Outcomes of patients with acute coronary syndrome according to COVID-19 vaccination status

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Background **COVID-19 vaccination has been associated with reduced risk of acute coronary syndrome (ACS); however, several studies have reported cardiovascular complications following vaccination. We aimed to investigate the effect of COVID-19 vaccination status on the treatment and outcome of ACS patients.**

Methods **The study was based on the 2021 Acute Coronary Syndrome Israeli Survey. Patients were stratified into two groups according to COVID-19 vaccination status, vaccinated compared to unvaccinated. Patients who had received at least 2 vaccination doses up to 1 week prior to ACS hospitalization were considered vaccinated. The primary endpoint was 1-year all-cause mortality.**

Results **A total of 1261 patients with ACS were included, of whom 990 (78.5%) were vaccinated. Vaccinated patients were older and less frequently smokers. There were no significant differences in coronary reperfusion rates and treatment with guideline-based medical therapy during hospital stay and at discharge. The primary endpoint of 1-year all-cause mortality occurred in 38 (3.8%) and 14 (5.2%) patients in the vaccinated and unvaccinated groups respectively ($P = 0.42$). 30-day MACE occurred in 94 (9.5%) in the vaccinated patients compared to 31 (11.5%) in the unvaccinated group ($P = 0.39$). These results remained similar following adjustment for confounders.**

Conclusion **There was no association between COVID-19 vaccination status and the outcomes of patients with ACS. Our findings provide support for the cardiovascular safety of COVID-19 mRNA vaccines in patients at high cardiovascular risk.** ***Coron Artery Dis*** **34: 470–474**

Coronary Artery Disease 2023, **34**:470–474

Keywords: acute coronary syndrome, COVID-19, COVID-19 vaccination

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Received 29 June 2023 **Accepted** 11 July 2023.

Background

The coronavirus 19 disease (COVID-19) was declared by the WHO as a worldwide pandemic in March 2020 [1]. Although predominantly affecting the respiratory system, cardiovascular manifestations have been identified as consequences of COVID-19 infection [2]. A higher risk of acute myocardial infarction was reported during the acute infection and as a late complication following recovery. While the association between COVID-19 infection and acute myocardial infarction may be multifactorial, increased thrombotic risk seems to be the major cause [3].

By the end of 2020, several mRNA-based vaccines against COVID-19 had been developed and subsequently were utilized worldwide. During 2021 the majority of the adult population in Israel received two doses of the BNT162b2 (Pfizer BioNTech) anti-COVID-19 vaccine in an emergency nationwide vaccination campaign [4]. Several large studies have demonstrated that COVID-19 mRNA vaccines appeared to be safe and highly effective in preventing infection and progression to severe disease, hospitalization, and death [5,6]. Vaccine-related adverse events were rare and included myocarditis (6–27 cases per million patients) [7] and thrombo-embolic complications (0.61 cases per million) [8,9]. Vaccination against COVID-19 was associated with a reduced risk of acute myocardial infarction and ischemic stroke following a recent COVID-19 infection [10]. However, the effect of COVID-19 vaccination on outcomes in patients admitted with acute coronary syndrome (ACS) following vaccination has not been evaluated yet.

The aim of the current study was to investigate the association between COVID-19 vaccination status and the treatment and outcomes of ACS patients enrolled in a nationwide survey.

Methods

Study population

The Acute Coronary Syndromes Israeli Survey (ACSIS) is carried out for 2 months every 2–3 years in all intensive coronary care units and cardiology departments in Israel. The study population consists of consecutive patients

0954-6928 DOI: 10.1097/MCA.0000000000001270

presenting with ST-elevation and non-ST-elevation myocardial infarction as well as unstable angina pectoris who were enrolled in the ACSIS during March-April 2021. Study physicians recorded all clinical and demographic data including COVID-19 vaccination status on pre-specified forms. The diagnosis of ACS was based on clinical, electrocardiographic, and biochemical criteria and patients were managed at the discretion of each medical center.

Patients who had received at least 2 vaccination doses up to 1 week prior to hospital admission were considered vaccinated. At the time of the 2021 ACSIS enrollment, the BNT162b2 vaccine (Pfizer–BioNTech) was the only available vaccine in Israel. Patients were divided into 2 groups according to vaccination status: vaccinated and unvaccinated. We compared baseline characteristics, treatments, and clinical outcomes between the 2 groups.

The primary endpoint of the study was 1-year all-cause mortality. Secondary outcomes included 30-day major adverse cardiovascular events (MACE) including death, recurrent myocardial infarction or unstable angina pectoris, cerebrovascular accident, and urgent revascularization therapy. Mortality rates were determined for all patients from hospital charts and by matching the identification numbers of the patients with the Israeli National Population Registry.

The study was approved by the local institutional ethics committee of each medical center in keeping with the principles of the Declaration of Helsinki. In accordance with Ministry of Health regulations, all participants sign a written informed consent prior to enrollment.

Statistical analysis

Patients' characteristics were presented as n (%) for categorical variables, and as mean (±SD) or median [inter-quartile range (IQR)] for normal/non-normal distributed continuous variables. The cohort was divided into two groups according to vaccination status (fully and not fully vaccinated). Baseline characteristics, treatment and clinical outcomes were compared between patients according to vaccination status. The groups were tested with chi-square test for categorical variables and with t-test or Mann–Whitney–Wilcoxon test as appropriate for normal/non-normal distributed continuous variables. Survival curves were presented, and the Kaplan–Meier log-rank test was used to test the status of vaccination on survival. Multivariable Cox proportional hazard regression model was performed, adjusted for baseline characteristics ($P < 0.05$ in univariable tests). Missing values in the included covariates were less than 10% and were not imputed. All analyses were performed using R (R-studio, V.4.0.3, Vienna, Austria).

Results

A total of 1261 ACS patients were included in the study of whom 990 (78.5%) were fully vaccinated. Median age was 64 (IQR: 55.2–72) years and 990 (78.5%) were males. Baseline characteristics according to COVID-19 vaccination status are presented in Table 1. Vaccinated patients were older and less frequently smokers. The rates of all other cardiovascular risk factors, past cardiovascular disease and treatment with cardiovascular medications were similar in the two groups.

Clinical characteristics of the study population upon hospital admission and treatments during hospitalization according to vaccination status are presented in Table 2. Killip class>1 and reduced left ventricular ejection fraction (LVEF) were more frequent in the unvaccinated patients group. There were no significant differences neither in the type of ACS (STEMI and NSTE-ACS) nor in the GRACE score between the two groups. There were no significant differences in referral rates for invasive strategy with coronary angiography and subsequent coronary revascularization and treatment with guideline-based medical therapy between the study groups.

During the first year following the ACS event 52 (4.1%) patients died. One-year all-cause mortality rates were 3.8% in the vaccinated and 5.2% in the unvaccinated group ($P = 0.1$). Kaplan–Meier curves comparing 1-year mortality according to COVID-19 vaccination status are presented in Fig. 1. There were no significant differences in 1-year mortality rates between the groups.

Table 1 Baseline characteristics according to COVID-19 vaccination status

	Not fully vaccinated	Fully vaccinated	*P*-value
n	271	990	
Baseline characteristics			
Age, years (median) (IQR)	59 [51- 68]	66 [58–73]	<0.001
Gender (male)	215 (79.3)	775 (78.3)	0.771
Dyslipidemia	181 (66.8)	707 (71.4)	0.161
Hypertension	164 (60.5)	633 (63.9)	0.335
Current smokers	135 (49.8)	377 (38.1)	0.001
Diabetes mellitus	126 (46.5)	408 (41.2)	0.136
Family history of CAD	76 (31.0)	261 (29.9)	0.795
BMI (kg/m^2) (median)	27.44	27.34	0.929
Prior MI	109 (40.2)	354 (35.8)	0.205
Prior CABG	14 (5.2)	65 (6.6)	0.481
Prior PCI	99 (36.5)	331 (33.4)	0.379
CKD	25 (9.2)	106 (10.7)	0.551
PVD	16 (5.9)	75 (7.6)	0.414
Prior CVA/TIA	25 (9.2)	85 (8.6)	0.834
History of CHF	23 (8.5)	57 (5.8)	0.133
Prior medications			
Aspirin	105 (38.7)	399 (40.3)	0.694
P2Y12 inhibitors	32 (11.8)	121 (12.2)	0.936
Statins	104 (38.4)	431 (43.5)	0.146
ACE-I/ARB	82 (30.3)	384 (38.8)	0.012
Beta-blockers	82 (30.3)	294 (29.7)	0.917

Data are presented as median (IQR), or number (percentage).

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack.

Table 2 In-hospital admission clinical characteristics and in hospital/discharge treatment

	Not fully vaccinated	Fully vaccinated	*P*-value
n	271	990	
Characteristics on admission			
Diagnosis			0.284
NSTEMI	116 (42.8)	427 (43.1)	
STEMI	118 (43.5)	392 (39.6)	
UAP	37 (13.7)	171 (17.3)	
Grace score >140	28 (11.7)	100 (12.1)	0.950
Killip class			0.018
I	210 (83.3)	794 (88.3)	
II	25 (9.9)	79 (8.8)	
III	13 (5.2)	16 (1.8)	
IV	4 (1.6)	10 (1.1)	
EF category			0.021
>50%	117 (46.1)	484 (52.8)	
40–50%	80 (31.5)	259 (28.3)	
30–40%	41 (16.1)	148 (16.2)	
<30%	16 (6.3)	25 (2.7)	
Reperfusion therapy			
Coronary angiography	253 (93.4)	941 (95.1)	0.343
PCI	212 (78.2)	783 (79.1)	0.823
CABG	21 (7.7)	80 (8.1)	0.959
Medical therapy at discharge			
Aspirin	241 (90.9)	894 (91.7)	0.792
P2Y12 inhibitors	232 (87.5)	860 (88.2)	0.852
Statins	250 (94.3)	922 (94.6)	1.000
ACE-I/ARB	202 (74.5)	734 (74.1)	0.957
Beta-blockers	199 (75.1)	730 (74.9)	1.000

Data are presented as number (percentage).
CABG, coronary artery bypass graft; EF, ejection fraction; NSTEMI, non-ST-elevation myocardial infraction; PCI, Percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

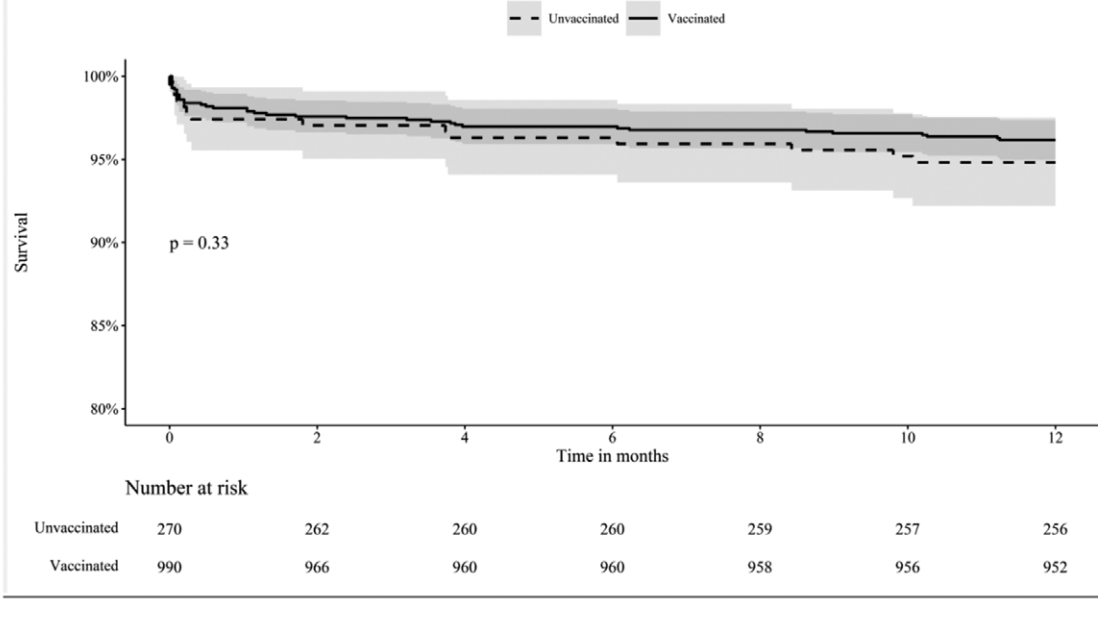
These results remained similar following a multivariate adjustment for age, gender, LVEF, Killip class and smoking status (Table 3). Additionally, vaccination status had no effect on 30-day mortality and MACE rates (Fig. 2).

Discussion

The present study evaluated differences in baseline characteristics, treatments, and outcomes between ACS patients who were fully vaccinated against COVID-19 compared to ACS patients who were not fully vaccinated. The study included nationwide cohort of consecutive ACS patients enrolled between March-April 2021 in the ACSIS. At the same time, a nationwide vaccination operation against COVID-19 was carried out in Israel, and thus a significant proportion of the ACS patients in the survey were already fully vaccinated. This allowed us to assess the influence of the vaccine on the management and outcome of patients with ACS.

We demonstrated similar 1-year survival rates between the two groups regardless of vaccination status. Moreover, there were no significant differences in 30-day MACE rates between patients from both groups. Among the study participants, vaccinated patients were older. This finding may be explained by the fact that in the early months of the nationwide vaccination campaign, elderly patients

Fig. 1



Kaplan-Meier curve of 1-year mortality in patients in the fully vaccinated group and not fully vaccinated groups.

Kaplan–Meier curve for 1-year mortality according to COVID-19 vaccination status.

were the highest priority for vaccination [5]. The lower rate of smokers in the vaccinated group is also not surprising considering different studies suggesting that smokers hold more negative attitudes toward different medical services including vaccines and are more likely to be undecided or unwilling to vaccinate against Covid-19 [11,12].

The LVEF was higher and the Killip class was better in the fully vaccinated patients compared to the unvaccinated group in our study. While there is no definite explanation for this finding, it may be as a result of higher rate of COVID-19 infection prior to the coronary event, among the patients who were not fully vaccinated. It was demonstrated by several large studies that COVID-19 mRNA vaccines are highly effective in preventing infection and deteriorating to severe disease [5,6]. COVID-19 infection had several cardiovascular manifestations [2,3] including direct cardiac injury causing reduced cardiac function and lower EF among patients who experienced COVID-19 infection, which may occur more frequently in the unvaccinated group.

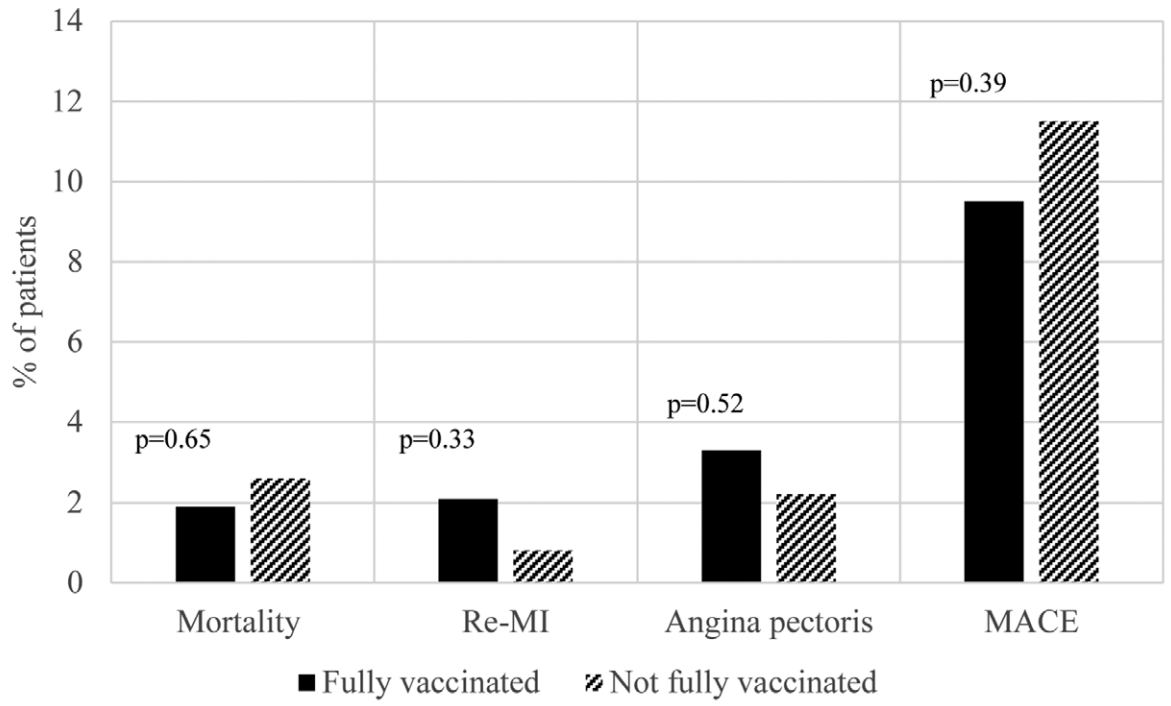
Table 3 **Multi-variant analysis for 1-year mortality.**

Subgroup	Hazard ratio (95% CI)	*P*-value
Fully vaccinated	0.6 (0.31–1.16)	0.14
Age (per year)	1.08 (1.05–1.11)	< 0.001
Male	1.55 (0.77–3.12)	0.22
Current smokers	0.85 (0.42–1.08)	0.67
Admission Killip class ≥2	2.44 (1.31–4.52)	0.005
EF moderate to severe	2.42 (1.33–4.38)	0.004

Cox regression for 1-year mortality presenting hazard ratio and 95% confidence interval.
Model was performed on 1170 patients with available data.
EF, ejection fraction.

The importance of vaccination in patients with established cardiovascular disease or high cardiovascular risk has been demonstrated mainly for influenza vaccine. A recent large prospective study including 2571 patients admitted with acute myocardial infarction, demonstrated that early influenza vaccination during the index hospitalization resulted in a lower risk of a composite of all-cause death, myocardial infarction or stent thrombosis,

Fig. 2



Secondary endpoints of 30-days mortality, recurrent myocardial infarction (Re-MI), angina pectoris, and MACE in the fully vaccinated group and not fully vaccinated group.

Values are presented in number (percentage).

30 days clinical outcomes according to vaccination status.

and a lower risk of all-cause death and cardiovascular death, at 12 months compared with placebo [13]. These findings were further supported by a meta-analysis including 217 072 patients with high cardiovascular risk or established cardiovascular disease, enrolled in 18 studies. Influenza vaccination reduced MACE, all-cause and cardiovascular mortality [14]. Full vaccination against COVID-19 has resulted in a reduced risk of AMI and ischemic stroke after COVID-19 infections. On the other hand, several studies have reported cardiovascular complications following COVID-19 vaccination which may range from asymptomatic myocardial injury to myocarditis, pericarditis, cardiac arrhythmias, and ACS [15–17]. These concerning findings were not supported by other studies that demonstrated a good safety profile of the BNT162b2 mRNA Covid-19 vaccine that was not associated with increased cardiovascular risk [18–20].

The current study presents, to the best of our knowledge, the first assessment of the association between COVID-19 vaccination status and outcomes of patients with ACS. We did not find any significant effect of vaccination status on neither the treatment nor the outcome of patients. While vaccinated patients were older, our results remain similar following age adjustment. Our findings provide further support to the existing data regarding the cardiovascular safety of the COVID-19 mRNA vaccines even in patients at very high cardiovascular risk such as patients with ACS.

This study has several limitations that warrant consideration. This is an uncontrolled observational study and therefore it is possible that other confounding parameters may be accountable for the lack of association between vaccination status and the outcome of ACS patients. Our study included only patients who have had an ACS. Therefore, whether vaccination was associated with increased risk of ACS cannot be determined by the dataset. The study was based on a nationwide survey from a single country in which only one specific vaccine was used (Pfizer–BioNTech), therefore our conclusions should be extrapolated to other countries with caution. We did not have data regarding COVID-19 infections during the first year following hospital admission. Finally, Patients who received only a single vaccine or had their second vaccine within a week of their ACS admission were included in the not fully vaccination group. Separate data regarding these patients were not available in our database.

In conclusion, COVID-19 vaccination status had no significant effect on the treatment and outcome of patients with ACS. Our findings provide further support for the cardiovascular safety of COVID-19 mRNA vaccines and should encourage the vaccination of patients at high cardiovascular risk.

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