Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Assessment of Myocardial ^{18}F-FDG Uptake at PET/CT in Asymptomatic SARS-CoV-2–vaccinated and Nonvaccinated Patients

Takehiro Nakahara, MD, PhD • Yu Iwabuchi, MD, PhD • Raita Miyazawa, MD • Kai Tonda, MD • Tohru Shiga, MD, PhD • H. William Strauss, MD • Charalambos Antoniades, MD, PhD • Jagat Narula, MD, PhD • Masahiro Jinzaki, MD, PhD

From the Department of Radiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan (T.N., Y.I., R.M., K.T., T.S., M.J.); Advanced Clinical Research Center, Fukushima Medical University, Fukushima, Japan (T.S.); Department of Cardiology, Icahn School of Medicine at Mount Sinai, New York, NY (H.W.S.); Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford Radcliffe Hospital, Oxford, UK (C.A.); and Department of Medicine and Cardiology, McGovern Medical School, Houston, Tex (J.N.). Received March 31, 2023; revision requested May 25; revision received July 29; accepted August 2. **Address correspondence to** T.N. (email: *takehironakahara@gmail.com*).

Conflicts of interest are listed at the end of this article.

See also the editorial by Bluemke in this issue.

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Background: Patients who developed myocarditis after SARS-CoV-2 vaccination show abnormalities on cardiac MRI scans. However, whether myocardial changes occur in asymptomatic individuals after vaccination is not well established.

Purpose: To assess myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake on PET/CT images in asymptomatic patients vaccinated against SARS-CoV-2 compared with nonvaccinated patients.

Materials and Methods: This retrospective study included patients who underwent ^{18}F-FDG PET/CT for indications unrelated to myocarditis during the period before (November 1, 2020, to February 16, 2021) and after (February 17, 2021, to March 31, 2022) SARS-CoV-2 vaccines were available. Myocardial and axillary ^{18}F-FDG uptake were quantitatively assessed using maximum standardized uptake value (SUV_{max}). The SUV_{max} in all patients and in patients stratified by sex (male or female), age (<40 years, 41–60 years, >60 years), and interval between vaccination and PET/CT were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test with post ad hoc Dwass-Steel-Critchlow-Fligner multiple comparison analysis.

Results: The study included 303 nonvaccinated patients (mean age, 52.9 years ± 14.9 [SD]; 157 female, 146 male) and 700 vaccinated patients (mean age, 56.8 years ± 13.7; 344 female, 356 male). Vaccinated patients had overall higher myocardial ^{18}F-FDG uptake compared with nonvaccinated patients (median SUV_{max}, 4.8 g/mL [IQR, 3.0–8.5 g/mL] vs 3.3 g/mL [IQR, 2.5–6.2 g/mL]; $P < .001$). Myocardial SUV_{max} was higher in vaccinated patients regardless of patient sex (median range, 4.7–4.9 g/mL [IQR, 2.9–8.6 g/mL]) or age (median range, 4.7–5.6 g/mL [IQR, 2.9–8.6 g/mL]) compared with corresponding nonvaccinated groups (sex: median range, 3.2–3.9 g/mL [IQR, 2.4–7.2 g/mL]; age: median range, 3.3–3.3 g/mL [IQR, 2.3–6.1 g/mL]; $P < .001$ to $P = .015$). Furthermore, increased myocardial ^{18}F-FDG uptake was observed in patients imaged 1–30, 31–60, 61–120, or 121–180 days after their second vaccination (median SUV_{max} range, 4.6–5.1 g/mL [IQR, 2.9–8.6 g/mL]) ($P < .001$ to $P = .001$), and increased ipsilateral axillary uptake was observed in patients imaged 1–30, 31–60, and 61–120 days after their second vaccination (median SUV_{max} range, 1.5–2.0 g/mL [IQR, 1.2–3.4 g/mL]) compared with the nonvaccinated patients ($P < .001$ to $P < .001$).

Conclusion: When compared with nonvaccinated patients, asymptomatic patients who received their second vaccination 1–180 days prior to imaging showed increased myocardial ^{18}F-FDG uptake on PET/CT scans.

Supplemental material is available for this article.

While vaccines to prevent SARS-CoV-2 infection have demonstrated effectiveness in reducing morbidity and mortality related to respiratory complications (1,2), infrequent but important side effects associated with vaccination have also been reported. One such rare side effect that the mRNA vaccines have been linked to is myocarditis (3–7).

Cardiac MRI (4,7,8) and fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) PET/CT imaging (9–11) have been routinely used in the noninvasive diagnosis of myocardial inflammation of diverse origin, including viral myocarditis, cardiac sarcoidosis, and cancer therapy–related cardiac dysfunction. Good agreement has been reported between late gadolinium enhancement or T2 hyperintensity on cardiac MRI scans and ^{18}F-FDG uptake on PET scans in patients suspected of having myocarditis (12).

A recent cardiac MRI study used late gadolinium enhancement and T2 intensity and reported myocardial injury from the SARS-CoV-2 vaccine was similar to that from myocarditis due to COVID-19, while severity was less (13). Similarly, an ^{18}F-FDG PET/MRI study showed myocardial inflammation after COVID-19 illness (14), but it is not known whether ^{18}F-FDG uptake would occur in asymptomatic individuals after SARS-CoV-2 vaccination.

The purpose of the current study was to semiquantitatively and quantitatively assess myocardial ^{18}F-FDG uptake on PET/CT scans in asymptomatic patients vaccinated against SARS-CoV-2 and asymptomatic nonvaccinated

Abbreviations

FDG = fluorodeoxyglucose, SUV = standardized uptake value, SUV_{max} = maximum SUV

Summary

Asymptomatic patients who underwent PET/CT 1–180 days after their second SARS-CoV-2 vaccination showed increased myocardial fluorine 18 fluorodeoxyglucose uptake on images compared with nonvaccinated patients, but patients imaged more than 180 days after vaccination did not.

Key Results

- In a retrospective study of 700 patients vaccinated against SARS-CoV-2 and 303 nonvaccinated patients who underwent PET/CT for indications other than myocarditis, patients who received their second vaccination 1–180 days before imaging showed higher myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake (median standardized uptake value [SUV_{max}] range, 4.6–5.1 g/mL [IQR, 2.9–8.6 g/mL]) than nonvaccinated patients (median SUV_{max}, 3.3 g/mL [IQR, 2.5–6.2 g/mL]; range, $P < .001$ to $P = .001$).
- Myocardial ^{18}F-FDG uptake was higher in vaccinated patients regardless of sex or patient age compared with corresponding nonvaccinated groups.

patients who underwent imaging for indications unrelated to myocardial inflammation.

Materials and Methods

Because of the retrospective nature of this study, the need for written informed consent was waived by our local institutional review board.

Study Sample

This retrospective study took advantage of a large consecutive repository of ^{18}F-FDG PET/CT studies that were obtained at our institution between November 2020 and March 2022 in adult patients to evaluate various malignancies or other unrelated indications, including comprehensive medical checkup. The study included one group of patients who had received one or two doses of the vaccine for SARS-CoV-2 with clear vaccination documentation from February 17, 2021, (the start of the vaccination program in Japan) to March 31, 2022, and a second group of patients who did not receive the SARS-CoV-2 vaccine during this period or during the period before vaccination was available (November 1, 2020, to February 16, 2021).

Patients who had blood glucose levels greater than 100 mg/dL (5.55 mmol/L) at the time of ^{18}F-FDG injection or who had fasted for less than 12 hours (15) were also excluded. Patients were also excluded if they had pre-existing diseases or conditions that could artifactually influence the myocardial FDG uptake. Specifically, patients with hematologic diseases, such as lymphoma and leukemia, cardiac sarcoidosis, and thyroid disease (16); those who had undergone cardiac surgery, chemotherapy likely to result in cardiac dysfunction, or chest irradiation within the past 6 months; and patients currently undergoing anti-inflammatory therapy, were all excluded. Because body movements and scan delay can affect the analysis, patients with hard body movement or delayed scan timing (over 10 minutes [ie, over 70 minutes have passed from intravenous injection of ^{18}F FDG to scanning]) were excluded from analysis. Patients who had a history of infection with SARS-CoV-2 or who had received a third dose were excluded from the current study. If patients had undergone multiple examinations during the study period, the most recent study was used for the main analysis (Fig 1).

PET/CT Procedure

All patients were routinely instructed to skip a meal, and vital signs and blood glucose level were measured prior to ^{18}F-FDG injection using a blood glucose meter (Medisafe FIT Pro II; Terumo) and lancing device (Medisafe Finetouch II; Terumo). Approximately 60 minutes after intravenous injection of 4.0 MBq per kilogram of body weight ^{18}F-FDG, whole-body PET/CT images were acquired with integrated PET/CT systems (Biograph mCT or Biograph Vision 600; Siemens Medical Solutions). Low-dose CT (100-kVp tube voltage, 50-mAs tube current, 0.5 second per rotation, 2-mm section thickness) was performed for attenuation correction and anatomic coregistration. No iodinated contrast material was administered. PET images were acquired from the vertex to the feet in three-dimensional mode for 2 minutes per bed position without respiratory or cardiac gating.

Evaluation of PET/CT Images

All PET/CT images were transferred to a workstation and reconstructed into coronal, axial, and sagittal planes with dedicated software (AW Server on Universal Viewer; GE HealthCare) by two observers. One observer (T.N., 20 years of expertise in cardiology) assessed all PET/CT images and assessed PET/CT images from the consecutive initial 71 patients 3 months later to assess intraobserver viability. The other observer (Y.I., 15 years of expertise in nuclear medicine) assessed PET/CT images from the same consecutive initial 71 patients to assess interobserver viability. Image evaluations were conducted independently, and observers were blinded to clinical data and previous PET/CT images. For visual analysis of myocardial FDG activity, a scale of standardized uptake value (SUV) was set from 0.0 g/mL to 6.0 g/mL. Myocardial visual scores were assessed using the following scale: 0, minimal uptake; 1, mostly minimal or mild uptake; 2, mostly intense or moderate uptake; and 3, homogeneous uptake (17) (Fig S1). For quantitative analysis, a volume of interest was set that included the whole heart and axillary nodes in the ipsilateral side, and a maximum SUV (SUV_{max} [in grams per milliliter]) (10) was measured. A 10-mm volume of interest was also set to measure SUV_{max} in the liver and spleen.

Statistical Analyses

Continuous data were tested for normality with the Kolmogorov-Smirnov test. Nonnormally distributed continuous data are presented as median and IQR, and normally distributed continuous data are presented as mean ± SD. Continuous data were compared using the Mann-Whitney *U* test between the two groups or the Kruskal-Wallis test with post ad hoc Dwass-Steel-Critchlow-Fligner multiple comparison analysis. For blood pressure, analysis of covariance was used, adjusting for age.

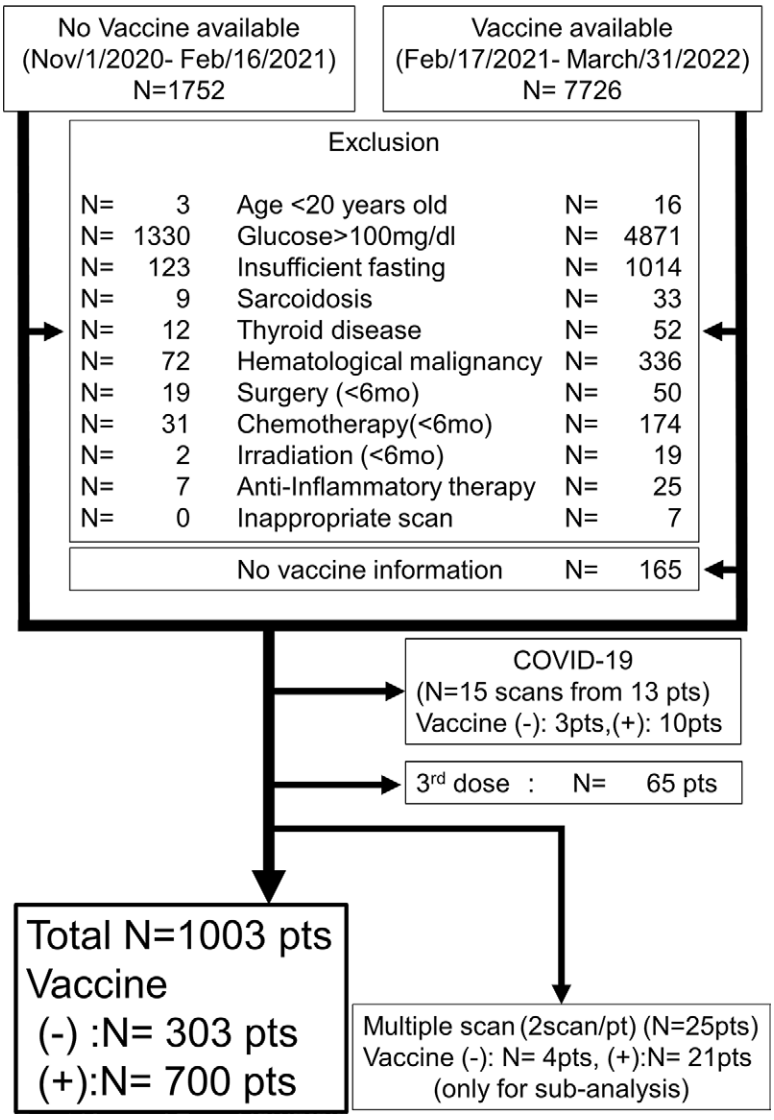

Figure 1: Flow diagram shows patient exclusion criteria. Of the cumulative total 9478 patients who underwent fluorine 18 fluorodeoxyglucose PET/CT, 1003 patients matched the study criteria, including 700 patients from the period during which SARS-CoV-2 vaccines were available (February 17, 2021, to March 31, 2022) and 303 patients from the period before SARS-CoV-2 vaccines were available (November 1, 2020 to February 16, 2021, *n* = 125) and 178 patients from the period after (February 17, 2021, to March 31, 2022). A total of 25 patients (four nonvaccinated, 21 vaccinated) underwent two examinations during the study period, but only the second study was used. A subanalysis including these patients was also performed using the first and second scans.

Categorical data are presented as proportions and percentages and were compared with the χ^2 test or Fisher exact probability test, as appropriate.

Intra- and interobserver variability of myocardial uptake scores were assessed with the Cohen κ coefficient. The strength of agreement for κ values is as follows: κ < 0.20 = poor agreement; κ = 0.21–0.40, fair agreement; κ = 0.41–0.60, moderate agreement; κ = 0.61–0.80, good agreement; and κ = 0.81–1.00, excellent agreement. Agreement between SUV_{max} values in the axilla, myocardium, liver, and spleen was assessed using Bland-Altman analysis, and linear correlation was assessed using Spearman rank correlation. In a subanalysis of patients without cancer or patients with homogeneous uptake, patients who have been diagnosed with cancer or who showed three points of myocardial visual score were excluded from the analysis.

To assess whether myocardial ^{18}F-FDG uptake differed based on the interval between vaccination and imaging, patients were divided into different interval groups, and axillary and myocardial SUV_{max} was compared between each group using the Kruskal-Wallis test with post ad hoc Dwass-Steel-Critchlow-Fligner multiple comparison analysis. A previous study showed effectiveness of the SARS-CoV-2 vaccine against COVID-19 was high during the 1st month after the second dose, declined after 4 months, and was effective until 6 months (18). Thus, we divided the patients into 2-month groups until 6 months (60, 120, and 180 days after vaccination) and divided them by 1 month (30 days after vaccination). To divide 30 days also seems reasonable because previous studies reported relatively high risk of myocarditis within 30 days after the second dose of mRNA vaccines (3–7).

Subjects with unknown vaccination dates or with ChAdOx1 nCoV-19 (Astra Zeneca) and miscellaneous vaccines were excluded when patients were stratified by interval or type of vaccine due to the small sample size. In a subanalysis of patients with more than one scan, ^{18}F-FDG uptake was compared across multiple scans using the Wilcoxon signed rank test.

Two-sided $P < .05$ was considered indicative of a significant difference. Statistical analyses were performed by an observer (T.N.) using SAS software (version 9.4; SAS Institute).

In the initial impression from 200 consecutive patients, the average myocardial SUV_{max} was 6.2 g/mL in 139 vaccinated patients and 4.8 g/mL in 61 nonvaccinated patients at 8 weeks; therefore, effect size was estimated to be 0.36, and allocation ratio was estimated to be 2.3. We determined that a target of 280 nonvaccinated and 644 vaccinated adjudicated primary outcomes would provide a power of 99% at a two-sided α level of .01.

Results

Patient Characteristics

In total, 9478 patients with available PET examinations were initially considered for inclusion. Patients younger than 20 years (*n* = 19), those with a blood glucose level higher than 100 mg/dL (5.55 mmol/L) (*n* = 6201), those with insufficient fasting at the time of FDG injection (*n* = 1137), those with pre-existing diseases (sarcoidosis, *n* = 42; thyroid disease, *n* = 64; hematologic malignancy, *n* = 408) or treatments in the past 6 months (surgery, *n* = 69; chemotherapy, *n* = 205; irradiation, *n* = 21; anti-inflammatory therapy, *n* = 32) that could artifactually influence myocardial FDG uptake, those in whom an inappropriate

Patient Characteristics

Characteristic	No Vaccine (n = 303)	Vaccine (n = 700)	P Value
No malignancies	150 (49.5)	372 (53.1)	…
Sex			
Female	157 (51.8)	344 (49)	.44
Male	146 (48.2)	356 (50.9)	…
Age (y)	52.9 ± 14.9	56.8 ± 13.7	<.001*
Height (cm)	163.1 ± 9.0	164.0 ± 8.8	.12
Weight (kg)	60.4 ± 15.2	61.5 ± 13.2	.08
Blood pressure			
Systolic (mmHg)	121.5 ± 17.1	124.3 ± 18.0	.014†
Diastolic (mmHg)	76.8 ± 11.2	78.4 ± 12.2	.057
Hypertension	36 (11.9)	108 (15.4)	.14
Dyslipidemia	15 (5.0)	75 (10.7)	.003*
Diabetes	1 (0.003)	11 (0.02)	.12
Hyperuricemia	5 (0.02)	15 (0.02)	.81

Note.—Categorical variables are presented as numbers of patients, with percentages in parentheses. Continuous variables are presented as means ± SDs. The χ^2 test and Fisher exact probability test were used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables between the two groups.

* P < .05.

† Significance lost after adjusting for age.

scan was performed (n = 7), those with no vaccine information (n = 165), those with previous SARS-CoV-2 infection (n = 13), and those who received a third dose of the vaccine (n = 65) (Fig 1) were excluded. Ultimately, the study included 1003 patients; 303 were not vaccinated (157 female, 146 male) and 700 were vaccinated (344 female, 356 male; 40 patients had one vaccine dose, 660 patients had two vaccine doses) at the time of PET/CT imaging (mean incubation time, 60.2 minutes ± 0.9). Patient characteristics are presented in the Table. Vaccinated patients were older (mean age, 56.8 years ± 13.7) than nonvaccinated patients (mean age, 52.9 years ± 14.9; P < .001) and more frequently had dyslipidemia (nonvaccinated, 5.0% [15 of 303]; vaccinated, 10.7% [75 of 700]; P = .003). Systolic blood pressure was also higher in the vaccinated group (mean, 124.3 mmHg ± 18.0) than in the nonvaccinated group (mean, 121.5 mmHg ± 17.1; P = .014) but not after adjustment for age (P = .31). In the vaccinated group, 372 of 700 (53.1%) patients did not have cancer, whereas in the nonvaccinated group, 150 of 303 (49.5%) patients did not have cancer. Details on the types of malignancies patients had and the therapies they underwent more than 6 months prior to imaging are reported in Tables S1 and S2, respectively.

Assessment of Myocardial ^{18}F-FDG Uptake Based on Vaccination Status

Myocardial ^{18}F-FDG uptake score and quantification of ^{18}F-FDG uptake in the axilla, myocardium, liver, and spleen showed excellent intra- and interobserver agreement (Appendix S1, Fig S2). Representative PET/CT images with myocardial ^{18}F-FDG uptake are shown in Figure 2 and Figures S3 and S4.

When compared with nonvaccinated patients, vaccinated patients had a higher myocardial ^{18}F-FDG uptake visual score (median, 2 [IQR, 0–3] vs 1 [IQR, 0–2]; P < .001) (Fig 3A) and SUV_{max} (median, 4.8 g/mL [IQR, 3.0–8.5 g/mL] vs 3.3 g/mL [IQR, 2.5–6.2 g/mL]; P < .001) (Fig 3B), which remained after age-adjustment for both measures (P < .001). In patients without cancer, 372 vaccinated individuals also showed a higher median myocardial FDG uptake visual score (median, 2 [IQR, 0–3]) and SUV_{max} (median, 4.8 g/mL [IQR, 3.2–8.3 g/mL]) compared with 150 nonvaccinated individuals (median visual score, 1 [IQR, 0–2]; median SUV_{max}, 3.3 g/mL [IQR, 2.6–6.3 g/mL]; P < .001 for both).

When only patients with myocardial visual scores less than 3 were analyzed, the vaccinated group (n = 479) demonstrated higher myocardial FDG uptake visual scores (median, 1 [IQR, 0–2]) and SUV_{max} (median, 3.6 g/mL [IQR, 2.7–5.1 g/mL]) compared with the nonvaccinated group (n = 248; median visual score, 0 [IQR, 0–1]; median SUV_{max}, 3.0 g/mL [IQR, 2.4–4.1 g/mL]; P < .001 for both).

Myocardial SUV_{max} remained higher in the vaccinated group, even after dividing by liver SUV_{max} (median, 2.1 g/mL [IQR, 1.3–3.6 g/mL]) or splenic SUV_{max} (median, 2.5 g/mL [IQR, 1.6–4.4 g/mL]), when compared with the nonvaccinated group (median when divided by liver SUV_{max}, 1.5 g/mL [IQR, 1.1–2.7 g/mL]; P < .001; median when divided by splenic SUV_{max}, 1.9 g/mL [IQR, 1.3–3.3 g/mL]; P < .001). The vaccinated group also showed higher FDG uptake in the liver (median SUV_{max}, 2.3 g/mL [IQR, 2.1–2.5 g/mL]) and spleen (median SUV_{max}, 1.9 g/mL [IQR, 1.7–2.1 g/mL]) compared with the nonvaccinated group (median liver SUV_{max}, 2.2 g/mL [IQR: 2.0–2.4 g/mL]; P < .001; median spleen SUV_{max}, 1.9 g/mL [IQR: 1.7–2.0 g/mL]; P = .007).

Myocardial ^{18}F-FDG Uptake in Patients with Vaccination Side Effects

After vaccination, 254 of 700 (36.3%) patients reported a fever, and 458 of 700 (65.4%) reported a sore arm, but no patients reported chest pain. The myocardial visual score was higher in patients who reported a sore arm (median score, 1 [IQR, 0–3]) compared with those who did not (median score, 2 [IQR, 1–3]; P = .032), but no difference was observed in myocardial SUV_{max} between the two groups (median, 4.6 g/mL [IQR, 2.8–8.2 g/mL] vs 4.9 g/mL [IQR, 3.2–8.6 g/mL]; P = .09). Additionally, no difference in visual score (median, 2 [IQR, 0–3] vs 2 [IQR, 0–3]; P = .40) or myocardial SUV_{max} (median, 4.8 g/mL [IQR, 3.1–8.1 g/mL] vs 4.8 g/mL [IQR, 2.9–9.3 g/mL]; P = .36) was observed between patients who developed a fever and those who did not.

Assessment of Myocardial ^{18}F-FDG Uptake in Patients Stratified by Interval between Vaccination and PET/CT

Patients were divided into seven groups based on the interval between vaccination and imaging: *(a)* nonvaccinated, *(b)* imaging after the first dose, and imaging *(c)* 30 days or less, *(d)* 31–60 days, *(e)* 61–120 days, *(f)* 121–180 days, and *(g)* more than 180 days after the second dose. Patients with an unclear date of vaccination were excluded from this analysis (n = 8). The median duration from the first vaccine dose to PET imaging was

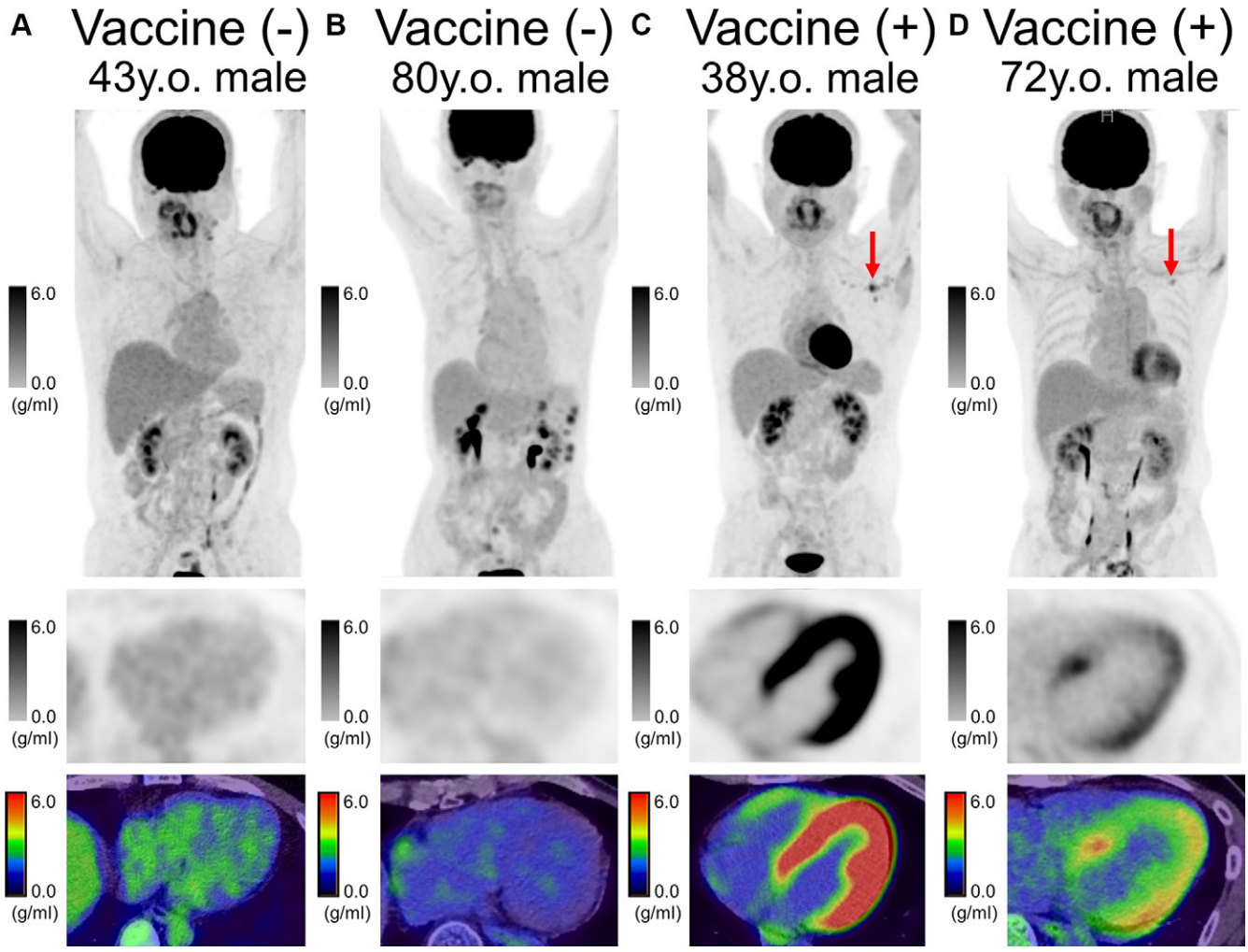

Figure 2: Representative whole-body and myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) PET images (top row) coronal and axial PET images (middle row), and axial color-blending PET/CT fusion images (bottom row) in patients vaccinated against SARS-CoV-2 and nonvaccinated patients. **(A)** Images in a 43-year-old man who underwent ^{18}F-FDG PET/CT for comprehensive medical checkup during the period before SARS-CoV-2 vaccines were available. The patient had a myocardial score of 2 and a myocardial maximum standardized uptake value (SUV_{max}) of 2.7 g/mL. Axillary, liver, and spleen SUV_{max} were 0.6, 2.8, and 2.1 g/mL, respectively. **(B)** Images in an 80-year-old man with pancreatic cancer who underwent PET/CT before SARS-CoV-2 vaccines were available. The patient had a myocardial score of 0 and a myocardial SUV_{max} of 2.2 g/mL. Axillary, liver, and spleen SUV_{max} were 1.1, 2.2, and 1.5 g/mL, respectively. **(C)** Images in a 38-year-old man who underwent PET/CT for comprehensive medical checkup 29 days after he received the first dose of the BNT16b2 vaccine in the left arm. High uptake of ^{18}F-FDG in the left axilla (arrow) and myocardium were observed. The patient had a myocardial score of 3 and a myocardial SUV_{max} of 14.6 g/mL. Axillary, liver, and spleen SUV_{max} were 5.0, 2.0, and 2.1 g/mL, respectively. **(D)** Images in a 72-year-old man who underwent PET/CT for comprehensive medical checkup 139 days after he received the second dose of the mRNA-1273 vaccine in the left arm. High uptake of ^{18}F-FDG in the left axilla (arrow) and myocardium were observed. The patient had a myocardial score of 2 and a myocardial SUV_{max} of 5.9 g/mL. Axillary, liver, and spleen SUV_{max} were 2.7, 2.6, and 2.1 g/mL, respectively.

13 days (range, 6–21 days), and the median duration from the second dose to PET imaging was 88 days (range, 41–135 days). Patients who underwent imaging 1–180 days after receiving their second vaccination had higher myocardial FDG uptake (median SUV_{max} range, 4.6–5.1 g/mL [range of IQRs, 2.9–8.6 g/mL]) than nonvaccinated patients (median SUV_{max}, 3.1 g/mL [IQR, 2.5–6.2 g/mL]; $P < .001$ to $P = .001$), but patients imaged more than 180 days after their second dose did not (median SUV_{max}, 4.5 g/mL [IQR, 2.7–9.3 g/mL]; $P = .15$) (Fig 4B). Furthermore, higher axillary FDG uptake was observed in patients who underwent imaging 1–120 days after receiving their second vaccination (median SUV_{max} range, 1.5–2.0 g/mL [range of IQRs, 1.2–3.4 g/mL]) compared with nonvaccinated patients (median SUV_{max}, 1.2 g/mL [IQR, 1.0–1.4 g/mL]; $P < .001$ to $P < .001$), but this was not observed in patients who underwent imaging more than 120 days after their second vaccination (median SUV_{max} range, 1.1–1.2 g/mL [IQR, 0.9–1.5 g/mL]; $P = .20$ to $P = .99$) (Fig 4A, Table S3).

Myocardial ^{18}F-FDG Uptake in Patients Stratified by Sex and Age

When patients were stratified by sex, myocardial ^{18}F-FDG uptake was higher in vaccinated male patients (median SUV_{max}, 4.9 g/mL [IQR, 3.3–8.6 g/mL]) than in nonvaccinated male patients (median SUV_{max}, 3.9 g/mL [IQR, 2.7–7.2 g/mL]; $P = .004$) and higher in vaccinated female patients (median SUV_{max}, 4.7 g/mL [IQR, 2.9–8.2 g/mL]) than in nonvaccinated female patients (median SUV_{max}, 3.2 g/mL [IQR, 2.4–5.1 g/mL];

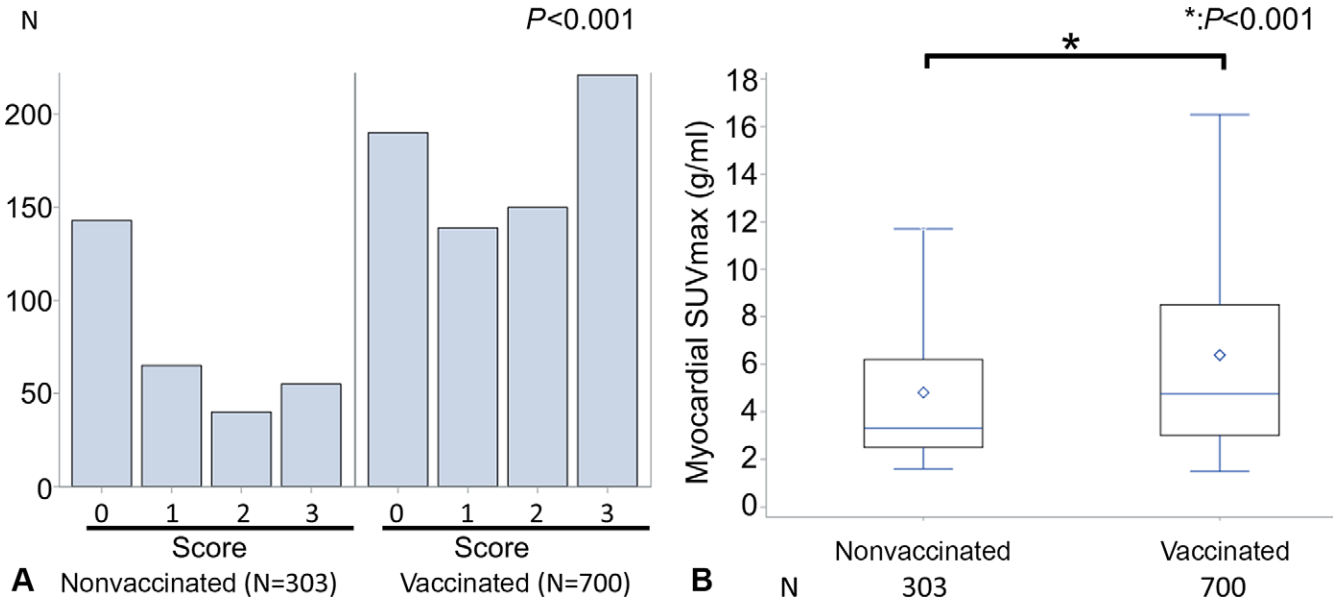

Figure 3: Qualitative and quantitative assessment of myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake in vaccinated and nonvaccinated patients. **(A)** Bar plot shows the number of patients who received each myocardial ^{18}F-FDG uptake visual score (range, 0–3) stratified by vaccination status (nonvaccinated, *n* = 303; vaccinated, *n* = 700). Myocardial ^{18}F-FDG uptake visual scores were higher in the vaccinated group than in the nonvaccinated group (Mann-Whitney *U* test, *P* < .001). **(B)** Boxplot shows myocardial ^{18}F-FDG uptake measured by maximum standardized uptake value (SUV_{max}) in nonvaccinated (*n* = 303) and vaccinated (*n* = 700) patients. Myocardial SUV_{max} was higher in the vaccinated group (median, 4.8 g/mL [IQR, 3.0–8.5 g/mL]) than in the nonvaccinated group (median, 3.3 g/mL [IQR, 2.5–6.2 g/mL]; *P* < .001). Horizontal bars in the boxplot represent median SUV_{max}, and whiskers represent interquartile range. The diamond in the box represents the average. Mann-Whitney *U* test was used to compare median SUV_{max} between groups.

P < .001) (Fig 5A). The axillary uptake was also higher in vaccinated male (median SUV_{max}, 1.4 g/mL [IQR, 1.1–1.8 g/mL]) and female (median SUV_{max}, 1.5 g/mL [IQR, 1.1–1.9 g/mL]) patients than in nonvaccinated patients of either sex (median SUV_{max} in male patients, 1.2 g/mL [IQR, 1.0–1.5 g/mL]; *P* < .001; median SUV_{max} in female patients, 1.2 g/mL [IQR, 1.0–1.4 g/mL]; *P* < .001) (Fig S5A).

Patients were also stratified into three age groups: those less than 40 years of age, those aged 41–60 years, and those aged more than 60 years. For each age group, the ^{18}F-FDG uptake of the axilla and myocardium were higher in vaccinated (median SUV_{max} range, 4.7–5.6 g/mL [IQR, 2.9–8.6 g/mL]) than in nonvaccinated (median SUV_{max} range, 3.3–3.3 g/mL [IQR, 2.3–6.1 g/mL]; *P* < .001 to *P* = .015) patients (Fig 5B). However, no difference in myocardial or axillary FDG uptake was observed between vaccinated (median SUV_{max} range, 1.4–1.6 g/mL [IQR, 1.1–1.9 g/mL]) and nonvaccinated (median SUV_{max} range, 1.1–1.3 g/mL [IQR, 0.7–1.6 g/mL]; *P* < .001 to *P* < .001) patients in each age group (Fig S5B).

Myocardial ^{18}F-FDG Uptake in Patients Stratified by Type of Vaccine

Of the vaccinated patients, the majority (543 of 700 [77.6%]) received BNT162b2 mRNA (Pfizer-BioNTech), while 147 of 700 (21.0%) received mRNA-1273 (Moderna). Patients who received ChAdOx1 nCoV-19 (AstraZeneca) (one of 700 [0.1%]) or miscellaneous types (nine of 700 [1.3%]) were excluded from analysis because of the small sample size. As compared with the unvaccinated group (median myocardial SUV_{max}, 3.3 g/mL [IQR, 2.5–6.2 g/mL]), the myocardial SUV_{max} was higher in both vaccinated groups (*P* < .001 for both), with no difference in ^{18}F-FDG uptake observed between BNT162b2 mRNA (median SUV_{max}, 4.7 g/mL [IQR, 2.9–8.4 g/mL]) and mRNA-1273 (median SUV_{max}, 5.1 g/mL [IQR, 3.4–8.7 g/mL]; *P* = .39) vaccine types. Axillary SUV_{max} was higher in both the BNT162b2 mRNA group (median, 1.4 g/mL [IQR, 1.1–1.8 g/mL]) and the mRNA-1273 group (median, 1.5 g/mL [IQR, 1.1–2.0 g/mL]) than in the nonvaccinated group (median, 1.2 g/mL [IQR, 1.0–1.4 g/mL]; *P* < .001 for both) (Fig S6A, S6B).

Myocardial ^{18}F-FDG Uptake in a Subset of Patients with Multiple PET/CT Studies

A total of 25 patients had more than one PET/CT study available. Among them, 16 patients who had not undergone chemotherapy underwent PET/CT both before vaccination and within 180 days after their second vaccination (median interval, 87.5 days [IQR, 56.5–104.5 days]; range 16–158 days). Compared with FDG uptake on PET/CT scans obtained before vaccination, both axillary and myocardial ^{18}F-FDG uptake were higher on scans obtained after vaccination (difference in axillary SUV_{max}, 0.2 g/mL [IQR, 0.1–0.7 g/mL]; *P* = .028) (difference in myocardial SUV_{max}, 1.0 g/mL [IQR, 0.2–2.8 g/mL]; *P* = .037) (Fig 6).

Discussion

Although patients who developed myocarditis after SARS-CoV-2 vaccination show abnormalities on cardiac MRI scans, whether myocardial changes occur in asymptomatic individuals after SARS-CoV-2 vaccination is not well established. It was reported that fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake

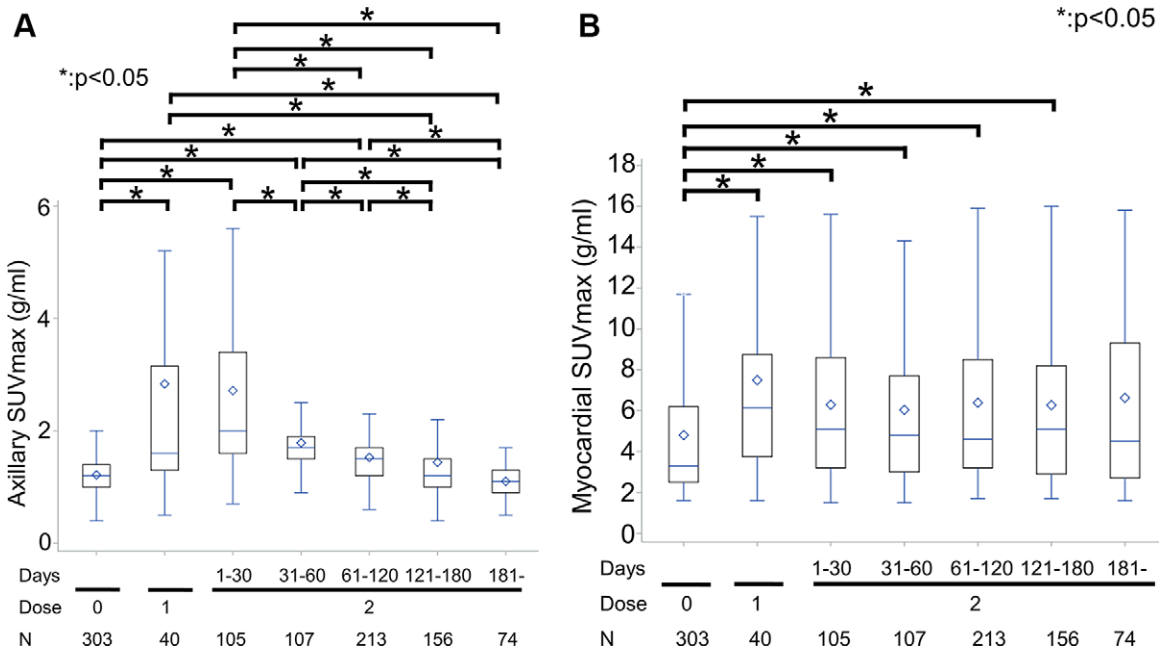

Figure 4: Boxplots show fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake in the **(A)** axillary and **(B)** myocardium of patients stratified by the interval between SARS-CoV-2 vaccination and PET/CT imaging. **(A)** Compared with the unvaccinated group (dose 0, median maximum standardized uptake value (SUV_{max}), 1.2 g/mL [IQR, 1.0–1.4 g/mL]), the axillary SUV_{max} was higher in patients imaged after their first dose (median, 1.6 g/mL [IQR, 1.3–3.2 g/mL]; $P < .001$). Patients imaged within 30 days (median, 2.0 g/mL [IQR, 1.6–3.4 g/mL]), 31–60 days (median, 1.7 g/mL [IQR, 1.5–1.9 g/mL]), and 61–120 days (median, 1.5 g/mL [IQR, 1.2–1.7 g/mL]) after they received their second dose of the vaccine also showed increased axillary SUV_{max} compared with the unvaccinated group ($P < .001$ to $P < .001$). There was no difference observed in axillary SUV_{max} between unvaccinated patients and patients imaged 121–180 days (median, 1.2 g/mL [IQR, 1.0–1.5 g/mL]; $P = .99$) or more than 180 days (median, 1.1 g/mL [IQR, 0.9–1.3 g/mL]; $P = .20$) after their second dose. **(B)** Boxplot shows myocardial SUV_{max} for nonvaccinated (dose 0) and vaccinated groups. The myocardial SUV_{max} was higher in patients imaged after their first dose (median, 6.2 g/mL [IQR, 3.8–8.8 g/mL]; $P = .004$) and in patients imaged 1–30 days (median, 5.1 g/mL [IQR, 3.2–8.6 g/mL]), 31–60 days (median, 4.8 g/mL [IQR, 3.0–7.7 g/mL]), 61–120 days (median, 4.6 g/mL [IQR, 3.2–8.5 g/mL]), and 121–180 days (median, 5.1 g/mL [IQR, 2.9–8.2 g/mL]) after their second dose compared with the unvaccinated group (median, 3.3 g/mL [IQR, 2.5–6.2 g/mL]; $P < .001$ to $P < .001$). There was no difference observed in myocardial SUV_{max} between unvaccinated patients and patients imaged more than 180 days after their second dose (median, 4.5 g/mL [IQR, 2.7–9.3 g/mL]; $P = .15$). For both boxplots, horizontal bars represent median SUV_{max} and whiskers represent interquartile range. The diamond in the box represents the average. Kruskal-Wallis test with post ad hoc Dwass-Steel-Critchlow-Fligner multiple comparison analysis was used to compare median SUV_{max} between groups.

on PET/CT scans correlated with late gadolinium enhancement or T2 intensity on cardiac MRI scans in patients with COVID-19 myocarditis. The aim of this study was to investigate myocardial ^{18}F-FDG uptake on PET/CT scans in asymptomatic patients vaccinated against SARS-CoV-2 compared with uptake in nonvaccinated patients.

In this observational study of patients who underwent PET/CT during comprehensive medical check-ups or to evaluate malignancies, patients who had received a SARS-CoV-2 mRNA-based vaccine showed increased myocardial ^{18}F-FDG uptake on scans compared with nonvaccinated patients (median visual score, 2 [IQR, 0–3] vs 1 [IQR, 0–2]; $P < .001$; median SUV_{max}, 4.75 g/mL [IQR, 3.0–8.5 g/mL] vs 3.3 g/mL [IQR, 2.5–6.2 g/mL]; $P < .001$). This increase in myocardial ^{18}F-FDG uptake in vaccinated patients was also observed in subgroup analyses that excluded individuals with cancer or homogeneous myocardial uptake. When patients were divided into groups based on the interval between vaccination and imaging, myocardial ^{18}F-FDG uptake was higher in all vaccinated groups (median SUV_{max} range, 4.6–5.1 g/mL [range of IQRs, 2.9–8.6 g/mL]) compared with the nonvaccinated group (median SUV_{max}, 3.1 g/mL [IQR, 2.5–6.2 g/mL]; $P < .001$ to $P = .001$) except for the vaccinated group including individuals imaged more than 180 days after their second vaccination (median SUV_{max}, 4.5 g/mL [IQR, 2.7–9.3 g/mL]; $P = .15$). No difference in myocardial or axillary ^{18}F-FDG uptake was observed between patients who received the BNT162b2 mRNA vaccine and those who received the mRNA-1273 vaccine. In 16 patients with more than one PET/CT study available, myocardial and axillary ^{18}F-FDG uptake were higher on PET/CT scans obtained after vaccination than those obtained before vaccination.

Although infrequent, incidences of myocarditis have been reported after SARS-CoV-2 vaccination (3–7,19–21) in patients younger than 40 years (6,19,21), in both male (4,5,21,22) and female patients (6), and in patients who received the mRNA-1273 vaccine (6,19) and those who received the BNT162b2 mRNA vaccine (20). In our study, no differences in myocardial ^{18}F-FDG uptake were observed in vaccinated patients when stratified by age, sex, or vaccine type.

Several studies have also reported that myocarditis incidents occurred no more than 28 days after patients had received their second vaccination (3–7,19,21). In our study, patients who underwent imaging 1–180 days after their second vaccination showed

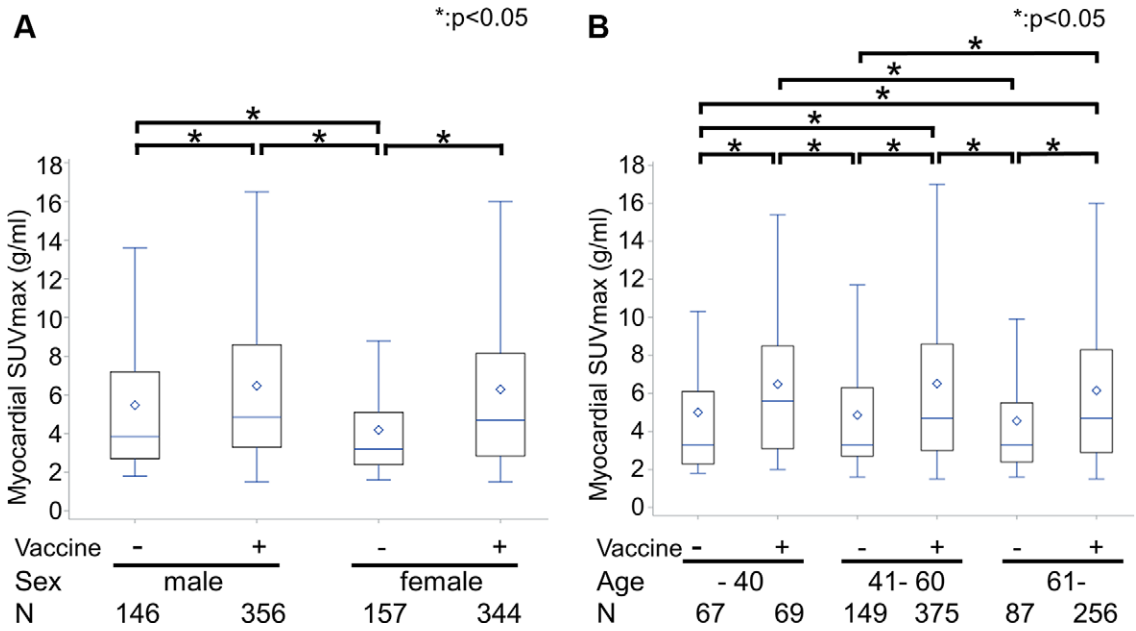

Figure 5: Boxplots show myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake as measured with maximum standardized uptake value (SUV_{max}) in nonvaccinated (-) and vaccinated (+) patients stratified by **(A)** sex and **(B)** age. **(A)** For both sexes, myocardial ^{18}F-FDG uptake was higher in the vaccinated group (male median SUV_{max}, 4.9 g/mL [IQR, 3.3–8.6 g/mL]; female median SUV max, 4.7 g/mL [IQR, 2.9–8.2 g/mL]) than in the nonvaccinated group (male median SUV_{max}, 3.9 g/mL [IQR, 2.7–7.2 g/mL]; $P < .001$; female median SUV_{max}, 3.2 g/mL [IQR, 2.4–5.1 g/mL]; $P < .001$). **(B)** For each patient age group assessed, myocardial SUV_{max} was higher in the vaccinated group (patients aged <40 years: median SUV_{max}, 5.6 g/mL [IQR, 3.1–8.5 g/mL]; patients aged 41–60 years: median SUV_{max}, 4.7 g/mL [IQR, 3.0–8.6 g/mL]; patients aged >60 years: median SUV_{max}, 4.7 g/mL [IQR, 2.9–8.3 g/mL]) than in the nonvaccinated group (patients aged <40 years: median SUV_{max}, 3.3 g/mL [IQR, 2.3–6.1 g/mL]; patients aged 41–60 years: median SUV_{max}, 3.3 g/mL [IQR, 2.7–6.3 g/mL]; patients aged >60 years: median SUV_{max}, 3.3 g/mL [IQR, 2.4–5.5 g/mL]; $P < .001$ to $P < .001$). For vaccinated patients, no differences in myocardial SUV_{max} were observed between age groups. For both boxplots, horizontal bars represent median SUV_{max} and whiskers represent interquartile range. The diamond in the box represents the average. Kruskal-Wallis test with post ad hoc Dwass-Steel-Critchlow-Fligner multiple comparison analysis was used to compare median SUV_{max} values between groups.

elevated myocardial ^{18}F-FDG uptake on PET/CT scans compared with nonvaccinated patients, but patients imaged more than 180 days after vaccination did not. A recent cardiac MRI study reported a similar pattern of myocardial injury between SARS-CoV-2 vaccine–associated myocardial inflammation and other causes of myocardial inflammation but found that vaccine-related myocardial abnormalities were less severe (13). Thus, even though vaccinated patients in this study showed elevated myocardial ^{18}F-FDG uptake on PET/CT scans up to 180 days after vaccination, this could result from relatively minor inflammation and may not represent severe myocardial abnormalities.

Previous studies have shown that increased ^{18}F-FDG uptake in the axillary lymph nodes of vaccinated patients can persist for 2–3 weeks (23–25). Data from the current study suggest this may persist for longer, as patients who underwent imaging 1–120 days after their second vaccination had higher axillary lymph node ^{18}F-FDG uptake compared with nonvaccinated patients. When compared with cardiac MRI (8), PET/CT can provide information about inflammation for the whole body, and in the current study, ^{18}F-FDG uptake in the liver and spleen was also found to be higher in the vaccinated group versus the nonvaccinated group.

There were several limitations of this study. First, this was a retrospective study from a single hospital; thus, our findings may lack generalizability. Second, we did not prepare participants to obviate myocardial glucose uptake, and we excluded participants who had fasted for less than 12 hours. This potentially led to physiologic uptake and affected the result, although it was statistically significant under the same preparation conditions. Third, myocardial ^{18}F-FDG uptake in scans that are not specifically performed to assess cardiac inflammation and that are influenced by many factors (age, sex, insulin resistance, diet, etc) are subject to inaccuracies.

In conclusion, in a set of patients who underwent PET/CT for indications other than myocardial inflammation, those who had received a SARS-CoV-2 vaccine showed increased myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) uptake on images up to 180 days after their second vaccination compared with patients imaged before SARS-CoV-2 vaccination was available. Vaccinated patients showed higher myocardial ^{18}F-FDG uptake on PET/CT scans compared with nonvaccinated patients, regardless of sex, age, or type of mRNA vaccine received. A prospective study would be needed to validate the findings of this study, including comparisons with cardiac enzyme levels, cardiac function, and non-mRNA vaccination.

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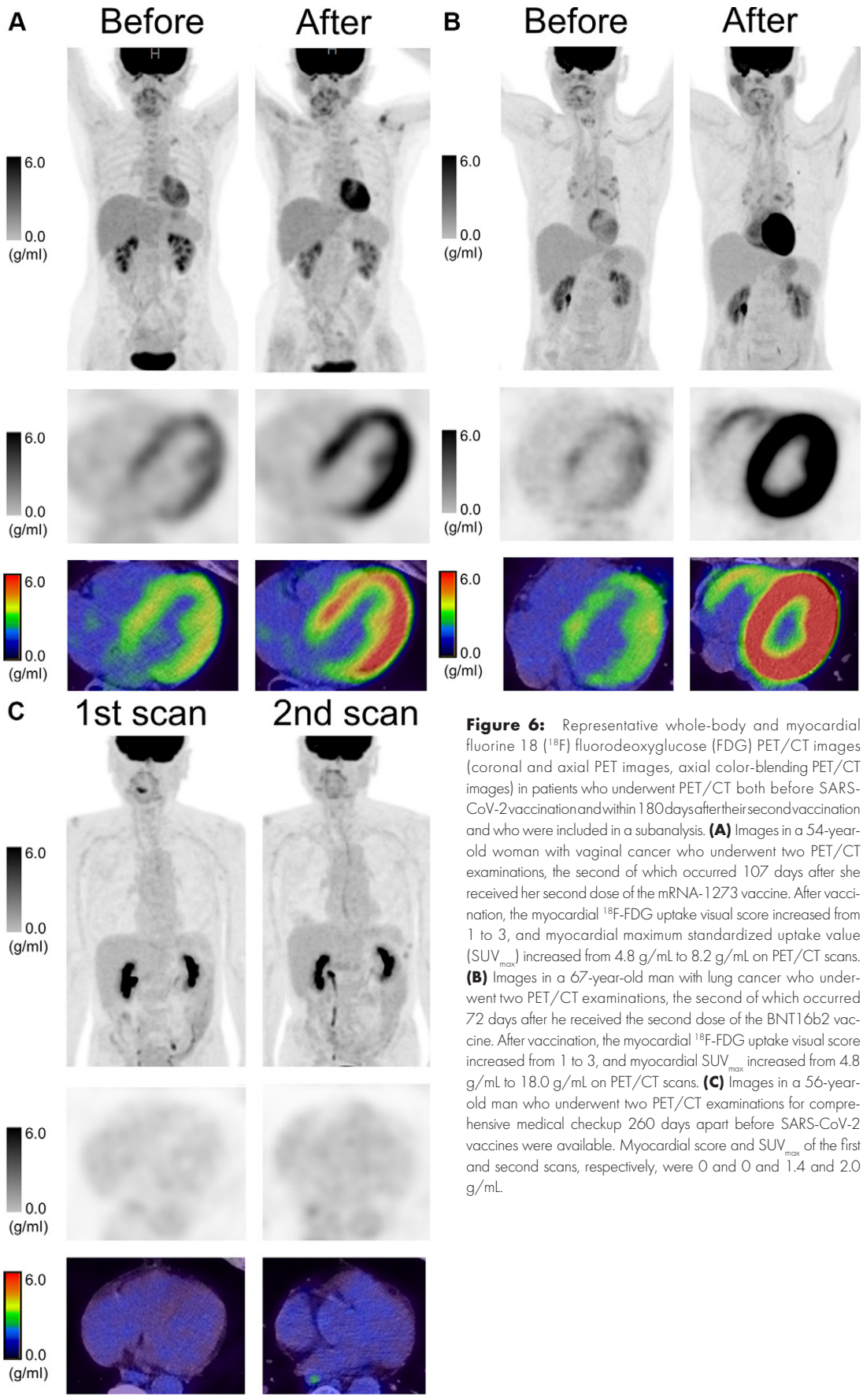

Figure 6: Representative whole-body and myocardial fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) PET/CT images (coronal and axial PET images, axial color-blending PET/CT images) in patients who underwent PET/CT both before SARS-CoV-2 vaccination and within 180 days after their second vaccination and who were included in a subanalysis. **(A)** Images in a 54-year-old woman with vaginal cancer who underwent two PET/CT examinations, the second of which occurred 107 days after she received her second dose of the mRNA-1273 vaccine. After vaccination, the myocardial ^{18}F-FDG uptake visual score increased from 1 to 3, and myocardial maximum standardized uptake value (SUV_{max}) increased from 4.8 g/mL to 8.2 g/mL on PET/CT scans. **(B)** Images in a 67-year-old man with lung cancer who underwent two PET/CT examinations, the second of which occurred 72 days after he received the second dose of the BNT16b2 vaccine. After vaccination, the myocardial ^{18}F-FDG uptake visual score increased from 1 to 3, and myocardial SUV_{max} increased from 4.8 g/mL to 18.0 g/mL on PET/CT scans. **(C)** Images in a 56-year-old man who underwent two PET/CT examinations for comprehensive medical checkup 260 days apart before SARS-CoV-2 vaccines were available. Myocardial score and SUV_{max} of the first and second scans, respectively, were 0 and 0 and 1.4 and 2.0 g/mL.

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