variance, depending on the number of groups. Comparisons for non-normally distributed continuous variables were performed using the Mann–Whitney *U*-test or Kruskal–Wallis test, depending on the number of groups. Categorical variables were compared between groups using the chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test. Adjustments for pairwise comparisons were made using the Bonferroni correction method. Multiple logistic regression analyses, utilizing the forward conditional selection method, were conducted to identify factors independently associated with MACE.

RESULTS

The study involved a total of 1890 patients, with a mean age of 57.43 ± 11.53 years and a male predominance of 79.15%. Diagnoses included 97 (5.13%) cases of USAP, 760 (40.21%) cases of NSTEMI, and 1033 (54.66%) cases of STEMI. Major adverse cardiovascular events occurred in 569 (30.11%) patients, and 271 (14.34%) patients died. Additionally, 462 (24.44%) patients experienced COVID-19 once, while 540 (28.57%) had the infection twice. During the prior month, 319 (16.88%) patients received a COVID-19 vaccine, and 334 (17.67%) contracted a COVID-19 infection. Detailed characteristics for all variables are presented in Table 1.

The post-vaccine group exhibited a significantly higher mean age compared to the non-exposure group ($P = .001$). Sex distribution showed no significant differences among the post-vaccine, post-COVID, and non-exposure groups. The post-vaccine group demonstrated a lower percentage of immigrants than the non-exposure group, while the post-COVID group had a significantly higher immigrant percentage than the post-vaccine group ($P = .004$). The mean BMI in the post-COVID group was significantly higher than that in the post-vaccine group ($P = .037$). In the post-vaccine group, the percentage of ex-smokers was significantly higher than in the non-exposure group, while the percentage of passive smokers was lower ($P = .018$). Conversely, in the post-COVID group, the percentage of passive smokers was significantly higher than in the post-vaccine group ($P = .018$). The mean creatine clearance in the post-vaccine group and the median eGFR in both the post-vaccine and post-COVID groups were significantly lower than in the non-exposure group ($P = .006$). The post-COVID group exhibited significantly higher percentages of MACE occurrence, mortality, and median hospital stay length compared to both the post-vaccine and non-exposure groups ($P < .001$). The median time for MACE occurrence in the post-COVID group was significantly higher than in the non-exposure group ($P = .005$) (Table 2).

In the MACE group, both mean age ($P < .001$) and the percentage of male patients ($P = .032$) were significantly higher than in the non-MACE group. Non-smokers constituted a higher percentage, while ex-smokers had a significantly lower percentage in the MACE group ($P = .019$). Furthermore, the MACE group had significantly higher percentages of patients with diabetes, previous cerebrovascular disease, renal disease, and malignancy ($P < .001$ for all), whereas the percentages of individuals with hyperlipidemia and those using antiplatelet drugs were significantly lower ($P < .001$ and $P = .045$, respectively). The MACE group also exhibited higher percentages of individuals with one-time COVID-19 infection and those with incomplete vaccination (non-vaccination or only Sinovac vaccine). Conversely, the percentages of individuals vaccinated 3 or more times and 4 times (Figure 1), as well as those who received only Biontech, Sinovac + Biontech, and Biontech + Turkovac vaccines, were significantly lower ($P < .001$ for all remaining, Figure 2). While the frequency of USAP and NSTEMI were lower in patients with MACE, STEMI frequency was higher ($P < .001$). Moreover, in the MACE group, the percentage of individuals without COVID-19 infection or vaccination in the last month was significantly lower, while the percentage of those with COVID-19 infection in the last month was significantly higher ($P < .001$ for all) (Figure 3).

Table 1. Study Group Descriptives

Age, years	57.43 ± 11.53
Sex	
Female	394 (20.85%)
Male	1496 (79.15%)
Race	
Domestic	1764 (93.33%)
Immigrant	126 (6.67%)
Body mass index, kg/m^2	28.29 ± 3.71
Smoking status	
Non-smoker	352 (18.62%)
Ex-smoker	366 (19.37%)
Passive smoker	136 (7.20%)
Active smoker	1016 (53.76%)
Unknown	20 (1.06%)
Hypertension	865 (45.77%)
Diabetes mellitus	700 (37.04%)
Hyperlipidemia	1122 (59.37%)
Chronic obstructive pulmonary disease	120 (6.35%)
Previous coronary artery disease	449 (23.76%)
Previous peripheral artery disease	60 (3.17%)
Previous cerebrovascular disease	85 (4.50%)
Previous pulmonary embolism	5 (0.26%)
Previous deep vein thrombosis	8 (0.42%)
Renal diseases	147 (7.78%)
Malignancy	44 (2.33%)
Antiplatelet drug use	431 (22.80%)
Anticoagulant drug use	26 (1.38%)
Contracted COVID-19	
Never	888 (46.98%)
One time	462 (24.44%)
Two times	540 (28.57%)
Number of vaccine shots received	
None	311 (16.46%)
1 time	69 (3.65%)
2 times	642 (33.97%)
3 times	543 (28.73%)
4 times	241 (12.75%)
5 times	84 (4.44%)
Type of vaccine	
None	311 (16.46%)
Only Sinovac	345 (18.25%)
Only Biontech	844 (44.66%)
Only Turkovac	2 (0.11%)
Sinovac + Biontech	357 (18.89%)
Sinovac + Turkovac	10 (0.53%)
Biontech + Turkovac	9 (0.48%)
Sinovac + Biontech + Turkovac	12 (0.63%)
Type of event	
Unstable angina pectoris	97 (5.13%)
NSTEMI	760 (40.21%)
STEMI	1033 (54.66%)
Pre-ACS exposure	
Non-exposure	1237 (65.45%)
Post-vaccine	319 (16.88%)
Post-COVID	334 (17.67%)
Glucose, mg/dL	141 (114-202)
Urea, mg/dL	32.5 (27-41)
Creatinine, mg/dL	0.88 (0.76-1.05)
Creatinine clearance, mL/min	104.17 ± 37.79
Glomerular filtration rate, mL/min per 1.73 m^2	92 (73-103)
Platelets (× 10^3)	246 (206-295)
Major adverse cardiac event	569 (30.11%)
Time of major adverse cardiac event, days	1 (1-2)
Length of stay in hospital, days	3 (2-4)
Mortality	271 (14.34%)

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.

Median glucose, urea, and creatinine levels were significantly higher, and mean creatinine clearance and median eGFR levels were significantly lower in the MACE group (P < .001). The median length of stay in the hospital was significantly higher in patients with MACE (P < .001) (Table 3).

Multiple logistic regression analysis revealed that increased age (OR: 1.021, 95% CI: 1.009-1.032, P < .001), STEMI (OR: 1.785, 95% CI: 1.427-2.233, P < .001), post-COVID ACS (OR: 1.793, 95% CI: 1.369-2.348, P < .001), and elevated glucose (OR: 1.003, 95% CI: 1.002-1.004, P < .001) were independently associated with an increased risk of MACE. Conversely, hyperlipidemia (OR: 0.661, 95% CI: 0.530-0.824, P < .001), 3 or more COVID vaccinations (OR: 0.581, 95% CI: 0.459-0.734, P < .001), Biontech vaccination (OR: 0.598, 95% CI: 0.475-0.751, P < .001), and elevated eGFR (OR: 0.982, 95% CI: 0.977-0.988, P < .001) were independently associated with decreased MACE risk. Other variables included in the analysis, such as sex, smoking status, diabetes mellitus, previous cerebrovascular disease, renal disease, malignancy, antiplatelet use, COVID-19 history, urea, creatinine, and creatinine clearance, were found to be non-significant (P > .05) (Table 4).

DISCUSSION

Atherosclerosis is a major contributor to ACS, the leading cause of death in developed nations. Severe acute respiratory syndrome coronavirus 2 infection could accelerate this inflammatory process, increasing the risk of thromboembolic events through plaque erosion or rupture.[36] It has been confirmed that a history of coronary artery disease leads to a worse prognosis for COVID-19, and some studies have raised concerns regarding the cardiac side effects of COVID-19 vaccines.[20,35,37] However, clinical data are limited in this respect. The current study revealed that the post-vaccine group was older, had a lower percentage of immigrants, and had lower creatinine clearance and eGFR than the non-exposure group. The post-COVID group had a higher

Table 2. Summary of Variables with Regard to Exposure

	COVID-19-related Exposure Within Prior Month			
	Non-exposure (n = 1237)	**Post-vaccine (n = 319)**	**Post-COVID (n = 334)**	***P***
Age, years	56.80 ± 11.58	59.39 ± 10.98*	57.90 ± 11.70	**.001[a]**
Sex				
Female	257 (20.78%)	70 (21.94%)	67 (20.06%)	.835[b]
Male	980 (79.22%)	249 (78.06%)	267 (79.94%)	
Race				
Domestic	1142 (92.32%)	311 (97.49%)	311 (93.11%)	**.004[b]**
Immigrant	95 (7.68%)	8 (2.51%)*	23 (6.89%)#	
Body mass index, kg/m^2	28.25 ± 3.76	28.01 ± 3.46	28.72 ± 3.72#	**.037[a]**
Smoking status				
Non-smoker	226 (18.46%)	62 (19.62%)	64 (19.39%)	**.018[b]**
Ex-smoker	218 (17.81%)	78 (24.68%)*	70 (21.21%)	
Passive smoker	95 (7.76%)	12 (3.80%)*	29 (8.79%)#	
Active smoker	685 (55.96%)	164 (51.90%)	167 (50.61%)	
Hypertension	541 (43.73%)	157 (49.22%)	167 (50.00%)	.051[b]
Diabetes mellitus	447 (36.14%)	119 (37.30%)	134 (40.12%)	.406[b]
Hyperlipidemia	735 (59.42%)	183 (57.37%)	204 (61.08%)	.626[b]
Chronic obstructive pulmonary disease	79 (6.39%)	21 (6.58%)	20 (5.99%)	.949[b]
Previous coronary artery disease	275 (22.23%)	81 (25.39%)	93 (27.84%)	.076[b]
Previous peripheral artery disease	40 (3.23%)	6 (1.88%)	14 (4.19%)	.238[b]
Previous cerebrovascular disease	52 (4.20%)	11 (3.45%)	22 (6.59%)	.107[b]
Previous pulmonary embolism	1 (0.08%)	2 (0.63%)	2 (0.60%)	.051[c]
Previous deep vein thrombosis	7 (0.57%)	1 (0.31%)	0 (0.00%)	.587[c]
Renal diseases	93 (7.52%)	18 (5.64%)	36 (10.78%)	.051[b]
Malignancy	25 (2.02%)	11 (3.45%)	8 (2.40%)	.320[b]
Antiplatelet drug use	275 (22.23%)	73 (22.88%)	83 (24.85%)	.599[b]
Anticoagulant drug use	17 (1.37%)	5 (1.57%)	4 (1.20%)	.916[c]
Type of ACS				
Unstable angina pectoris	69 (5.58%)	14 (4.39%)	14 (4.19%)	.067[b]
NSTEMI	469 (37.91%)	138 (43.26%)	153 (45.81%)	
STEMI	699 (56.51%)	167 (52.35%)	167 (50.00%)	
Glucose, mg/dL	140 (113-195.5)	140 (115-203)	148.5 (116 228)	.118[d]
Urea, mg/dL	32.65 (26.95-41.0)	31.15 (27.0-39.0)	33.0 (26.3-41.7)	.357[d]
Creatinine, mg/dL	0.87 (0.75-1.04)	0.89 (0.77-1.04)	0.90 (0.77-1.10)	.075[d]
Creatinine clearance, mL/min	105.99 ± 38.83	99.27 ± 33.24*	102.08 ± 37.51	**.006[a]**
Glomerular filtration rate, mL/min per 1.73 m^2	93 (74-104)	90 (73-101)*	90 (70-101)*	**.006[d]**
Platelets (× 10^3)	247 (206-295)	240.5 (203-295)	249 (207-294)	.814[d]
Major adverse cardiac event	337 (27.24%)	93 (29.15%)	139 (41.62%)*#	**<.001[b]**
Time of major adverse cardiac event, days	1 (1-2)	1 (1-2)	2 (1-3)*	**.005[d]**
Length of stay in hospital, days	3 (2-4)	3 (2-4)	3 (2-5)*#	**<.001[d]**
Mortality	157 (12.69%)	42 (13.17%)	72 (2×1.56%)*#	**<.001[b]**

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
[a]One-way analysis of variance.
[b]Chi-square test.
[c]Fisher–Freeman–Halton test.
[d]Kruskal–Wallis test.
*Significantly different from "Non-exposure" group.
#Significantly different from "Post-vaccine" group.

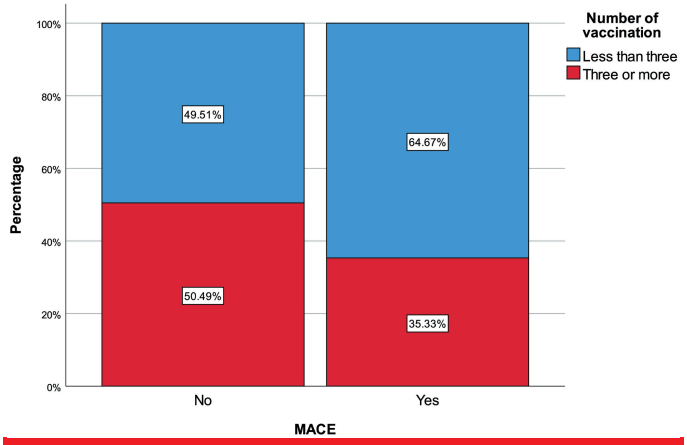

Figure 1. Number of vaccination shots received (categorized), percentages reported based on presence/absence of MACE.

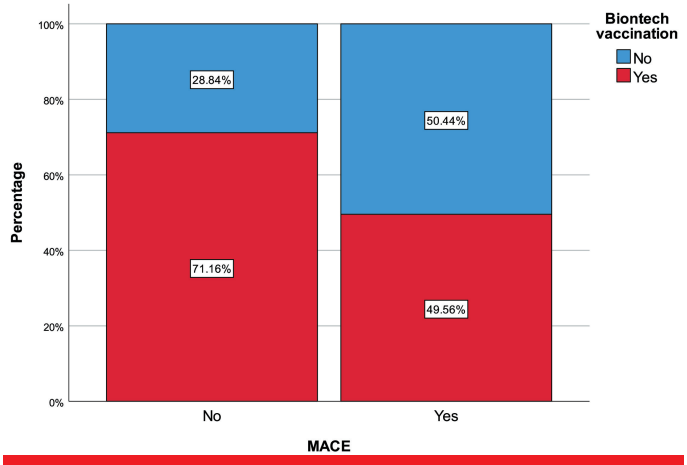

Figure 2. Frequency of Biontech vaccine recipients, based on MACE groups.

percentage of immigrants, higher BMI, higher percentage of MACE and mortality, and longer hospital stays compared to the post-vaccine group. The non-exposure group had higher eGFR, lower frequency of MACE and mortality, shorter

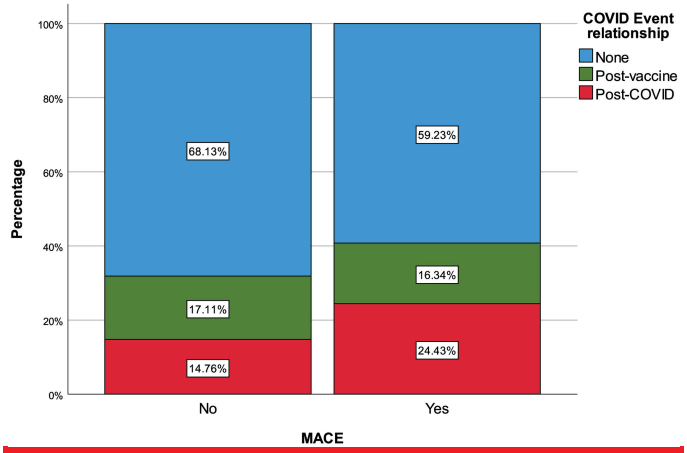

Figure 3. Pre-ACS exposure frequencies in groups with and without MACE.

MACE duration, and shorter hospitalization than the post-COVID group. Advanced age, STEMI diagnosis, contraction of COVID-19 within the prior month, and high glucose were associated with an increased risk of MACE, while hyperlipidemia, having received 3 or more COVID-19 vaccines, having received the Biontech vaccine, and high eGFR were associated with a decreased risk of MACE.

In the literature, there is insufficient information on the incidence of ACS patients with concomitant COVID-19, the impact of this association on the risk profile, and the resultant clinical outcomes. In the current study, 17.67% of ACS patients were found to have suffered from COVID-19 infection within the prior month. These patients had higher BMI values, lower eGFR, and increased MACE likelihood, as well as prolonged hospital stays and greater mortality risks compared to those who had not contracted COVID-19 in the last month. A study in Serbia showed that individuals with COVID-19 and ACS had a higher prevalence of underlying comorbidities, including hypertension, diabetes, kidney disease, and a history of previous PCI, lower blood pressure, higher heart rate, higher incidence of acute heart failure, and major complications compared to individuals with ACS without COVID-19. Significant differences in inflammatory and heart failure biomarkers were also seen in ACS patients with COVID-19.[18] Alharbi et al[38] showed that in-patient mortality and length of stay in the hospital were higher in STEMI patients with concurrent COVID-19 infection. In the study by Rashid et al,[19] ACS patients with COVID-19 were shown to be older and have more comorbidities, elevated cardiac troponin, pulmonary edema, cardiogenic shock, and poor left ventricular systolic function compared to patients with ACS without COVID-19. But interestingly, ACS patients with COVID-19 were less likely to receive invasive coronary angiography, PCI, and dual antiplatelet medication. A multicenter examination of 4 countries showed a high rate of stent thrombosis in STEMI patients with COVID-19, indicating that STEMI management should be adapted for COVID-19 patients.[39] Early studies reported contradictory angiographic and clinical findings in ACS patients with COVID-19 compared to ACS patients without COVID-19.[19,40,41]

The results of studies suggesting an association between the COVID-19 vaccines and cardiac events are important to consider despite limited evidence.[20,42] In the current study, 16.88% of patients had received the COVID-19 vaccine within the month before ACS occurrence. These patients were more likely to be immigrants and had lower eGFR and lower creatinine clearance compared to ACS patients who had not received any COVID-19 vaccination in the last month. In a systematic review of 16 studies, findings showed that patients who developed cardiovascular findings associated with the COVID-19 vaccine were predominantly male, and those with acute myocardial infarction were older. Events typically occurred within 24 hours of vaccination, and the majority of cases had developed after the first vaccine dose.[20] Acute coronary syndrome cases that have been attributed to COVID-19 vaccination have been reported in a number of case series and reports.[21,22] Some possible pathophysiological mechanisms have been suggested for these cardiovascular

pathologies: (i) the prothrombotic state following vaccination may be the result of an autoimmune response against platelets.[37] (ii) Another hypothesis is that stress from receiving the COVID-19 vaccine may lead to demand ischemia resulting in a cardiovascular event.[22] (iii) Others believe that acute myocardial infarction occurring after vaccination may result from vaccine-induced allergic vasospasm and that high levels of immunoglobulin E antibodies may be a risk factor for myocardial infarction, a condition called Kounis syndrome.[43] On the other hand, complete vaccination against COVID-19 has been associated with a reduced risk of myocardial infarcts after COVID-19.[44] Despite limited literature data supporting the relationship between cardiac symptoms and COVID-19 vaccination, these relationships must be supported by comprehensive studies, as the cause—effect relationship and pathophysiological mechanisms are unclear.[19] To our knowledge, there is no large-scale study reporting mortality differences among ACS patients with and without a history of COVID-19 vaccination.[45] Our data also show a lack of association between vaccination and mortality. As mentioned, the effects of COVID-19 infection on mortality are more pronounced and rely on strong evidence, whereas the majority of vaccine-attributed cardiac adverse events are reported very rarely.

In previous studies, mortality rates in ACS patients with COVID-19 have been reported to range between 25% and 72%.[18,19,39,41,46] The mortality rates in our study were 12.69% in the non-exposure group, 13.17% in the post-vaccine group, and 21.56% in the post-COVID group. The increased mortality rate in the post-COVID group was significant, and this elevated risk may be explained by various means. The virus, which enters the myocyte through angiotensin-converting enzyme-2 membrane receptors, may increase myocardial inflammation and injury by direct toxicity. The respiratory (or other systems) severity of COVID-19, increased oxygen demand, and induced procoagulant status may increase mortality. Increased supply—demand mismatch in the setting of a proinflammatory state such as acute respiratory distress syndrome (ARDS) may also result in differential effects on other organs and biochemical pathways, yielding a poor prognosis.[47,48] Finally, the treatment of COVID-19 could have critical implications on cardiovascular function.

Our data regarding other factors associated with outcomes are reasonably similar to what has been reported in the literature; nonetheless, it may be valuable to describe some interesting findings. During the pandemic, mortality was dramatically higher in patients with ARDS on mechanical ventilation than in patients without ARDS,[46] which supported the multisystem impact of COVID-19. Milovancev et al found higher mortality in STEMI patients with COVID-19 compared to those without. They also identified aortic regurgitation, serum creatinine levels, and the need for respiratory failure treatment as independent predictors of mortality due to ACS,[18] which are largely supported by our data. In another study, similarly, hospital and 30-day mortality of ACS patients with COVID-19 was found to be significantly higher compared to ACS patients without COVID-19, and creatinine, peak troponin, heart rate, left ventricular systolic dysfunction, angiotensin-converting enzymes inhibitor or angiotensin receptor blockers use were found to be independent risk factors for 30-day mortality. Acute coronary syndrome patients with COVID-19 had over 6-fold increase in mortality within 30 days.[19] Although the identified factors vary from study to study, the point to emphasize appears to be the fact that the coexistence of COVID-19 and ACS (or temporal proximity) has a strong influence on increasing the risks for mortality and worse outcomes.

Numerous conventional risk factors (short-, mid-, or long-term) associated with MACE in individuals experiencing acute myocardial infarction have been recognized. Smoking history, elevated blood pressure or cholesterol, diabetes, insufficient physical activity, and excessive weight or obesity are among the most relevant risk factors in this respect.[49] Our multiple analysis showed that older age, STEMI, COVID-19 infection, and high glucose levels were independent risk factors for in-hospital MACE. However, the presence of hyperlipidemia, receiving 3 or more vaccine shots, receiving the Biontech vaccine, and having high eGFR were associated with a decreased MACE likelihood. In a multinational collaborative study spanning 10 centers across 5 countries in Europe and Australia (Italy, Sweden, UK, Australia, Spain), the investigation focused on potential predictors of in-hospital MACE among patients admitted for COVID-19. The study revealed that individuals who experienced MACE tended to exhibit advanced age, elevated body temperature, increased creatinine levels, heightened high-sensitivity troponin levels, and elevated white blood cell and platelet counts upon admission. Additionally, this group was predisposed to systemic hypertension, renal failure, chronic obstructive pulmonary disease, atrial fibrillation, and cardiomyopathy. However, in the multiple analysis, only troponin levels and renal failure emerged as independent factors significantly associated with the occurrence of MACE.[50] In another study, adjusted analyses identified age, male sex, chronic obstructive pulmonary disease, lung infiltration on computed tomography, and history of cardiovascular disease as independent risk factors for in-hospital death or MACE.[51] Studies exploring vaccine-associated complications have not provided convincing evidence of an increased risk of MACE after vaccination.[52] Our study has a rather notable result in this respect; we found that receiving at least 3 vaccine shots and receipt of the Biontech vaccine were among the factors that independently reduced the risk for MACE development. Although intriguing, such results are undoubtedly impacted by vaccine availability as well as temporal/dosage-related differences.

An important clinical implication of our study is that recent COVID-19 infection poses a high risk of mortality and MACE for ACS patients. Advanced age and decreased kidney function were noteworthy risk factors among patients who developed ACS either following infection or vaccination. It is therefore safe to say that recent infections must be taken into consideration when assessing ACS prognosis.

The present study holds value as it is one of the few studies that has analyzed and compared the ACS-related influences of COVID-19 infection and vaccination, which has been an

Table 3. Summary of Variables with Regard to Major Adverse Cardiac Event

	Major Adverse Cardiac Event		
	No (n = 1321)	**Yes (n = 569)**	***P***
Age, years	55.96 ± 10.79	60.85 ± 12.45	**<.001**[a]
Sex			
Female	258 (19.53%)	136 (23.90%)	**.032**[b]
Male	1063 (80.47%)	433 (76.10%)	
Race			
Domestic	1239 (93.79%)	525 (92.27%)	.223[b]
Immigrant	82 (6.21%)	44 (7.73%)	
Body mass index, kg/m^2	28.26 ± 3.78	28.35 ± 3.54	.637[a]
Smoking status			
Non-smoker	231 (17.58%)	121 (21.76%)*	**.019**[b]
Ex-smoker	249 (18.95%)	117 (21.04%)	
Passive smoker	107 (8.14%)	29 (5.22%)*	
Active smoker	727 (55.33%)	289 (51.98%)	
Hypertension	591 (44.74%)	274 (48.15%)	.172[b]
Diabetes mellitus	441 (33.38%)	259 (45.52%)	**<.001**[b]
Hyperlipidemia	832 (62.98%)	290 (50.97%)	**<.001**[b]
Chronic obstructive pulmonary disease	84 (6.36%)	36 (6.33%)	.979[b]
Previous coronary artery disease	303 (22.94%)	146 (25.66%)	.202[b]
Previous peripheral artery disease	38 (2.88%)	22 (3.87%)	.326[b]
Previous cerebrovascular disease	42 (3.18%)	43 (7.56%)	**<.001**[b]
Previous pulmonary embolism	2 (0.15%)	3 (0.53%)	.164[c]
Previous deep vein thrombosis	4 (0.30%)	4 (0.70%)	.252[c]
Renal diseases	67 (5.07%)	80 (14.06%)	**<.001**[b]
Malignancy	24 (1.82%)	20 (3.51%)	**.038**[b]
Antiplatelet drugs use	318 (24.07%)	113 (19.86%)	**.045**[b]
Anticoagulant drugs use	17 (1.29%)	9 (1.58%)	.772[b]
Contracted COVID-19			
Never	635 (48.07%)	253 (44.46%)	**.038**[b]
One time	301 (22.79%)	161 (28.30%)*	
Two times	385 (29.14%)	155 (27.24%)	
Number of vaccine shots received			
None	156 (11.81%)	155 (27.24%)*	**<.001**[b]
One time	51 (3.86%)	18 (3.16%)	
Two times	447 (33.84%)	195 (34.27%)	
Three times	405 (30.66%)	138 (24.25%)*	
Four times	196 (14.84%)	45 (7.91%)*	
Five times	66 (5.00%)	18 (3.16%)	
Type of vaccine			
None	156 (11.81%)	155 (27.24%)*	**<.001**[d]
Only Sinovac	216 (16.35%)	129 (22.67%)*	
Only Biontech	650 (49.21%)	194 (34.09%)*	
Only Turkovac	1 (0.08%)	1 (0.18%)	
Sinovac + Biontech	272 (20.59%)	85 (14.94%)*	
Sinovac + Turkovac	8 (0.61%)	2 (0.35%)	
Biontech + Turkovac	9 (0.68%)	0 (0.00%)*	
Sinovac + Biontech + Turkovac	9 (0.68%)	3 (0.53%)	

(*Continued*)

Table 3. Summary of Variables with Regard to Major Adverse Cardiac Event (*Continued*)

	Major Adverse Cardiac Event		
	No (n = 1321)	**Yes (n = 569)**	***P***
Type of event			
Unstable angina pectoris	78 (5.90%)	19 (3.34%)*	**<.001**[b]
NSTEMI	574 (43.45%)	186 (32.69%)*	
STEMI	669 (50.64%)	364 (63.97%)*	
Pre-ACS exposure			
Non-exposure	900 (68.13%)	337 (59.23%)*	**<.001**[b]
Post-vaccine	226 (17.11%)	93 (16.34%)	
Post-COVID	195 (14.76%)	139 (24.43%)*	
Glucose, mg/dL	135 (112-186)	162 (124-250)	**<.001**[e]
Urea, mg/dL	31.2 (26-38)	36.1 (29-47)	**<.001**[e]
Creatinine, mg/dL	0.86 (0.74-0.99)	0.96 (0.79-1.18)	**<.001**[e]
Creatinine clearance, mL/min	109.89 ± 36.42	90.80 ± 37.56	**<.001**[a]
Glomerular filtration rate, mL/min per 1.73 m^2	95 (80-105)	80 (60-97)	**<.001**[e]
Platelets (× 10^3)	246 (207-291)	247 (203-299)	.764[e]
Length of stay in hospital, days	3 (2-4)	3 (2-6)	**<.001**[e]

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. Values in bold indicate statistical significance.
[a]Student *t*-test.
[b]Chi-square test.
[c]Fisher's exact test.
[d]Fisher–Freeman–Halton test.
[e]Mann–Whitney *U* test.
*Significantly different category.

important topic for the general public. The investigation encompassed 3 distinct groups: the vaccination group, the infection group, and a group without exposure to either. The results support the use of vaccines and do not reveal a link between vaccines and cardiovascular adverse events.

This study showed that the time to MACE was significantly longer among post-COVID patients compared to the non-exposure group. This could be explained by the fact that post-COVID patients are likely to have received anti-inflammatory treatment during treatment. Given the association of MACE occurrence with severe systemic inflammation, it is likely that the anti-inflammatory treatment delayed MACE emergence. Another possible reason could be that the post-COVID group received a higher rate of antiplatelet therapy than the other groups, as shown by our data.

Most importantly, the present study shows that hyperlipidemia is independently associated with decreased MACE likelihood, contradicting classical knowledge. It must be noted that although the presence of hyperlipidemia appears to be protective in terms of MACE, the frequency of hyperlipidemia is higher in the post-COVID group. Furthermore, the frequencies of hypertension, diabetes mellitus, previous coronary artery disease, previous pulmonary arterial hypertension, and previous cerebrovascular events were also higher in this patient group. It is possible that regular antilipidemic and other anti-inflammatory treatments were very common among patients with such a high burden of chronic disease. Therefore, the anti-inflammatory and antioxidant effects of anti-lipidemic therapy could have impacted MACE likelihood and our analyses. Taken together, and considering that

Table 4. Significant Factors İndependently Associated with MACE, Multiple Logistic Regression

	***β*-coefficient**	**Standard Error**	***P***	**Exp(*β*)**	**95% CI for Exp(*β*)**	
Age	0.021	0.006	<.001	1.021	1.009	1.032
Hyperlipidemia	−0.414	0.112	<.001	0.661	0.530	0.824
Number of vaccine shots, ≥3	−0.544	0.120	<.001	0.581	0.459	0.734
Type of vaccine, Biontech	−0.515	0.117	<.001	0.598	0.475	0.751
Type of event, STEMI	0.579	0.114	<.001	1.785	1.427	2.233
Exposure (post-COVID group)	0.584	0.138	<.001	1.793	1.369	2.348
Glucose	0.003	0.001	<.001	1.003	1.002	1.004
Glomerular filtration rate	−0.018	0.003	<.001	0.982	0.977	0.988
Constant	−0.784	0.530	.139	0.457		

CI, confidence interval, Nagelkerke R^2=0.217.

severe systemic inflammation contributes strongly to the occurrence of MACE, anti-lipidemics, and other anti-inflammatory therapies could be associated with a decreased likelihood of MACE development. However, this hypothesis needs to be supported by further studies.

However, certain limitations must be acknowledged in the interpretation of the study results. It is essential to consider that individuals in the non-exposure group may have had potential contact with COVID-19 and might have undergone a silent infection. The study was confined to a single center, and data acquisition relied on retrospective screening. Not only these, but the fact that the vaccines examined in this study (the most common vaccines in Turkey) had been introduced to the public at different time points and different "waves" of the pandemic is an important factor that could influence the outcomes. Taken together, external validity may be exceedingly limited for other countries, but a moderate level of generalizability should be expected for other populations in Turkey. We must also clarify that several pivotal parameters, such as COVID-19 treatment, the severity of COVID-19, mechanical ventilation needs, ARDS development, and post-vaccination side effects were not assessed, which are parameters that have the potential to bias results. Finally, we were also unable to obtain complete data regarding interventions (for instance, PCI count), the duration between symptom onset and PCI, the impact of COVID-19 on ACS diagnosis and management, and angiography-related findings, which could have yielded more comprehensive results.

CONCLUSION

Among ACS patients, recent COVID-19 infection demonstrated associations with increased mortality, elevated risk of MACE, and prolonged hospitalization. Apart from recent COVID-19 infection, factors such as older age, STEMI, and elevated glucose levels were factors that emerged as being independently associated with elevated MACE likelihood. Our data underscore the importance of recognizing that ACS patients with recent COVID-19 infection may experience an unfavorable prognostic trajectory, necessitating appropriate precautions and management strategies.

Data Availability: The datasets used or analyzed during the current case reports are available from the corresponding author on reasonable request.

Ethics Committee Approval: The protocol for this study was approved by the Clinical Research Ethics Committee of Haseki Training and Research Hospital (decision date: November 09, 2022, decision number: 201-2022). All procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

Informed Consent: Consent form was not obtained because this study was a retrospective study.

Peer-review: Externally peer-reviewed.

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