Association of SARS-CoV-2 immunoserology and vaccination status with myocardial infarction severity and outcome

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ABSTRACT

Background: The COVID-19 pandemic adversely affected the severity and prognosis of patients with acute myocardial infarction (MI) caused by atherothrombosis (type 1 MI). The effect, if any, of COVID-19 vaccination and natural SARS-CoV2 serologic immunity in these patients is unclear. Our aim was to analyze the association between the severity and outcome of patients with type 1 MI and their previous SARS-CoV2 vaccination and serostatus.

Methods: A single-center retrospective cohort study conducted between March 1, 2020 and March 1, 2023. Clinical and follow-up information was collected from medical records and patients. Total antibodies (IgM, IgA, IgG) to nucleocapsid (N) antigens were measured by ECLIA (electrochemiluminescence-based immunoassay) to test the immune response to natural infection. If positive, IgM and IgG antibodies to spike (S) surface antigens were measured by CLIA to test the immune response to vaccine or natural infection. Multivariable logistic regression analysis was performed, adjusting for age, sex, hypertension, diabetes, and dyslipidemia.

Results: Total sample of 949 patients, 656 with ST-segment elevation MI (STEMI) and 293 with non-ST-segment elevation MI (NSTEMI). Mean age was 64 (SD 13) years, 80 % men. Pre-admission vaccination status was: $\geq$ 1 dose, 53 % of patients; complete vaccination, 49 %; first booster dose, 25 %. The majority (84 %) of vaccines administered were mRNA-based. Six months after MI, 92 (9.7 %) patients had a major adverse cardiac event (MACE) and 50 died; 11 % of patients had severe heart failure or cardiogenic shock (Killip III-IV) after STEMI. Vaccinated patients with STEMI and positive serology (Pos/Vax group) had a higher risk of Killip III-IV on admission: OR 2.63 (1.27–5.44), $p = 0.010$. SARS-CoV-2 S-specific IgG titers were highest in this group (median > 2080 AU/mL, [IQR 1560- >2080] vs 91 [32–198] in the unvaccinated group). In the overall sample, a higher incidence of 6-month MACE was not demonstrated (OR 1.89 [0.98–3.61], $p = 0.055$).

Conclusions: The combination of vaccination and natural SARS-CoV2 infection was associated with the development of severe heart failure and cardiogenic shock in patients with STEMI, possibly related to an increased serological response.

1. Introduction

Patients with myocardial infarction (MI) admitted during the COVID-19 pandemic had a higher rate of cardiogenic shock and a higher incidence of life-threatening ventricular arrhythmias after successful culprit artery revascularization compared with those admitted before the pandemic [1–3]. An increased risk of acute MI has also been reported, not only during the acute phase of COVID-19 disease [4,5], but

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also as a late complication after recovery, even in those who did not require hospitalization [6].

In addition, myocardial infarction has been associated with COVID-19 vaccination in several studies, but causality cannot be established and no definitive association has been demonstrated [7,8]. Overall, the increased risk of serious hematologic and vascular events after SARS-CoV-2 infection was found to be significantly higher and more prolonged than after vaccination [7].

During the course of SARS-CoV-2 infection, serologic techniques detect total antibodies, IgM and IgG, with increasing sensitivity, reaching greater than 90 % by the second week after symptom onset [10–14]. In individuals who recover from COVID-19, the humoral response remains relatively stable for 6–12 months after infection [9,15], although the ability to detect antibodies may decline significantly over time in symptom-free or mildly symptomatic individuals [16]. Vaccination has been shown to increase all components of the humoral response [9].

One study examined the effect of vaccination status on the prognosis of patients with acute coronary syndrome and found no association [17]. The aim of the present study was to analyze the association of COVID-19 vaccination status with the severity and outcome of patients with MI caused by acute atherothrombotic coronary artery disease (type 1 MI) according to their serological stage on admission.

2. Methods

2.1. Patients

A single-center, retrospective cohort study was conducted at a tertiary hospital in Madrid between March 1, 2020 and March 1, 2023. To investigate the association between asymptomatic SARS-CoV2 infection and acute coronary syndrome, patients admitted with type 1 MI from March 1, 2020, were asked to donate a serum sample for serological analysis of SARS-CoV-2 infection and to receive a follow-up phone call if they were not followed up at our center. In 2022, one year after the start of the vaccination campaign, the objectives of the study were set. The final recruitment date was March 1, 2023 for patients with ST-elevation myocardial infarction (STEMI) and August 18, 2022 for patients with non-ST-elevation myocardial infarction (NSTEMI). The study was approved by the the Ethics Committee of our institution (Project ID 159.20) and all participants signed an informed consent form.

STEMI was defined as ST-segment elevation >0.2 mV in 2 or more contiguous chest leads, >0.1 mV in 2 or more limb leads, or new left bundle branch block on the electrocardiogram, combined with symptoms of myocardial ischemia and troponin I levels >99th percentile. NSTEMI was diagnosed in patients with acute coronary syndrome and troponin elevation but without ECG changes consistent with STEMI. Diabetes mellitus was defined by prior diagnosis or random plasma glucose >200 mg/dL on admission. Hypertension and dyslipidemia were defined by active medical treatment on admission or prior diagnosis. Previous ischemic heart disease was determined by history of myocardial infarction (MI), PCI, or coronary artery bypass grafting.

Epidemiologic, clinical, and angiographic data were collected from electronic medical records and coronary angiograms. Vaccination status was obtained from the electronic medical record or, in the case of patients from outside the Community of Madrid, from an electronic certificate. After hospital discharge, patients were routinely followed up in the cardiology office or by a previously consented telephone interview.

2.2. SARS CoV-2 serologic testing

Blood samples were collected by venipuncture on admission after coronary angiography. After collection, samples were centrifuged at 3500 rpm for 5 min and serum was extracted for analysis.

Total antibodies (IgM, IgA, IgG) to nucleocapsid (N) antigens were measured by electrochemiluminescence-based immunoassay (ECLIA)

[Elecsys Anti-SARS-CoV-2 (ROCHE)] as a test of the immune response to natural infection. In patients who tested positive, IgM and IgG antibodies to spicular or spike (S) surface antigens were measured by chemiluminescence-based immunoassays (CLIA) [LIAISON SARS-CoV-2 IgM assay; LIAISON SARS-CoV-2 Trimerics IgG assay, DIASORIN] as evidence of immune response to vaccine or natural infection. In positive cases, IgG levels were quantified using a detection interval of 13.0–2080 AU/mL.

2.3. Statistical analysis

Descriptive analysis was performed using mean and standard deviation or median and 25th and 75th percentiles, as appropriate. Categorical variables were described using absolute and relative frequencies. A composite endpoint of major adverse cardiovascular events (MACE) was defined as the presence of at least one of the following: death, reinfarction, urgent revascularization, and hospitalization for heart failure.

First, we hypothesized a linear trend association between the time elapsed from the date of vaccination to the onset of MI and the occurrence of MACE in the 6 months after MI. Therefore, we performed a univariable analysis with MACE at 6 months as the dependent variable and time since last vaccination (with 3 categories: No vaccination, last vaccination ≤30 days before MI, and > 30 days before MI) as the independent variable. If the linear trend was not observed, we would discard the time from vaccination to MI and consider only vaccination or no vaccination.

Multivariable explanatory analysis was performed for two outcomes: MACE at 6 months in patients with type 1 MI, and severe heart failure (HF)/cardiogenic shock (Killip III-IV) after STEMI. To assess the association between serology and SARS CoV-2 vaccination status and MACE at 6 months, we first performed an unadjusted logistic regression analysis and then adjusted the model for potential confounders, i.e., variables associated with outcome and exposure but not a consequence of serology or SARS CoV-2 vaccination status. Potential confounders were adjusted for according to statistical and clinical criteria. The effect size was estimated using the odds ratio (OR) and the corresponding 95 % confidence interval (95 % CI). The same approach was used for the outcome of severe HF/cardiogenic shock after STEMI. Finally, a
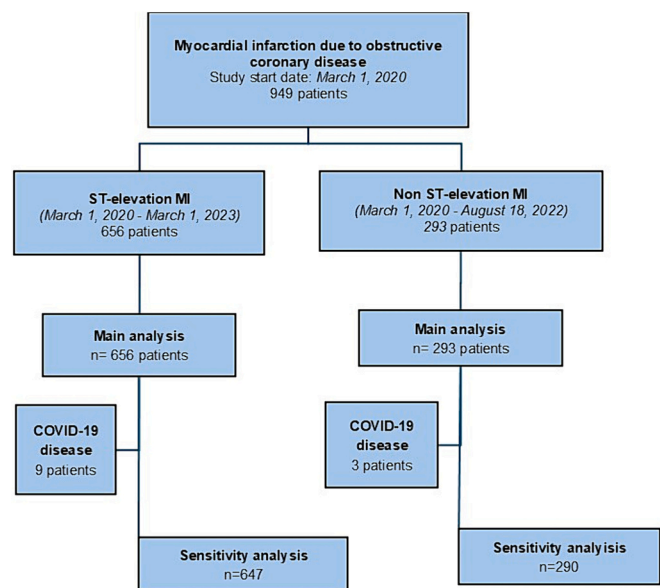

Fig. 1. Flowchart of patients.
Abbreviations: MI, myocardial infarction.
Sensitivity analysis was performed excluding patients with COVID19 symptoms at admission.

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The significance level was set at 0.05. Stata v 18 software was used for statistical analysis.

3. Results

A flow chart of the patients is shown in Fig. 1. A total of 949 patients were enrolled, 656 with STEMI and 293 with NSTEMI. The mean age of the patients was 64 (SD 13) years and 80 % were men.

Median follow-up was 20.4 (95 %CI 19.3–21.1) months. The proportion of patients with MACE after MI was 9.7 % (*n* = 92) at 6 months. The 6-month mortality rate was 5.3 % (*n* = 50): 39 (78 %) of the deaths

were cardiac, 9 (18 %) were non-cardiac and 2 (4 %) were of unknown cause. In patients with STEMI, the Killip classification on admission was I, 77.6 % (*n* = 517); II, 11.3 % (*n* = 75); III, 2.3 % (*n* = 15); and IV, 8.9 % (*n* = 59).

Baseline patient characteristics, vaccination status and serologic testing for SARS CoV-2 at admission are shown in Table 1. Nearly 53 % of patients had received at least one dose of vaccine prior to admission; 49 % had completed the initial vaccination schedule (2 doses or 1 dose of the JNJ-78436735 vaccine); a quarter of patients had received the first booster dose and only 2 % had received a second booster dose. The majority (84 %) of the vaccines administered were mRNA-type: BNT162b2, 820 vaccinations (68 %) or mRNA-1273, 188 (16 %). The remainder (16 %) were non-replicating viral vector types. The type of

Table 1
Baseline characteristics of patients.

	Total (*n* = 949)	STEMI (*n* = 656)	NSTEMI (*n* = 293)
Epidemiological and clinical features			
Age, mean (SD), years	64.4 (13.0)	63.0 (13.1)	67.7 (12.1)
Male, no. (%)	759 (80.0)	514 (78.4)	245 (83.6)
BMI, median (IQR)	27.1 (24.5–29.6)	27.0 (24.3–29.4)	27.6 (24.8–29.8)
Hypertension, no. (%)	486 (51.2)	308 (47.0)	178 (60.8)
Smoking status, no. (%)[a]			
Current smoker	358 (37.7)	280 (42.7)	78 (26.6)
Former smoker	271 (28.6)	161 (24.5)	110 (37.5)
Nonsmoker	320 (33.7)	215 (32.8)	105 (35.8)
Dyslipidemia, no. (%)	463 (48.8)	308 (47.0)	155 (52,9)
Diabetes, no. (%)	216 (22.8)	127 (19.4)	89 (30.4)
Ischemic heart disease, no. (%)	194 (20.4)	97 (14.8)	97 (33.1)
Chronic autoimmune disease, no. (%)	59 (6.2)	36 (5.5)	23 (7.9)
Chronic immunological treatment, no. (%)	37 (3.9)	30 (4.6)	7 (2.4)
Cancer history, no. (%)	86 (9.1)	45 (6.9)	41 (14)
Current cancer therapy, no. (%)	16 (1.7)	10 (1.5)	6 (2.1)
Killip status III or IV, no. (%)	n/a	71 (10.8)	n/a
SARS-CoV2 vaccination ≥ 1 dose	501 (52.8)	360 (54.9)	141 (48.1)
Time from last vaccine dose to MI (days), median (IQR)	142 (56–235)	158 (76–282)	97 (42–167)
Angiography			
Time symptom-balloon (min), median (IQR)	N/A	195 (141–316)	N/A
Culprit vessel, no. (%)			
RCA	300 (32.3)	240 (36.7)	60 (20.5)
LAD	418 (44.1)	290 (44.3)	128 (43.7)
Cx	175 (18.9)	110 (16.9)	65 (22.2)
LMCA	35 (3.7)	13 (2.1)	22 (7.5)
Undefined	n/a	0	18 (6.1)
Arterial segment, proximal, no. (%)	345 (36.4)	250 (38.1)	95 (32.4)
Infarction due to stent thrombosis, no. (%)	43 (4.5)	38 (5.8)	5 (1.7)
Coronary vessels w. severe disease, >1, no. (%)	352 (37.1)	210 (32.0)	142 (48.5)
TIMI flow after PCI II or III, no. (%)[b]	884 (93.2)	629 (95.9)	255 (87.0)
LVEF at hospital discharge			
LVEF <35 %, no. (%)	53 (5.6)	44 (6.7)	9 (3.1)
LVEF 35–50 %, no. (%)	244 (25.8)	191 (29.1)	53 (18.1)
LVEF ≥50 %, no. (%)	649 (68.6)	419 (64.1)	230 (78.8)
Laboratory values on admission			
Leukocyte count, median (IQR), cells/ µL	10.67 (8.51–13.8)	11.61 (9.30–14.44)	9.14 (7.32–11.44)
Hemoglobin, median (IQR), g/dL	14.9 (13.4–16.0)	14.9 (13.4–16.0)	15.0 (13.6–16.0)
Platelet count, median (IQR), cells x10^3/µL	230 (188–276)	230 (188–279)	228 (186–267)
Total cholesterol, median (IQR), mmol/L	165 (135–197)	169 (138–198)	154 (129–195)
LDL-cholesterol, median (IQR), mmol/L	69 (70–125)	99 (75–126)	86 (63–119)
Glucose on admission, median (IQR), mmol/L	129 (107–163)	137 (114–172)	112 (98–141)
Laboratory values on admission			
Peak hs-cTnI, median (IQR)	34,500 (6,774–110,000)	66,369 (25,479–154,580)	2,584 (635–14,695)
GFR (CKD-EPI), median (IQR), ml/min/1.73 m2	72.9 (51.9–91.6)	75.8 (53.0–93.0)	66.5 (48.1–88.7)
Serological testing for SARS CoV2, no. (%)[c]	*n* = 844	*n* = 589	*n* = 255
IgM+ to SARS CoV2	37 (4.4)	22 (3.8)	15 (5.9)
IgG+ to SARS CoV2	219 (28.2)	162 (27.5)	57 (24.0)
IgM and IgG+ to SARS CoV2	35 (4.5)	20 (3.7)	15 (5.9)

Abbreviations: BMI, body mass index; Cx, circumflex coronary artery; hs-cTnI, high-sensitive cardiac troponin I; GFR (CKD-EPI), glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); IQR, interquartile range; LAD, left anterior descending artery; LDL, low-density lipoprotein; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; n/a, not applicable; NSTEMI, Non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction grade flow.

[a] Non-smoker refers to never smokers and ex-smokers for more than 1 month. Smokers refers to current smokers or former smokers for less than one month.

[b] TIMI grade flow: 0, no perfusion; I, penetration without perfusion; II, partial perfusion; and III, complete perfusion.

[c] Nucleocapsid specific antibodies measured by ECLIA (electrochemiluminescence-based immunoassay). Serological groups are not mutually exclusive.

Table 2
SARS CoV-2 immunization and pre-admission doses.

SARS CoV-2 vaccine	Patients, no. (%) (n = 501)			
	Number of doses			
	1st	2nd	3rd	4th
BNT162b2[a]	334 (66.7)	316 (67.8)	148 (63.0)	22 (95.7)
mRNA-1273[b]	49 (9.8)	53 (11.4)	85 (36.2)	1 (4.3)
AZD1222[c]	94 (18.7)	75 (16.1)	2 (0.8)	0
JNJ-78436735[d]	22 (4.4)	–	–	–
Unknown	2 (0.4)	0	0	0
Total	501	466*	235	23

Abbreviations: NSTEMI, Non-ST-elevation myocardial infarction; STEMI, ST-Segment Elevation Myocardial Infarction.
SARS CoV2 vaccine types (Developer): [a] mRNA (*Pfizer/BioNTech*); [b] mRNA (*Moderna*); [c] Non replicating viral vector (*Oxford/AstraZeneca*); [d] Non replicating viral vector (*Johnson&Johnson*).

* The 22 patients who received JNJ-78436735 are included, since immunization with this vaccine required only one dose.

vaccine administered could not be determined in only 2 patients (0.2 %) (Table 2). The median time from the last vaccine dose to MI was 142 (IQR 56–235) days; this interval was shorter in patients with NSTEMI (97 [42–167]) than in those with STEMI (158 [76–282]) (Table 1).

In an univariable logistic regression analysis, an association was found between the occurrence of MACE at 6 months after MI and vaccination against SARS CoV-2 before MI (last vaccine dose ≤30 days before MI: OR 2.09 (1.01–4.33), $p = 0.048$; >30 days before MI: OR 1.57 (0.99–2.5), $p = 0.057$). Based on these results, we discarded the time from the last vaccine dose to MI in the analysis, and then focused on whether the patient had received a vaccine dose or not. No significant association was found between MACE at 6 months and positive SARS CoV-2 antibodies to N-antigens (OR 1.44 [0.88–2.35]). Baseline characteristics and SARS CoV-2 serology of patients by vaccination status are shown in Table 3.

In patients with STEMI, univariable analysis showed an association between the presence of severe heart failure or cardiogenic shock (Killip III-IV) on admission and pre-MI vaccination against SARS CoV-2 (OR

Table 3
Patient characteristics by SARS CoV-2 vaccination status.

	Patients, no (%), n = 949*		p-value
	Vaccination ≥ 1 dose		
	No (n = 447)	Yes (n = 498)	
Patient baseline characteristics			
Age, mean (SD), years	63.2 (12.5)	65.6 (13.5)	0.005
Male, no. (%)	368 (82.3)	387 (77.7)	0.077
BMI, median (IQR)	27.1 (24.6–29.7)	27.1 (24.4–29.6)	0.480
Hypertension, no. (%)	218 (48.8)	266 (53.4)	0.154
Smoking status, no. (%)[a]			0.015
Current smoker	185 (41.6)	170 (35.0)	
Former smoker	134 (30.1)	136 (28.0)	
Nonsmoker	126 (28.3)	180 (37.0)	
Dyslipidemia, no. (%)	204 (45.6)	258 (51.8)	0.058
Diabetes, no. (%)	95 (21.3)	71 (22.9)	0.298
IHD, no. (%)	94 (21.0)	100 (20.1)	0.718
SARS CoV-2 serological test, no. (%)[b]	n = 358	n = 476	
IgM (+)	19 (5.3)	18 (3.8)	0.290
IgG (+)	49 (16.4)	167 (35.1)	<0.001
IgM and IgG (+)	17 (5.7)	18 (3.8)	0.206

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; IQR, interquartile range; SD, standard deviation.

* Vaccination status unknown in 2 patients.
[a] Non-smoker refers to never smokers and ex-smokers for more than 1 month. Smoker refers to current smokers or former smokers for less than one month.
[b] Nucleocapsid specific antibodies measured by ECLIA (electrochemiluminescence-based immunoassay).

1.78, 95 %CI 1.06–2.99). Killip III-IV was present in 7.9 % of unvaccinated patients compared to 13.7 % of those vaccinated within 30 days before MI and 13.3 % of those vaccinated >30 days before admission ($p = 0.085$). This association was most pronounced in younger patients (<65 years): 4.8 % in the unvaccinated, 14.3 % in those vaccinated ≤30 days before admission, and 11.8 % in those vaccinated >30 days before STEMI ($p = 0.034$). We observed a higher proportion of Killip III/IV in patients who received at least one non-replicating viral vector vaccine (Oxford/AstraZeneca, J&J) (16.9 %) than in those who received only mRNA-based vaccines (12.5 %) (Killip III/IV in unvaccinated 24 (7.95), viral vector vaccine 14 (16.87), non-viral vector vaccine 35 (12.50), p-value = 0.040).

In patients with STEMI, univariable analysis also showed an association between Killip III-IV and positive testing for SARS CoV-2 antibodies to N-antigens (OR 1.93, 95 %CI 1.12–3.30). Killip III-IV at admission was present in 8.6 % of patients without N-specific antibodies and in 15.3 % of patients with positive serology ($p = 0.016$). An interaction between vaccination and serology was examined but excluded.

Because no relevant differences were found in the univariable analysis regarding the time of vaccination (≤ or > 30 days before MI), four groups were created for the multivariable analysis according to serologic and vaccination status. The epidemiological and clinical characteristics of the patients in the four subgroups are shown in Table 4.

IgG levels against S antigens were significantly higher ($p < 0.001$) in vaccinated patients (median > 2080 UA/ml, IQR 1560- >2080) than in unvaccinated patients (66 UA/ml, 20–182) in the whole sample and also in STEMI patients with similar levels (Fig. 2). The percentage of patients with positive antibodies according to the type of vaccine received in the last dose before admission was 37 % (37/99) for mRNA-1273, 36 % (116/324) for BNT162b2, 32 % (13/41) for AZD1222 and 25 % (3/12) for JNJ-78436735.

The unadjusted analysis showed an association between testing positive for N-specific antibodies to SARS CoV-2 in vaccinated patients (Pos/Vax group) and the occurrence of major cardiac events at 6 months (OR 1.92 [1.01–3.63], $p = 0.045$). After adjustment for age, sex, hypertension, diabetes and dyslipidemia the effect size remained but the statistical association was no longer present (OR 1.89 [0.98 to 3.61], $p = 0.055$) (Table 5).

In patients with STEMI, the results of multivariable analysis to assess the association between serology/vaccination status and severe HF/cardiogenic shock after infarction are shown in Table 6. Vaccinated patients with positive serology (Pos/Vax group) had an increased risk of presenting with Killip III-IV on admission: OR 2.63 (1.27–5.44), $p = 0.010$ when adjusted for age, hypertension, diabetes mellitus and dyslipidemia. This association was maintained when the 9 patients with COVID-19 on admission were excluded from the analysis.

4. Discussion

The main finding of the present study was the association between post-infection SARS CoV-2 seropositivity in vaccinated patients and the development of severe heart failure and cardiogenic shock after STEMI. A higher incidence of adverse cardiac events in the 6 months after type 1 MI (STEMI and NSTEMI) was not demonstrated.

Patients admitted with acute MI during the COVID-19 pandemic were observed to have a higher rate of cardiogenic shock, with greater need for inotropic and hemodynamic support, and increased early mortality [1,2,18–22]. However, the mechanisms underlying the worst short-term outcomes cannot be deduced from these experiences. The pandemic significantly altered the workflow of acute MI, prolonging the time from symptom onset to hospital admission and revascularization [23], and the psychosocial environment [24], which would adversely affect infarct outcome.

Type 1 MI in patients with COVID-19 may be triggered by a pro-inflammatory state that could favor destabilization of the coronary atherosclerotic plaque, a phenomenon already observed during

Table 4
Patient characteristics by SARS CoV-2 serological testing and vaccination status.

	Patients, no (%), n = 834				p-value
	SARS CoV2 serological testing/ Vaccination ≥1 dose				
	Neg./No vax (n = 302)	Neg./Vax (n = 310)	Pos./No vax (n = 56)	Pos./Vax (n = 166)	
Baseline characteristics					
Age, mean (SD), years	62.6 (12.2)	66.6 (12.9)	65.2 (13.4)	62.8 (13.8)	<0.001
Male, no. (%)	247 (81.8)	240 (77.4)	47 (83.0)	131 (78.9)	0.496
BMI, median (IQR)	27.2 (24.6–30.1)	26.7 (24.2–29.4)	26.5 (24.0–29.1)	27.7 (25.2–30.4)	0.022
Hypertension, no. (%)	143 (47.3)	177 (57.3)	26 (46.4)	76 (45.5)	0.030
Smoking status, no. (%)[a]					<0.001
Current smoker	142 (47.2)	105 (34.9)	13 (23.6)	60 (36.8)	
Former smoker	84 (27.9)	82 (27.2)	26 (47.3)	47 (28.8)	
Nonsmoker	75 (24.9)	114 (37.9)	16 (29.1)	56 (34.4)	
Dyslipidemia, no. (%)	140 (46.4)	158 (51.0)	25 (44.6)	90 (54.2)	0.308
Diabetes, no. (%)	70 (23.2)	71 (22.9)	12 (21.4)	44 (26.5)	0.714
IHD, no. (%)	57 (18.9)	63 (20.3)	11 (19.6)	31 (18.7)	0.956
SARS CoV-2 serology					
IgM (+), no. (%)[b]	–	–	19 (33.9)	18 (10.8)	<0.001
IgG (+), no. (%)[b]	–	–	49 (87.5)	166 (100)	<0.001
IgM and IgG (+), no. (%)[b]	–	–	17 (30.4)	18 (10.8)	<0.001
IgG level, median (IQR), UA/ml[c]	–	–	66 (20–182)	>2080 (1560- > 2081)	

Abbreviations: BMI, body mass index; IHD, ischemic heart disease; IQR, interquartile range; SD, standard deviation.

[a] Non-smoker refers to never smokers and ex-smokers for more than 1 month. Smokers refers to current smokers or former smokers for less than one month.
[b] Nucleocapsid-specific antibodies measured by ECLIA (electrochemiluminescence-based immunoassay).
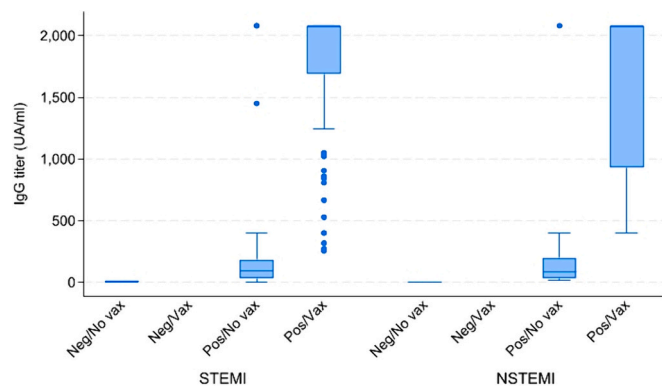[c] Spike surface-specific antibodies measured by CLIA (chemiluminescence-based immunoassay).

Fig. 2. Comparison of IgG levels to the spike (S) antigens of SARS CoV-2 in previously vaccinated and unvaccinated patients with STEMI.
Abbreviations: IgG, immunoglobulin G; NSTEMI, non-ST-elevation myocardial infarction; Neg, negative serologic test results for SARS CoV2; Pos, positive serologic test results for SARS CoV2; STEMI, ST-elevation myocardial infarction; Vax, vaccination.

influenza outbreaks [25,26]. Other mechanisms, such as endothelial and microvascular injury induced by SARS-CoV-2, may further enhance inflammation, leading to thrombosis [27], coronary vasospasm [28] and myocardial perfusion defects [29,30]. The mechanism(s) underlying the association between COVID-19 and the development of cardiovascular disease in the post-acute phase of the disease are unclear [31–33]. Possible mechanisms include direct viral invasion of cardiomyocytes, endotheliitis, complement-mediated coagulopathy and micro-angiopathy, or elevated levels of pro-inflammatory cytokines [34]. A persistent aberrant hyperactivated immune response, autoimmunity or persistence of the virus in immunoprivileged sites have also been suggested as possible explanations for the extrapulmonary (including cardiovascular) post-acute sequelae of COVID-19 [35–39].

Cases of MI have also been reported in association with vaccination against the SARS CoV-2 virus [40–45], although this association remains controversial. In a systematic review, Mani et al. [46] note that MI was the most common type of arterial thrombosis (about 20 %) reported after SARS CoV-2 vaccination, followed by ischemic stroke. All but one of these myocardial infarctions were associated with the AstraZeneca vaccine. In another systematic review [47], myocardial infarction and cardiac arrest were very rarely reported in the over-75 age group; all cardiac events, including MI, were more common after mRNA vaccination (Moderna & Pfizer-BioNTech). However, Kim et al. [48] in a retrospective cohort study comparing the incidence of MI and ischemic stroke after COVID-19 infection between patients who were never vaccinated and those who were fully vaccinated (2 doses of mRNA vaccine or viral vector vaccine) found that vaccination was associated with a reduced risk of both. It should be borne in mind that the clinical suspicion of a vaccine adverse reaction following a common clinical event such as MI will be lower in daily practice than in clinical trials [49], especially if it does not occur immediately after vaccination. Indeed, published cases of myocardial infarction associated with the SARS CoV-2 vaccine have been reported 24 h to several days after vaccination [45].

In terms of infarct severity and evolution, Hilu et al. [17], based on the Acute Coronary Syndrome Israeli Survey, compared the outcome of ACS patients (44 % STEMI, 43 % NSTEMI) vaccinated with two doses of COVID-19 mRNA vaccine with that of unvaccinated patients. One-year survival and 30-day MACE were similar regardless of vaccination status, while Killip class >1 and reduced left ventricular ejection fraction (LVEF) were more common in unvaccinated patients. The authors do not have data on COVID-19 infection before or after admission and speculate that their findings may be due to a higher rate of COVID-19 infection prior to the coronary event in patients who were not fully vaccinated.

Vaccination began in the Community of Madrid at the end of December 2020. Initially, priority was given to health care workers and nursing home residents. Subsequently, the vaccination campaign was extended to other essential workers and gradually expanded from people over 80 to younger age groups. This would explain the two years older age of the vaccinated patients in our series. However, when subgroups based on vaccination and serologic status were established, patients in the Pos/Vax group were younger (Table 4).

Although ischemic heart disease was not a priority criterion in the SARS-CoV2 vaccination campaign in our country, the possibility of selection bias due to a higher prevalence of risk factors in vaccinated patients was considered. Therefore, in addition to age and sex, the classic risk factors of hypertension, diabetes, and dyslipidemia were adjusted for in the multivariable analysis. Furthermore, these were not overrepresented in either the vaccinated or the Pos/Vax group (Tables 3

Table 5
Association between serology/vaccination status and 6-month MACE after type 1 MI.

	Univariate analysis OR (95 % CI)	p-value	Multivariable analysis* OR (95 % CI)	p-value	Sensitivity analysis** OR (95 % CI)	p-value
SARS CoV-2 serology /vaccine						
Neg./No vax	Ref.cat.					
Neg./Vax	.54 (0.87–2.74)	0.141	1.39 (0.77–2.50)	0.269	1.40 (0.78–2.52)	0.261
Pos./No vax	1.31 (0.47–3.62)	0.607	1.22 (0.43–3.42)	0.709	0.53 (0.12–2.36)	0.403
Pos./Vax	1.92 (1.01–3.63)	0.045	1.90 (0.99–3.63)	0.052	1.89 (0.98–3.61)	0.055
Patient baseline characteristics						
Age*	1.04 (1.02–1.06)	<0.001				
Gender (female)*	1.56 (0.96–2.55)	0.074				
BMI	0.98 (0.93–1.03)	0.468				
Hypertension*	1.47 (0.95–2.28)	0.083				
Smoking status						
Current smoker	0.77 (0.47–1.25)	0.288				
Former smoker	0.61 (0.35–1.07)	0.086				
Dyslipidemia	1.05 (0.68–1.62)	0.815				
Diabetes*	2.06 (1.30–3.25)	0.002				
Previous IHD	1.42 (0.87–2.34)	0.161				

Abbreviations: BMI, body mass index; CI, confidence interval; IHD, ischemic heart disease; IQR, interquartile range; MACE, major adverse cardiovascular events (death, reinfarction, urgent revascularization, heart failure hospitalization); MI, myocardial infarction, including ST-elevation MI and non-ST-elevation MI; OR, odds ratio; SD, standard deviation; Vax, vaccination.

* Multivariable analysis adjusted for age, sex, hypertension, diabetes and dyslipidemia.
** Patients with COVID-19 disease at the time of admission (*n* = 12) excluded.

Table 6
Association of SARS CoV-2 serology/vaccination status with Killip class post-STEMI.

	Killip I-II (*n* = 592)	Killip III-IV (*n* = 74)	Univariate analysis OR (95 % CI)	*p*-value	Multivariable analysis[a] OR (95 % CI)	p-value	Sensitivity analysis[b] OR (95 % CI)	
Serology/vaccination, no. (%)								
Neg./No vax	193 (36.7)	14 (23.0)	Ref. cat		Ref. cat		Ref. cat	
Neg./Vax	191 (36.3)	22 (36.1)	1.59 (0.79–3.21)	0.190	1.56 (0.77–3.15)	0.219	1.56 (0.77–3.16)	0.218
Pos./No vax	35 (6.7)	5 (8.2)	1.97 (0.67–5.81)	0.220	1.93 (0.65–5.72)	0.237	1.78 (0.55–5.81)	0.337
Pos./Vax	107 (20.3)	20 (32.8)	2.55 (1.24–5.26)	0.011	2.63 (1.27–5.44)	0.009	2.61 (1.26–5.40)	0.010
Age, mean (SD), years	62.7 (13.1)	65.8 13.3	1.02 (1.00–1.04)	0.059				
Male, no. (%)	465 (78.6)	58 (78.4)	1.01 (0.56–1.82)	0.973				
BMI, median (IQR)	26.9 (24.3–29.4)	27.2 (24.5–30.9)	1.03 (0.97–1.08)	0.373				
Hypertension, no. (%)	273 (46.1)	43 (58.1)	1.62 (0.99–2.64)	0.053				
Smoking status, no. (%)								
Nonsmoker	192 (32.4)	26 (35.1)						
Current smoker	249 (42.1)	33 (44.6)	0.98 (0.57–1.69)	0.939				
Former smoker	151 (25.5)	15 (20.3)	0.73 (0.38–1.43)	0.365				
Dyslipidemia, no. (%)	273 (46.1)	38 (51.4)	1.23 (0.76–2.00)	0.395				
Diabetes, no. (%)	112 (18.9)	21 (28.4)	1.70 (0.98–2.93)	0.057				
IHD, no. (%)	87 (14.7)	13 (17.6)	1.24 (0.65–2.35)	0.515				

Abbreviations: BMI, body mass index; CI, confidence interval; IHD, ischemic heart disease; IQR, interquartile range; OR, odds ratio; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.
[a] Multivariable analysis adjusted for age, hypertension, diabetes and dyslipidemia.
[b] Patients with COVID-19 disease at the time of admission excluded (n = 9).

and 4). Hypertension was less common in the Pos/Vax group (*p* = 0.030) and smokers were overrepresented in the unvaccinated group (*p* < 0.001).

In the present study, 11.1 % of patients were in Killip class III-IV after STEMI. This percentage was maintained after excluding symptomatic SARS CoV-2 patients and is higher than the 5.8 % observed in a prospective registry of 14,841 STEMI patients undergoing primary angioplasty between 2010 and 2017 in Catalunya, Spain [50]. Patients with prior SARS CoV-2 infection who had detectable antibodies and received one or more doses of vaccine had significantly higher S-specific IgG levels and were more likely to develop severe heart failure or cardiogenic shock after STEMI. This association was independent of age and was even more pronounced in younger patients in a subgroup analysis. The median time from vaccination to MI in the present study was 4.7 months (1.9–7.8), and slightly longer in patients with STEMI (5.3 months, 2.5–9.4). We do not know whether SARS CoV-2 infection occurred before or after vaccination in patients admitted for MI after the start of vaccination in Madrid. The levels of antibodies produced after natural SARS CoV-2 infection are increased by vaccination [9,51,52]; it is also possible that infection in vaccinated patients resulted in a higher antibody titer.

Inflammation associated with acute SARS CoV-2 infection may persist for weeks or even months [53,54]. In a large cohort of individuals hospitalized with asymptomatic, mild, and severe disease, Ong et al. [54] showed that individuals who recovered from COVID19 had elevated levels of proinflammatory and angiogenic markers at 6 months compared to healthy controls. On the other hand, post-acute sequelae of SARS-CoV-2 infection appear to be associated with increased immune activation over time, and higher levels of biomarkers such as TNF-alpha and IL-6 have been described in early and late recovery [55]. This author suggests that alterations in both inflammation and immune responses in the setting of convalescent COVID-19 may also influence future risk of various conditions such as cardiovascular, pulmonary, and neurological diseases.

Consistent with the above, we hypothesize that an enhanced immune response would lead to more severe infarcts. In our series, patients with STEMI and Killip class III-IV had significantly higher leukocyte counts and CRP levels on admission than patients without HF or with mild HF (data not shown), but with our data we cannot be certain that the inflammatory mechanism is related to the increased immune response. Other inflammatory markers such as interleukin or TNF levels were not measured.

Finally, it has been proposed that the thrombotic phenomenon after vaccination is caused by vaccine-induced thrombotic thrombocytopenia (VITT) as a possible mechanism, a condition related to heparin-induced thrombocytopenia (HIT) [56,57]. HIT is mediated by the generation of pathogenic antibodies against the heparin-PF4 complex, which releases more F4 from platelets and creates a hypercoagulable state [46]. However, Cari et al. [58] found that most venous thrombotic serious adverse events associated with the ChAdOx1 (Oxford/AstraZeneca) and Ad26.COV2·S (J&J) vaccines were not associated with thrombocytopenia, suggesting that VITT is not the only type of thrombosis observed after virus-based vaccines. Furthermore, Peluso et al., [59] observed no differences in markers of abnormal blood clotting such as D-dimer between those with and without persistent symptoms after COVID-19 infection. In our series, we found no difference in platelet levels between groups.

This study has several limitations. First, it is not possible to thoroughly analyze the effect of the different vaccine types because different combinations were given to each patient. Second, we do not know whether SARS CoV-2 infection occurred before or after vaccination in patients admitted for MI after the start of vaccination in Madrid. Third, we did not have comprehensive information on symptoms associated with previous SARS CoV-2 infection in patients, so we could not analyze the influence of COVID-19 severity on our results. Finally, because of the study design, it cannot be determined whether vaccinated patients with positive SARS-CoV-2 serology had an increased risk of type 1 MI.

In conclusion, the combination of vaccination and natural immunization against SARS-CoV2 may predispose to the development of severe heart failure and cardiogenic shock in patients with STEMI. This appears to be associated with an enhanced serologic immune response. The combination of vaccination and natural immunization against SARS-CoV2 may also adversely affect the outcome of patients with type 1 infarction in the medium term, although we were not able to demonstrate this association. Further studies are needed to confirm these results.

Acknowledgments and affiliations

CRediT authorship contribution statement

Ana Blasco: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Conceptualization. **Ana Royuela:** Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Sergio García-Gómez:** Writing – original draft, Data curation. **Natalia Gómez-Lozano:** Writing – review & editing, Validation, Resources. **Alberto Sánchez-Arjona:** Writing – review & editing, Data curation. **Jorge de la Fuente:** Writing – review & editing, Data curation. **Jorge Anel:** Writing – original draft, Validation,

Resources. **Icíar Sánchez-Galarraga:** Investigation, Data curation. **Marina Pérez-Redondo:** Investigation, Conceptualization. **Elisa González:** Investigation. **Lorenzo Silva:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ANA BLASCO reports article publishing charges was provided by the Foundation for Biomedical Research of the Hospital Universitario Puerta de Hierro Majadahonda. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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