Radiology

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

Manuscript type: Original Research

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Funding: Authors declared no funding for this work.

Data sharing statement: Data generated or analyzed during the study are available from the corresponding author by request.

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See also the editorial by Bluemke in this issue.

Summary Statement:

Asymptomatic patients who underwent PET/CT 1-180 days after their second SARS-CoV-2 vaccination showed increased myocardial ^{18}Fluorine-fluorodeoxyglucose uptake on images compared to nonvaccinated patients, but patients imaged >180 days after vaccination did not.

Key Results:

- In a retrospective study of 700 SARS-CoV-2 vaccinated and 303 nonvaccinated patients who underwent PET/CT for indications other than myocarditis, patients who received their 2nd vaccine 1-180 days before imaging showed higher myocardial ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake (median SUVmax range, 4.6-5.1 [IQRs: 2.9-8.6]) than nonvaccinated patients (median SUVmax, 3.3 [IQR: 2.5-6.2]; *P* range, <.001 - .001).
- Myocardial ^{18}F-FDG uptake (SUVmax) was higher in vaccinated patients regardless of sex or patient age compared to corresponding nonvaccinated groups.

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ABSTRACT

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

Purpose: To assess myocardial ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake on PET/CT in asymptomatic SARS-CoV-2 vaccinated patients compared to 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 (11/1/2020 – 2/16/2021) and after (2/17/20121 – 3/31/2022) SARS-CoV-2 vaccines were available. Myocardial and axillary FDG uptake were quantitatively assessed using maximum standardized uptake value (SUVmax). SUVmax values in all patients and in patients stratified by sex (male/female), age (<40, 41-60, >60 years), and time interval between vaccination and PET/CT were compared using Mann-Whitney U test or 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 females) and 700 vaccinated patients (mean age, 56.8 years ± 13.7 [SD]; 344 females). Vaccinated patients had overall higher myocardial FDG uptake compared to nonvaccinated patients (median SUVmax, 4.8 [IQR: 3.0-8.5] vs median SUVmax, 3.3 [IQR: 2.5-6.2]; $P <$

.0001). Myocardial SUVmax was higher in vaccinated patients regardless of sex (median range, 4.7-4.9 [IQR: 2.9-8.6]) or patient age (median range, 4.7-5.6 [IQR: 2.9-8.6]) compared to corresponding nonvaccinated groups (sex median range, 3.2-3.9 [IQR: 2.4-7.2]; age median range, 3.3-3.3 [IQR: 2.3-6.1]; *P* range, <.001-.015). Furthermore, increased myocardial FDG uptake was observed in patients imaged 1-30, 31-60, 61-120, and 121-180 days after their second vaccination (median SUVmax range, 4.6-5.1 [IQR: 2.9-8.6]) and increased ipsilateral axillary uptake was observed in patients imaged 1-30, 31-60, 61-120 days after their 2nd vaccination (median SUVmax range, 1.5-2.0 [IQR: 1.2-3.4]) compared to the nonvaccinated patients (*P* range, <.001-<.001).

Conclusion: Compared to nonvaccinated patients, asymptomatic patients who received their 2nd vaccination 1-180 days prior to imaging showed increased myocardial FDG uptake on PET/CT.

INTRODUCTION

While vaccines to prevent SARS-CoV-2 infection have demonstrated effectiveness in reducing morbidity and mortality related to respiratory complications (1, 2), infrequent but significant 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 ^{18}F-fluorodeoxyglucose (FDG) PET-CT imaging (9-11) have been routinely employed for 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 (LGE) or T2 hyperintensity on cardiac MRI and FDG-PET uptake in patients with suspected myocarditis (12).

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

The purpose of the current study was to semi-quantitatively and quantitatively assess myocardial FDG uptake on PET/CT in asymptomatic SARS-CoV-2 vaccinated and

nonvacinated patients who underwent imaging for indications unrelated to myocardial inflammation.

MATERIALS AND METHODS

Due to 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 scans that were performed 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 1 or 2 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 SARS-CoV-2 vaccine in this period and in the period before vaccination was available (November 1, 2020 - February 16, 2021).

Patients who had blood glucose levels greater than 100mg/dl at the time of FDG injection or 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 artefactually influence the myocardial FDG uptake. Specifically, patients with hematologic diseases such as lymphoma and leukemia, cardiac sarcoidosis, and thyroid disease (16), or patients who had received cardiac surgery, chemotherapy likely to result in cardiac dysfunction, and chest irradiation within the last 6 months, as well as patients currently being treated with 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, i.e., over 70 min have passed from intravenous injection of FDG to scan) were excluded from analysis. Patients who had a history of infection with SARS-CoV-2 or who had received a 3rd dose were excluded from the current study. If patients had undergone multiple scans during the study period, the most recent scan was used for the main analysis (Fig 1).

PET-CT Procedure

All patients were routinely instructed to skip a meal and vitals and blood glucose levels were measured prior to ^{18}F-FDG injection using a Medisafe FIT Pro II with Medisafe Finetouch II (Terumo). Approximately 60 min after intravenous injection of 4.0MBq/kg ^{18}F-FDG, whole body PET-CT images were acquired on integrated PET-CT systems (Biograph mCT or Biograph Vision 600, Siemens Medical Solutions). A low dose CT (tube voltage 100 kVp, tube

current with 50 mAs, 0.5 second per rotation, and 2 mm slice thickness) was performed for attenuation correction and anatomic co-registration. No iodinated contrast material was administered. PET images were acquired from the vertex to feet in 3-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 the consecutive initial 71 patients' PET-CT images 3 month later to assess intra-observer viability. The other observer (Y.I., 15 years of expertise in nuclear medicine) assessed the same consecutive initial 71 patients' PET-CT images to assess inter-observer 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 minimum or mild uptake), 2 (mostly intense or moderate uptake), and 3 (homogeneously 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 (SUVmax(g/ml))(10) was measured. A 10 mm volume of interest was also set to measure the SUVmax(g/ml) on the liver and spleen.

Statistical Analysis

Continuous data were tested for normality with the Kolmogorov-Smirnov test. Non-normally distributed continuous data are presented as median (IQR) and normally distributed continuous data are presented as Mean ± SD. Continuous data were compared using Mann-Whitney U test between the 2 groups or Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis. For blood pressure, analysis of co-variance was used adjusting for age. Categorical data are presented as proportions and percentages and were compared with Chi Square test or Fisher's exact probability test as appropriate.

Intra- and inter-observer variability of myocardial uptake scores were assessed by Cohen's Kappa coefficient. The strength of agreement for Kappa values is as follows: <.20 = poor, 0.21 – 0.40 = fair, 0.41 – 0.60 = moderate, 0.61 – 0.80 = good, and 0.81 – 1.00 = excellent.

Agreement between SUVmax of axilla, myocardium, liver, and spleen were assessed using Bland-Altman analysis and linear correlation was assessed using Spearman's rank correlation.

In a sub-analysis of patients without cancer patients or homogeneous uptake, patients who have

diagnosed with cancer or who showed 3 points of myocardial visual score were excluded for the analysis.

To assess whether myocardial FDG uptake differed based on the time interval between vaccination and imaging, patients were divided into different time interval groups and axillary and myocardial SUVmax were compared between each group using Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis. Previous study showed high effectiveness SARS-CoV-2 vaccine against COVID-19 during the first month after 2nd dose, declined after 4 months and effective until 6 months (18). Thus, we divided the patients divided every 2 months until 6 months (60, 120 and 180 days) and divided by one month (30 days). To divide 30 days also seems reasonable because previous studies reported relatively high risk of myocarditis within 30days after 2nd 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 time interval or type of vaccine due to the small sample size. In a sub-analysis of patients with more than one scan, FDG uptake was compared across multiple scans using Wilcoxon signed-rank test.

A two-sided P <.05 was considered statistically significant. Statistical analyses were performed by T.N. using SAS software (version 9.4, SAS Institute Inc.).

In the initial impression from consecutive 200 patients, the average of myocardial SUVmax was 6.2 in 139 vaccinated patients and 4.8 in 61 non-vaccinated patients in 8 weeks, therefore effect size was estimated at 0.36 and allocation ratio was estimated at 2.3. We determined that a target number of 280 of non-vaccinated and 644 of vaccinated adjudicated primary outcomes would provide a power of 99 % at a two-sided alpha level of 0.01.

RESULTS

Patients Characteristics

A total of 9478 patients with available PET exams were initially considered. Patients with <20 years of age (n = 19); blood glucose levels >100 mg/dl (n = 6,201) or insufficient fasting (n = 1137) at the time of FDG injection; pre-existing diseases (sarcoidosis n = 42, thyroid disease n = 64, hematological 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 artefactually influence myocardial FDG uptake; inappropriate scan performed (n =7); no vaccine information (n = 165); previous SARS-CoV-2 infection (n = 13); and a receival of a third vaccine dose (n = 65) (Fig 1) were excluded. Ultimately, the study included 1003 patients, 303 who were not vaccinated (157 females, 146 males) and 700 who were vaccinated (356

males, 344 females; 40 patients with one vaccine dose, 660 patients with two vaccine doses) at the time of PET/CT imaging (incubation time, 60.2 min ± 0.9 [SD]). Vaccinated patients were older (mean age, 56.8 years ± 13.7 [SD]) than nonvaccinated patients (mean age, 52.9 years ± 14.9 [SD]; $P < .001$) and more frequently had dyslipidemia (nonvaccinated, 5% [15/303], vaccinated, 10.7% [75/700]; $P = .003$). Systolic blood pressure was also higher in the vaccinated group (mean, 124.3 mmHg ± 18.0 [SD]) than in the nonvaccinated group (mean, 121.5 mmHg ± 17.1 [SD]; p=.014), but not after adjustment for age (p=.31). In the vaccinated group, 372/700 (53.1%) patients did not have cancer whereas in the nonvaccinated group 150/303 (49.5%) patients did not have cancer (Table). Details on the types of malignancies patients had and the therapies they received >6 months prior to imaging are reported in Tables S1 and S2, respectively.

Assessment of myocardial FDG uptake Based on Vaccination Status

Myocardial FDG uptake score and quantification of FDG uptake in axilla, myocardium, liver and spleen demonstrated excellent intra-observer and inter-observer agreement (Fig S2, Appendix S1). Representative PET/CT images with myocardial FDG uptake are shown in Figure 2 and Figures S3 and S4.

Compared to nonvaccinated patients, vaccinated patients had a higher myocardial FDG uptake visual score (median, 2 [IQR: 0-3] vs 1 [IQR: 0-2], *P* <.001) (Fig 3A) and SUVmax (median, 4.8 [IQR:3.0-8.5] vs 3.3 [IQR: 2.5-6.2], *P* <.001) (Fig 3B), which remained after age-adjustment for both measures (*P* <.001). In patients without cancer, vaccinated 372 individuals also showed a higher median myocardial FDG uptake visual score (median, 2 [IQR:0-3]) and SUVmax (median, 4.8 [IQR: 3.2-8.3]) compared to 150 nonvaccinated individuals (median visual score, 1 [IQR: 0-2]; median SUVmax, 3.3 [IQR: 2.6- 6.3]; *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 SUVmax (median, 3.6 [IQR: 2.7-5.1]) compared to the nonvaccinated group (n = 248; median visual score, 0 [IQR: 0-1]; median SUVmax, 3.0 [IQR: 2.4-4.1]; *P* < .001 for both). Myocardial SUVmax remained higher in the vaccinated group even after dividing by liver SUVmax (median, 2.1 [IQR: 1.3-3.6]) or splenic SUVmax (median, 2.5 [IQR: 1.6-4.4]) compared with the nonvaccinated group (median when divided by liver SUVmax, (1.5 [IQR: 1.1-2.7], *P*<.001); median when divided by splenic SUVmax, 1.9 [IQR: 1.3-3.3], *P* <.001). The vaccinated group also showed higher FDG uptake in the liver (median SUVmax, 2.3 [IQR: 2.1-2.5]) and spleen (median SUVmax, 1.9 [IQR: 1.7-2.1]) compared to the nonvaccinated group

(median liver SUVmax, 2.2 [IQR: 2.0-2.4]; $P < .001$; median spleen SUVmax, 1.9 [IQR: 1.7-2.0]; $P = .007$).

Myocardial FDG Uptake in Patients with Vaccination Side Effects

Following vaccination, 254/700 (36.3%) patients reported a fever and 458/700 (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 to those who did not (median score, 2 [IQR: 1-3], p= .032), but no difference was observed in myocardial SUVmax between the two groups (median, 4.6 [IQR: 2.8-8.2] vs 4.9 [IQR: 3.2-8.6], p= .09). Additionally, no difference in visual score (median, 2 [IQR: 0-3] vs 2 [IQR: 0-3]; $P = .40$) or myocardial SUVmax (median, 4.8 [IQR: 3.1-8.1] vs 4.8 [IQR: 2.9-9.3]; $P = .36$) was observed between patients who did and did not develop a fever.

Assessment of Myocardial FDG Uptake in Patients Stratified by Time Interval Between Vaccination and PET/CT

Patients were divided into 7 groups based on the interval of time between vaccination and imaging: nonvaccinated, imaging after 1st dose, and imaging ≤30 days, 31-60 days, 61-120 days, 121-180 days, and >180 days after the 2nd dose. Patients with an unclear date of vaccination

were excluded from this analysis (n = 8). The median duration from the 1st vaccine dose to PET imaging was 13 days (6-21) and from the 2nd dose to imaging was 88 days (41-135). Patients who underwent imaging 1-180 days after receiving their 2nd vaccination had a higher myocardial FDG uptake (median SUVmax range, 4.6-5.1 [range of IQRs: 2.9-8.6]) than nonvaccinated patients (median SUVmax, 3.1 [IQR: 2.5-6.2]; *P* range, <.001 - .001), but patients imaged >180 days after their 2nd dose did not (median SUV max, 4.5 [IQR: 2.7-9.3]; *P* = .15) (Fig 4B). Furthermore, higher axillary FDG uptake was observed in patients who underwent imaging 1-120 days after receiving their 2nd vaccination (median SUVmax range, 1.5-2.0 [range of IQRs: 1.2-3.4]) compared with nonvaccinated patients (median SUVmax, 1.2 [IQR: 1.0-1.4]; *P* range, <.001 -<.001), but this was not observed in patients who underwent imaging >120 days after their 2nd vaccination (median SUV max range, 1.1-1.2 [IQR: 0.9-1.5]; *P* = .20-.99) (Fig 4A, Table S3).

Myocardial FDG Uptake in Patients Stratified by Sex and Age

When patients were stratified by sex, the myocardium FDG uptake was higher in vaccinated males (median SUVmax, 4.9 [IQR:3.3-8.6]) than in nonvaccinated males (median SUVmax, 3.9 [IQR: 2.7-7.2]; *P* = .004) and higher in vaccinated females (median SUVmax, 4.7 [IQR: 2.9-8.2]) compared to nonvaccinated females (median SUVmax, 3.2 [IQR: 2.4 -5.1]; *P* <.001) (Fig

5A). The axillary uptake was also higher in vaccinated males (median SUVmax: 1.4 [IQR: 1.1-1.8]) and vaccinated females (median SUVmax, 1.5 [IQR: 1.1-1.9]) compared to unvaccinated patients of both sexes (median SUVmax males, 1.2 [IQR: 1.0-1.5]; *P*<.001; median SUVmax females, 1.2 [IQR: 1.0-1.4] ; *P*<.001) (Fig S5A).

Patients were also stratified into three age groups, <40, 41-60, and >60 years of age. For each age group, the FDG uptake of axilla and myocardium were higher in vaccinated (median SUVmax ranges, 4.7-5.6 [IQR: 2.9-8.6]) than nonvaccinated patients (median SUVmax ranges, 3.3-3.3 [IQR: 2.3-6.1]: *P* range, <.001-.015) (Fig 5B). However, no difference in myocardial or axillary FDG uptake was observed between vaccinated (median SUVmax ranges, 1.4-1.6 [IQR: 1.1-1.9]) and unvaccinated patients in each age group (median SUVmax ranges, 1.1-1.3 [IQR: 0.7-1.6]: *P* range, <.0001-.0002) (Fig S5B).

Myocardial FDG Uptake in Patients Stratified by type of vaccine

Of the vaccinated patients, the majority (543/700 [77.6%]) received BNT162b2 mRNA (Pfizer-BioNTech), followed by mRNA-1273 (Moderna, 147/700 [21%]). Patients who received ChAdOx1 nCoV-19 (AstraZeneca) (1/700 [0.1%]) or miscellaneous types (9/700 [1.3%]) were excluded from the following analysis due to the small sample size. As compared to the

unvaccinated group (median myocardial SUVmax, 3.3 [IQR: 2.5-6.2]), the myocardial SUVmax was higher in both vaccinated groups (p <.001-<.001), with no difference in FDG uptake observed between BNT162b2 mRNA (median SUVmax, 4.7 [IQR: 2.9-8.4]) and mRNA-1273 (median SUVmax, 5.1 [IQR: 3.4-8.7]; *P* = .39) vaccine types. Axillary SUVmax for both BNT162b2 mRNA (median, 1.4 [IQR: 1.1-1.8]) and mRNA-1273 (median, 1.5 [IQR: 1.1-2.0]) were also higher than the nonvaccinated group (median, 1.2 [IQR: 1.0-1.4]; *P* <.001-<.001) (Fig S6).

Myocardial FDG Uptake in a Subset of Patients with multiple PET/CT scans

A total of 25 patients had more than one PET/CT scan available. Among them, 16 patients who had not received chemotherapy had a PET-CT both before vaccination and within 180 days after their second vaccination [median interval, 87.5 days (56.5 -104.5), range 16-158 days]. Compared to FDG uptake on PET/CT scans taken before vaccination, axillary and myocardial FDG uptake were both higher on scans taken after vaccination [Difference in axillary SUVmax, 0.2 (0.1-0.7), p =0.028; Difference in myocardial SUVmax, 1.0 (0.2-2.8), p=0.037)] (Fig 6).

DISCUSSION

Although patient who developed myocarditis following SARS-CoV-2 vaccination show abnormalities on cardiac MRI, whether myocardial changes occur in asymptomatic individuals following SARS-CoV-2 vaccination is not well established. It was reported that ^{18}F-FDG uptake in PET/CT correlated LGE or T2 intensity on cardiac MRI in myocarditis following SARS-CoV-2 vaccination and recent study showed in COVID-19 myocarditis. The aim of this study is to investigate myocardial ^{18}F-FDG uptake on PET/CT in asymptomatic SARS-CoV-2 vaccinated patients compared to nonvaccinated patients.

In this observational study of patients who underwent PET/CT during comprehensive medical checkups or to evaluate malignancies, patients who had received SARS-CoV-2 mRNA-based vaccination showed increased myocardial FDG uptake on scans compared to nonvaccinated patients (visual score median, 2 [IQR: 0-3] vs 1 [IQR: 0-2], P <.001, SUVmax median, 4.75 [3.0-8.5] vs 3.3 [IQR: 2.5-6.2], P <.001). This increase in myocardial FDG uptake in vaccinated patients was also observed in subgroup analyses that excluded individuals with cancer or homogenous myocardial uptake. When patients were divided into groups based on the time interval between vaccination and imaging, myocardial FDG uptake was higher in all vaccinated groups (median SUVmax range, 4.6-5.1 [range of IQRs: 2.9-8.6]) compared to the nonvaccinated group (median SUVmax, 3.1 [IQR: 2.5-6.2]; P range, <.001-.001) except for the vaccinated group including individuals imaged >180 days after their 2nd vaccination (median

SUV max, 4.5 [IQR: 2.7-9.3]; P =.15). No difference in the myocardial or axillary FDG uptake was observed between patients who received the BNT162b2 mRNA and mRNA-1273 vaccines. In 16 patients with more than one PET/CT scan available, myocardial and axillary FDG uptake was higher on PET/CT scans taken after vaccination than those taken before vaccination.

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

Several studies have also reported that myocarditis incidents occurred ≤28 days after patients had received their 2nd dose (3-7, 19, 21). In our study, patients who underwent imaging 1-180 days after their 2nd vaccination showed elevated myocardial FDG uptake on PET/CT compared to nonvaccinated patients, but patients imaged >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 FDG uptake on PET/CT 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 FDG uptake in the axillary lymph nodes of vaccinated patients can persist for 2-3 weeks (23-25). Data from the current study suggests this may persist for longer as patients who underwent imaging 1-120 days after their 2nd vaccination, but not >120 days after their second vaccination, all had higher axillary lymph node FDG uptake compared to nonvaccinated patients. Compared with cardiac MRI (8), PET-CT can provide information about inflammation for the whole body, and in the current study, FDG uptake in the liver and spleen was also found to be higher in the vaccinated vs nonvaccinated group.

There are several limitations of this study. First, this is retrospective study from a single hospital and thus our findings may lack generalizability. Second, we did not prepare participants to obviate myocardial glucose uptake and excluded participants who had fasted for less than 12-hours and potentially lead physiological uptake and affect the result, although it showed statistically significant. Third, myocardial FDG uptake in scans that are not specifically

performed for the assessment of cardiac inflammation and influenced by many factors (age, sex, insulin resistance, diet, etc.) is 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 vaccination showed increased myocardial FDG uptake on images up to 180 days after their 2nd vaccination compared to patients imaged before SARS-CoV-2 vaccination was available. Vaccinated patients showed higher myocardial FDG uptake on PET/CT compared to 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, cardiac functions and non-mRNA vaccination.

Acknowledgments:

Thanks to Drs. Suketaka Momoshima, Shigeo Okuda, Keiichi Narita and Masashi Tamura for their support to prepare IRB documents.

Disclosures:

T.N. Grants from Nihon Medi-Physics and Bayer Yakuhin, Osaka, Japan. **Y.I.** No relevant relationships. **R.M.** No relevant relationships. **K.T.** No relevant relationship. **T.S.** No relevant relationships. **H.W.S.** No relevant relationships. **C.A.** Grants from Nihon Medi-Physics and Bayer Yakuhin, Osaka, Japan; consulting fees from and founder, shareholder, and director of

Caristo Diagnostics. **J.N.** No relevant relationships. **M.J.** Grants from Nihon Medi-Physics and Bayer Yakuhin, Osaka, Japan.

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Table

Patient Characteristics

	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 (years)	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

Notes.—Categorical variables are presented as number of patients with percentages in parentheses and continuous variables are presented as mean ± standard deviation. Chi Square test or Fisher's exact probability test was used to compare categorical variables and Mann-Whitney U test was used to compare continuous variables between the two groups.

* $p<0.05$

† Significance lost after adjusting for age.

Figures

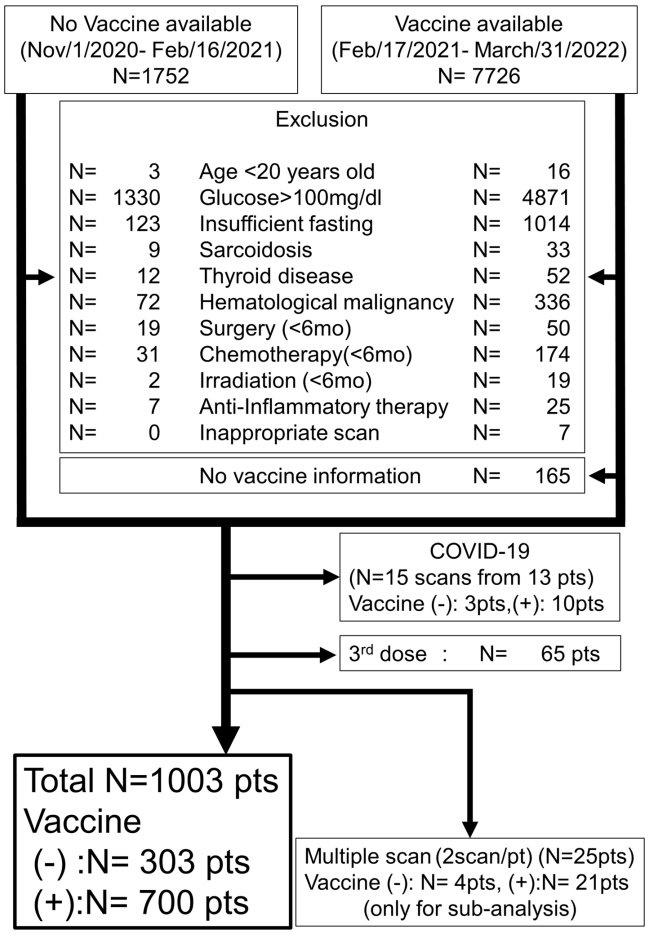
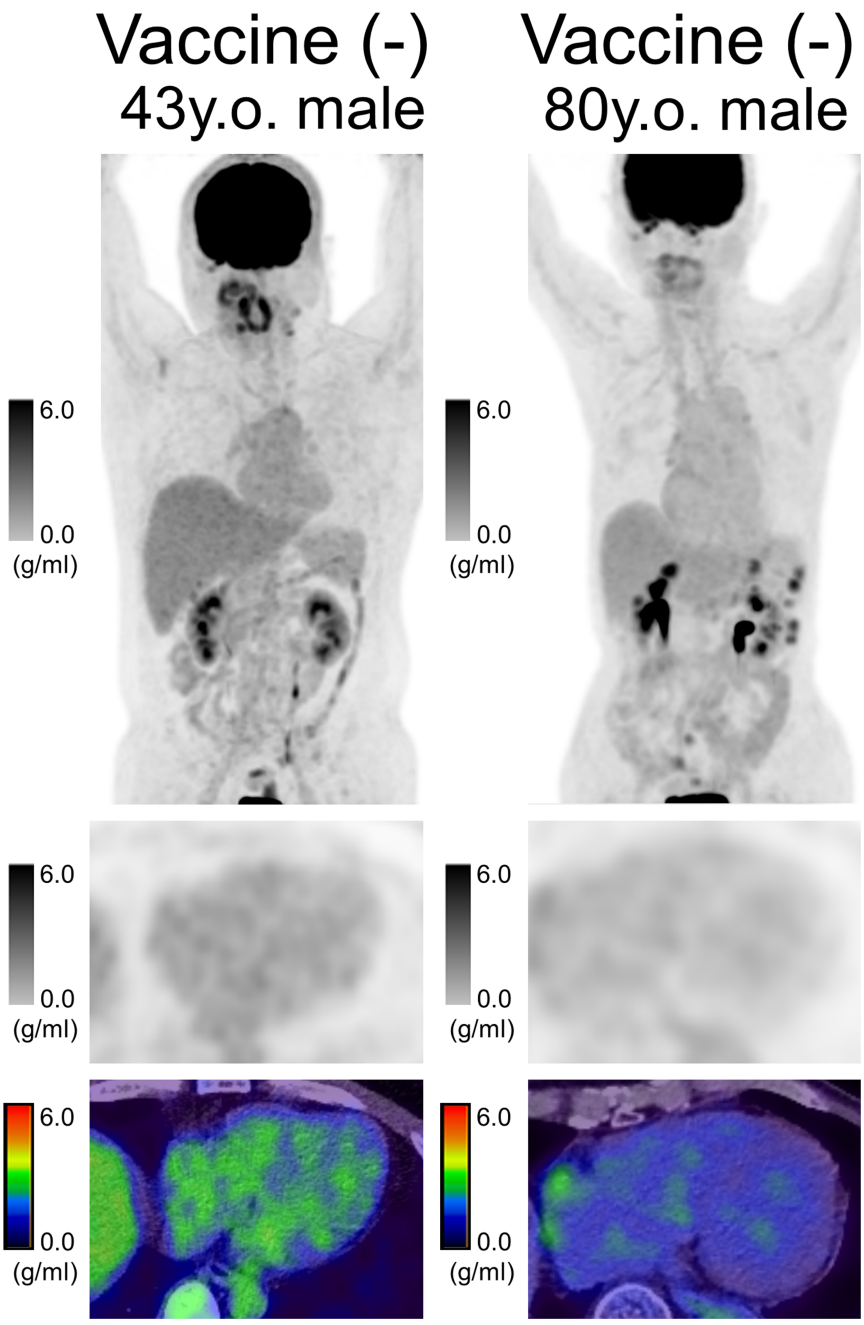


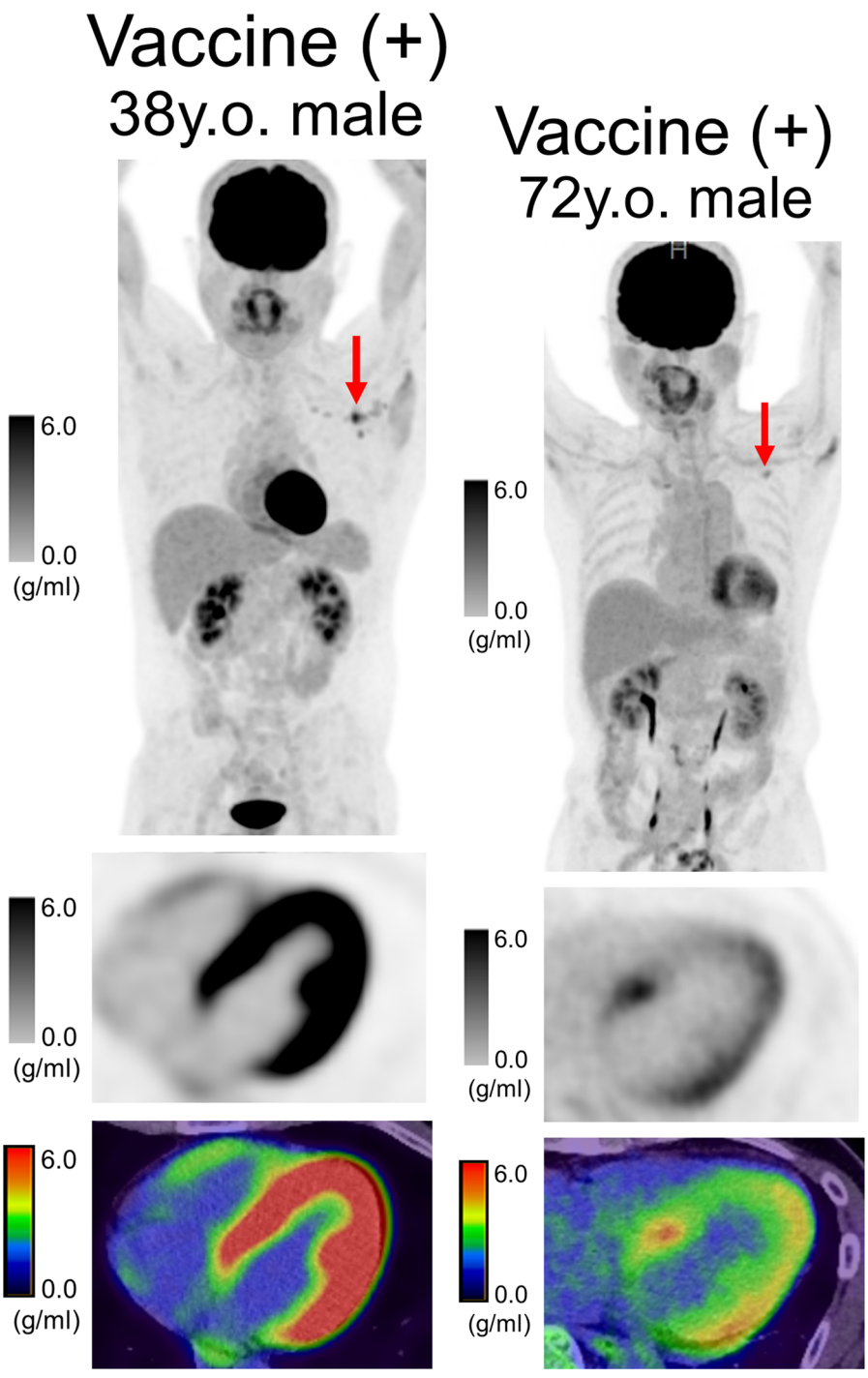
Figure 1: Flow diagram of patient exclusion. Of the cumulative total 9478 patients who received ^{18}Fluorine- fluorodeoxyglucose PET/CT, 1003 patients matched the study criteria, including 700 patients from the period during which SARS-CoV-2 vaccines were available (February 17, 20121 – March 31, 2022) and 303 patients from the period before (November 1, 2020 – February 16, 2021, N= 125) and after (N=178) SARS-CoV-2 vaccines were available. Twenty-five patients, 4 nonvaccinated and 21 vaccinated, received two scans during the study

period but only the 2nd scan was utilized. A sub-analysis including these patients was also performed using both the 1st and 2nd scan.

Radiology



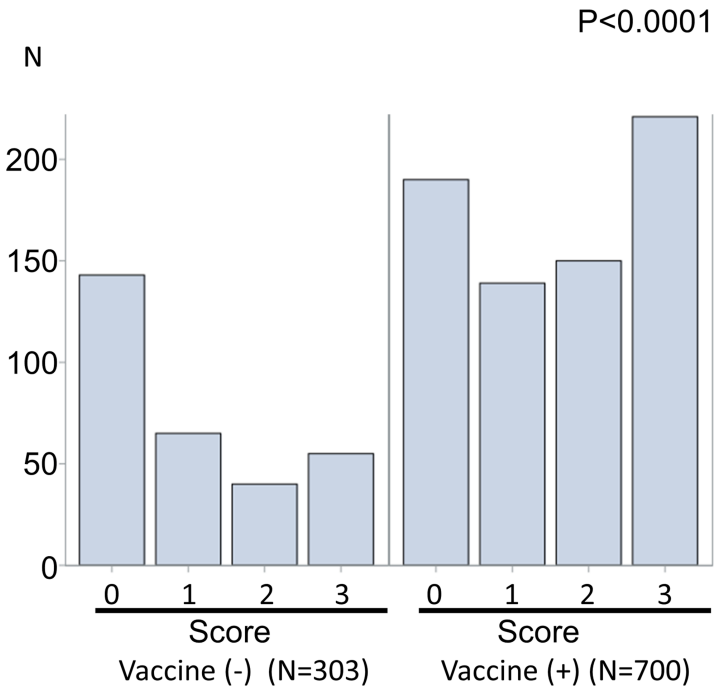
A **B**



C D

Figure 2: Representative whole body and myocardial ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) PET/CT images (PET coronal images, PET axial images, and color blending PET-CT fusion axial images) in patients with and without vaccination. **(A)** Images in a 43-year-old male who received ^{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 SUVmax of 2.7. The axillary, liver, and spleen SUVmax were 0.6, 2.8, and 2.1, respectively. **(B)** Images in an 80-year-old male with pancreatic cancer who was underwent PET/CT during the period before SARS-CoV-2 vaccines were available. The patient had a myocardial score of 0 and a myocardial SUVmax of 2.2. The axillary, liver, and spleen SUVmax were 1.1, 2.2, and 1.5, respectively. **(C)** Images in a 38-year-old male who underwent PET/CT imaging for comprehensive medical checkup 29 days after receiving the first dose of the BNT16b2 vaccine at the left arm. A 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 SUVmax of 14.6. The axillary, liver, and spleen SUVmax were 5.0, 2.0, and 2.1, respectively. **(D)** Images in a 72-year-old male who underwent PET/CT imaging for comprehensive medical checkup 139 days after receiving the second dose of the mRNA-1273 vaccine at the left arm. A 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 SUVmax of 5.9. The axillary, liver, and spleen SUVmax were 2.7, 2.6, and 2.1, respectively.



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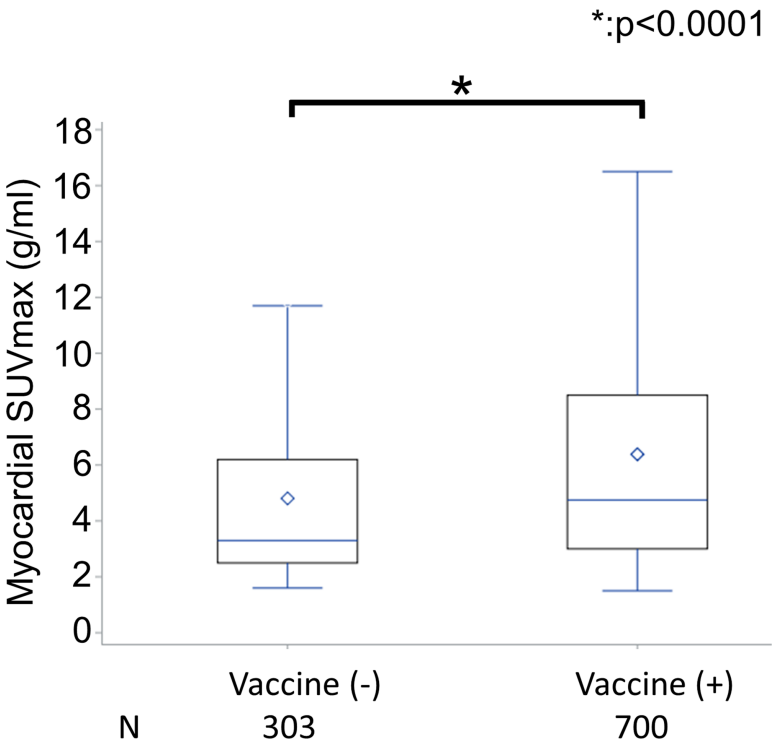
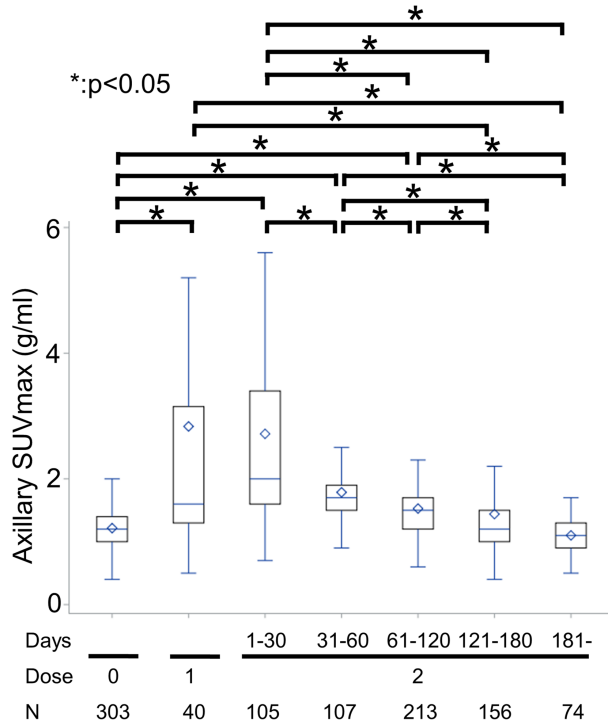


B

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



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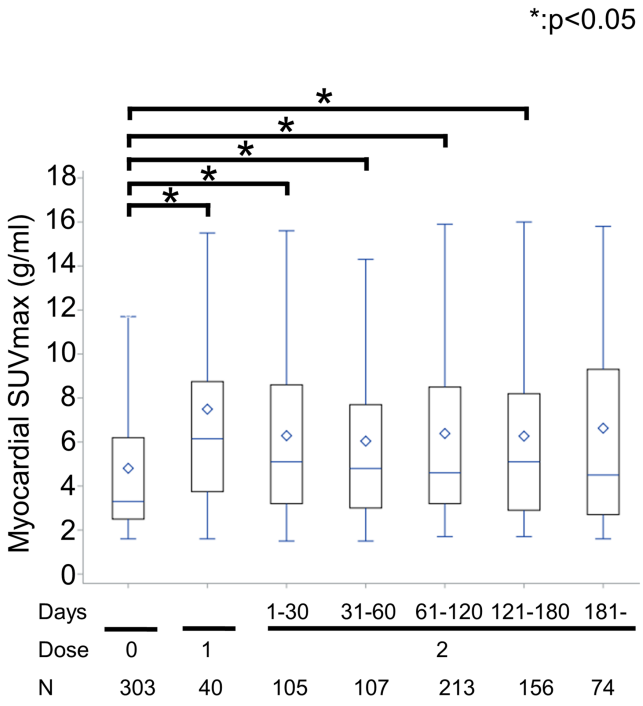
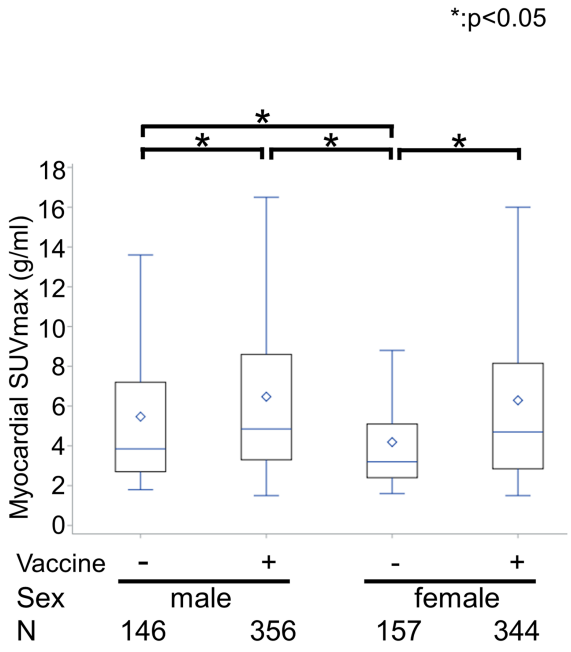


B

Figure 4: Boxplots showing ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) uptake in the **(A)** axillary and **(B)** myocardium of patients stratified by the interval of time between SARS-CoV-2 vaccination and PET/CT imaging. **(A)** Compared to the unvaccinated group (Dose 0, median SUVmax, 1.2 [IQR: 1.0-1.4]), the axillary SUVmax was higher in patients imaged after their 1st dose (median, 1.6 [IQR: 1.3-3.2]; *P* <.001). Patients imaged ≤30 days (median, 2.0 [IQR: 1.6-3.4]), 31-60 days (median, 1.7 [IQR: 1.5-1.9]), and 61-120 days (median, 1.5 [IQR: 1.2-1.7]) after their 2nd dose also showed increased axillary SUVmax values compared to the unvaccinated group (*P* range, <.001-<.001). There was no difference observed in axillary SUVmax between unvaccinated patients and patients imaged 121-180 days (median, 1.2 [IQR: 1.0-1.5]; *P* = .99) or >180 days (median, 1.1 [IQR: 0.9-1.3]; *P* = .20) after their 2nd dose. **(B)** Boxplot showing myocardial SUVmax for nonvaccinated (Dose 0) and vaccinated groups. The myocardial SUVmax was higher in patients imaged after their 1st dose (median, 6.2 [IQR: 3.8-8.8] ; *P*=.004) as well as in patients imaged 1-30 days (median, 5.1 [IQR: 3.2-8.6]), 31-60 days (median, 4.8 [IQR: 3.0-7.7]), 61-120 days (median, 4.6 [IQR: 3.2-8.5]), and 121-180 days (median, 5.1 [IQR: 2.9-8.2]) after their 2nd dose compared to the unvaccinated group (median, 3.3 [IQR: 2.5-6.2]; *P* range, <.001-<.001). There was no difference observed in myocardial SUVmax between unvaccinated patients and patients imaged >180 days after their 2nd dose (median, 4.5 [IQR: 2.7-9.3]; *P* = .15). For both boxplots, horizontal bars represent the median

SUVmax value and whiskers represent the interquartile range. The diamond in the box represents average. Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis was used to compare median SUVmax values between groups.

Radiology



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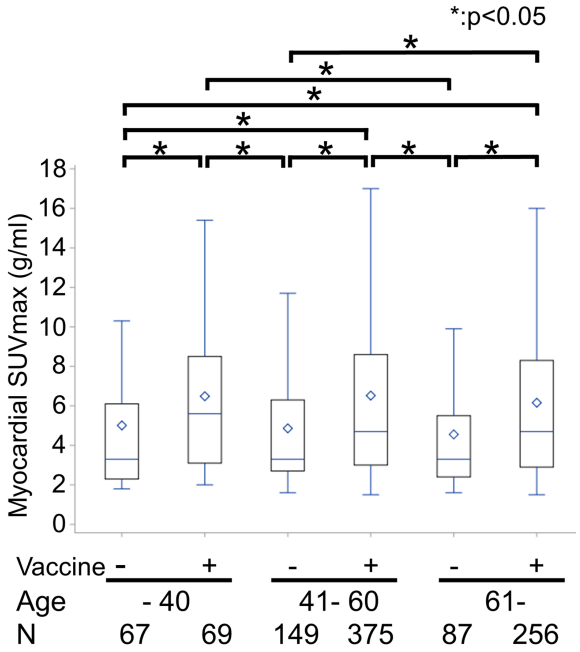
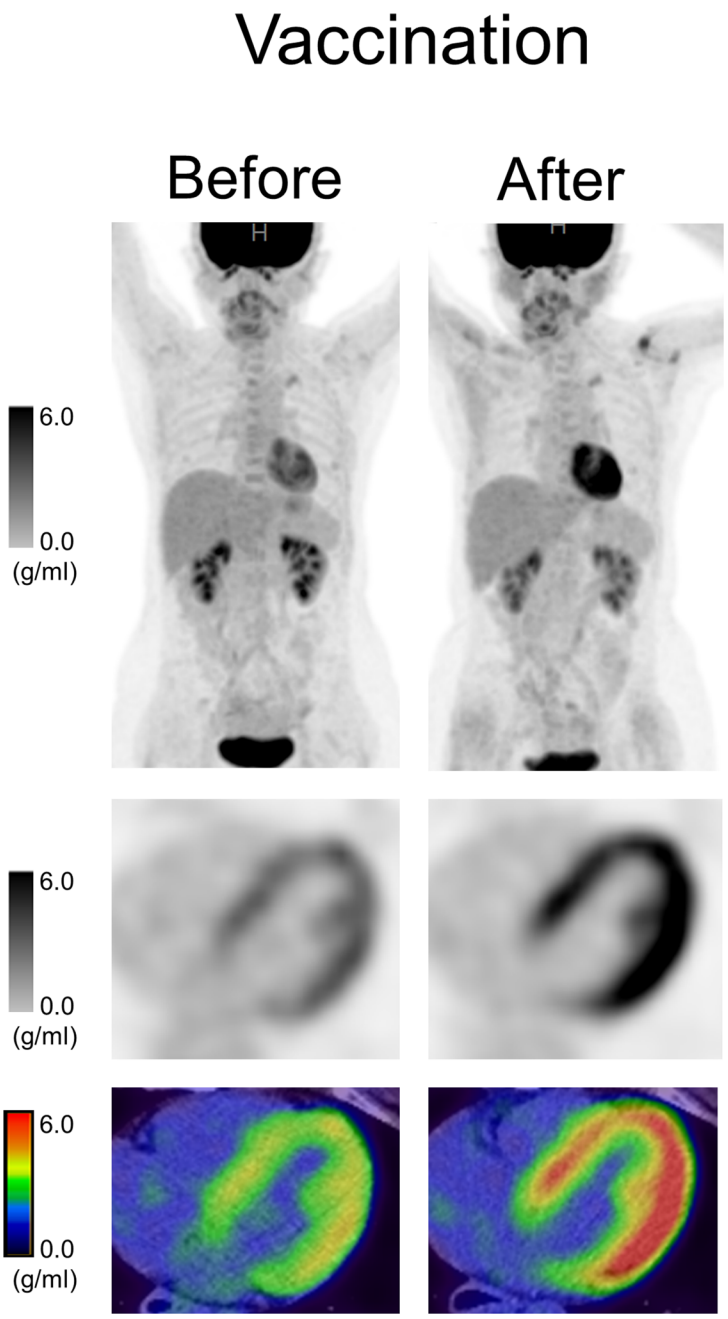


B

Figure. 5: Boxplots showing myocardial ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) uptake as measured by SUVmax in nonvaccinated (-) and vaccinated (+) patients stratified by **(A)** sex and **(B)** age. **(A)** For both sexes, the myocardium FDG uptake were higher in the vaccinated group (males median SUVmax, 4.9 [IQR: 3.3-8.6]; females median SUV max, 4.7 [IQR: 2.9-8.2]) than in the non-vaccinated group (males median SUVmax, 3.9 [IQR: 2.7-7.2]; *P* <.001; females median SUVmax, 3.2 [IQR: 2.4 -5.1]; *P* <.001). **(B)** For each patient age group assessed, the myocardial SUVmax was higher in the vaccinated group (<40 years median SUVmax, 5.6 [IQR: 3.1-8.5]; 41-60 years median SUVmax, 4.7 [IQR: 3.0-8.6]; >60 years median SUVmax, 4.7 [IQR: 2.9-8.3]) than in the non-vaccinated group (<40 years median SUVmax, 3.3 [IQR: 2.3-6.1]; 41-60 years median SUVmax, 3.3 [IQR: 2.7-6.3]; >60 years median SUVmax, 3.3 [IQR: 2.4-5.5] ; *P* range, <.0001-.0002). For vaccinated patients, no differences in myocardial SUVmax was observed between age groups. For both boxplots, horizontal bars represent the median SUVmax value and whiskers represent the interquartile range. The diamond in the box represents average. Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis was used to compare median SUVmax values between groups.

Radiology



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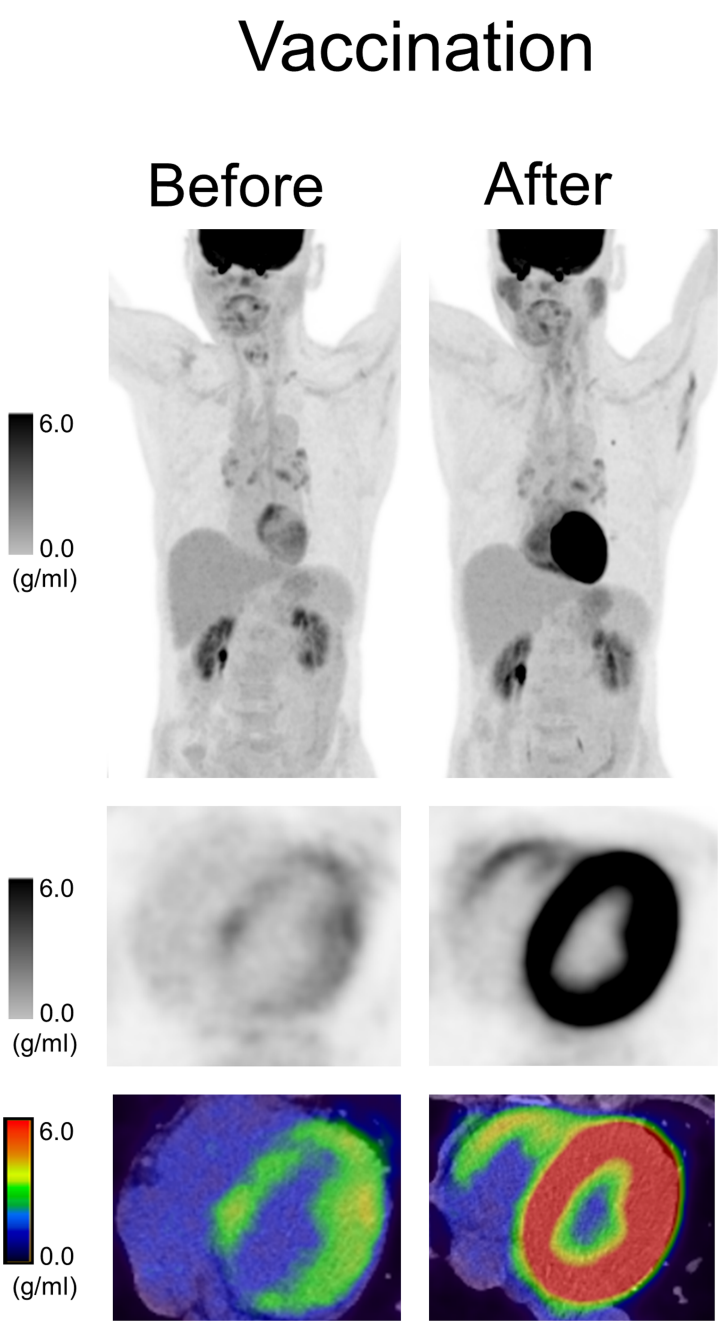

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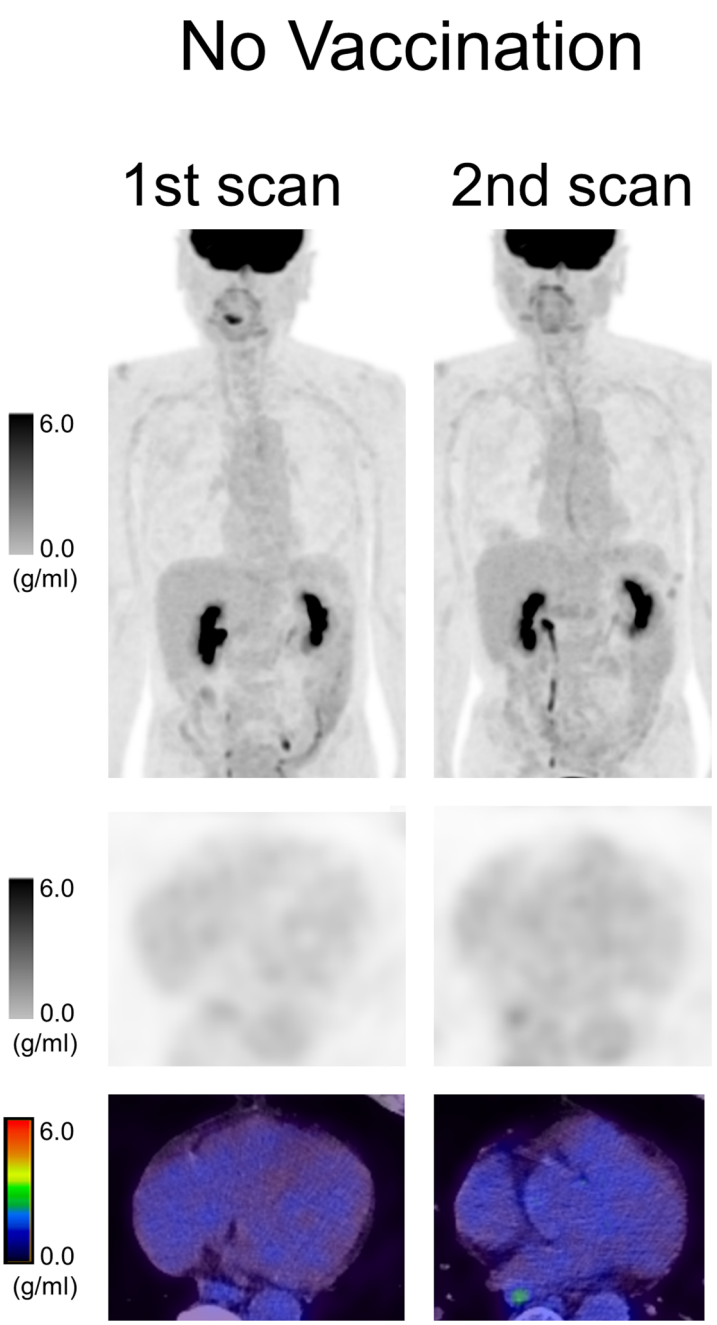


C

Figure. 6: Representative whole body and myocardial ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) PET/CT images (PET coronal images, PET axial images, and color blending PET-CT fusion axial 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 sub-analysis. **(A)** Images in a 54-year-old female with vaginal cancer who underwent two PET/CT exams, the second of which occurred 107 days after receiving the second dose of the mRNA-1273 vaccine. Following vaccination, the myocardial FDG uptake visual score increased from 1 to 3 and myocardial SUVmax increased from 4.8 to 8.2 (g/ml) on PET/CT. **(B)** Images in 67-year-old male with lung cancer who underwent two PET/CT exams, the second of which occurred 72 days after receiving the second dose of the BNT16b2 vaccine. Following vaccination, the myocardial FDG uptake visual score increased from 1 to 3 and myocardial SUVmax increased from 4.8 to 18.0 (g/ml) on PET/CT. **(C)** Images in a 56-year-old male who underwent two PET/CT exams for comprehensive medical checkup 260 days apart during the period before SARS-CoV-2 vaccines were available. Myocardial score and SUVmax of 1st/2nd scan were 0/0 and 1.4/2.0 (g/ml).

Radiology

Appendix S1: Supplemental Text

To evaluate the reproducibility of myocardial SUVmax, intra- and inter- observer variability is assessed by Bland-Altman analysis and Spearman's R. Intra-observer viability for myocardial, axillary, liver, and spleen SUVmax. An observer (T.N.) assessed 71 patients twice 3 months apart. The Bland-Altman analyses showed agreement of intra observer reproducibility and the Spearman's R shows high correlation（myocardial SUVmax, R= 0.999, p<.001, axillary SUVmax, R= 0.88, p<.001, liver SUVmax, R= 0.85, p<.001, and spleen SUVmax, R= 0.86, p<.001). For Inter-observer viability, two observers (T.N. and Y.I.) assessed the same 71 patients independently. The Bland-Altman analyses showed agreement of inter observer reproducibility and the Spearman's R shows high correlation（myocardial SUVmax, R= 0.998, p<.001, axillary SUVmax, R= 0.89, p<.001, liver SUVmax, R= 0.80, p<.001, and spleen SUVmax, R= 0.85, p<.001).

Radiology

Supplemental Tables

Table S1: Patients' cancer types

Tumor type	N(pts)	Tumor Type	N(pts)	Tumor Type	N(pts)
Lung cancer	86(8.6)	Mediastinal tumor	18(1.8)	Brest cancer	81(8.1)
Uterus cancer	65(6.5)	Ovarian cancer	19(1.9)	Esophageal cancer	16(1.6)
Gastric cancer	13(1.3)	Duodenal cancer	2(2.0)	GIST	1(0.1)
Colon cancer	33(3.3)	Appendix cancer	2(2.0)	Liver cancer	3(0.3)
Bile duct cancer	10(1.0)	Pancreatic cancer	16(1.6)	Kidney cancer	3(0.3)
Bladder cancer	1(0.1)	Urinary tract cancer	1(0.1)	Prostate cancer	8(0.8)
Testicular cancer	3(0.3)	Ocular cancer	2(2.0)	Dental cancer	8(0.8)
Ear cancer	5(0.5)	Pharyngeal cancer	10(1.0)	Tongue cancer	19(1.9)
Bone cancer:	12(1.2)	Leiomyosarcoma	2(0.2)	Chondrosarcoma	2(0.2)
Osteosarcoma	4(0.4)	Sarcoma	2(0.2)	Schwannoma	6(0.6)
Peritoneal tumor	2(0.2)	Soft tissue tumor	1(0.1)	Skin cancer	6(0.6)
Malignant melanoma	10(1.0)	Mesothelioma	2(0.2)	Cancer of unknow primary	4(0.4)

Notes.—Categorical variables are presented as number of patients with percentages in parentheses.

Table S2: Type of therapy before more than 6 months

Type of therapy	**N (pts)**
Surgery	151 (15.1)
chemotherapy	42 (4.2)
immunotherapy	1 (0.1)
Irradiation	25 (2.5) (for chest: 12(1.2))

Notes.—Categorical variables are presented as number of patients with percentages in parentheses.

Table S3: ^{18}F-FDG uptake in the axillary of patients stratified by the interval of time between SARS-CoV-2 vaccination and PET/CT imaging

	P Value						
	No Vaccine	1st dose	2nd dose (1-30 days)	2nd dose (31-60 days)	2nd dose (61-120 days)	2nd dose (121-180 days)	2nd dose (181- days)
No Vaccine median SUV max, 1.2 [IQR:1.0-1.4](n = 303)	N/A	<.001*	<.001*	<.001*	<.001*	0.99	0.20
1st dose median SUV max, 1.6 [IQR:1.3-3.2] (n=40)	<.001*	N/A	0.32	1.00	0.19	<.001*	<.001*
2nd dose (1-30 days) median SUVmax, 2.0 [IQR:1.6-3.4] (n=105)	<.001*	0.32	N/A	<.001*	<.001*	<.001*	<.001*
2nd dose (31-60 days) mediain SUVmax, 1.7 [IQR:1.5-1.9] (n=107)	<.001*	1.00	<.001*	N/A	<.001*	<.001*	<.001*
2nd dose (61-120 days) median SUVmax, 1.5 [IQR: 1.2-1.7] (n=213)	<.001*	0.19	<.001*	<.001*	N/A	<.001*	<.001*
2nd dose (121-180 days) median SUVmax,1.2 [IQR:1.0-1.5] (n=156)	0.99	<.001*	<.001*	<.001*	<.001*	N/A	0.15
2nd dose (181- days) median SUVmax, 1.1 [IQR: 0.9-1.3] (n=74)	0.20	<.001*	<.001*	<.001*	<.001*	0.15	N/A

Notes.— SUVmax variables are presented as median [IQR]. Kruskal-Wallis test with post ad - hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis to compare the F-FDG uptake in the axillary of patients stratified by the interval of time between SARS-CoV-2 vaccination and PET/CT imaging. * p<0.05

Radiology

Supplemental Figures

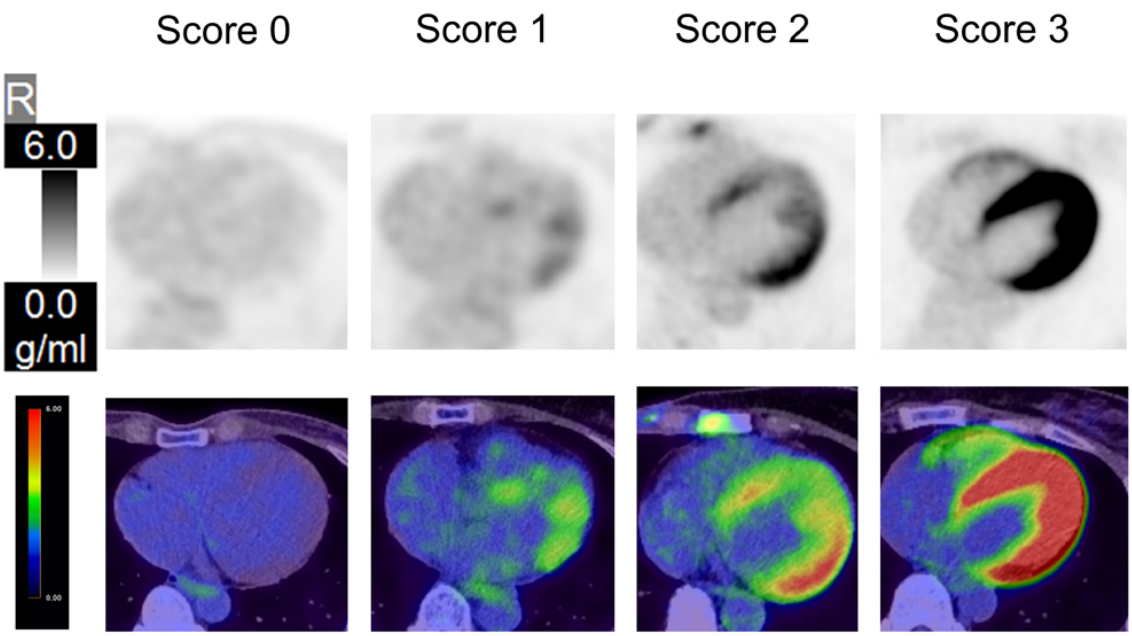
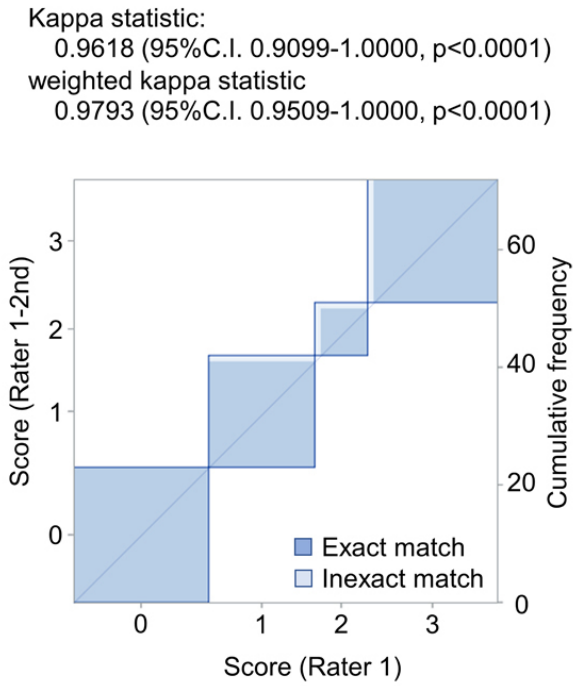
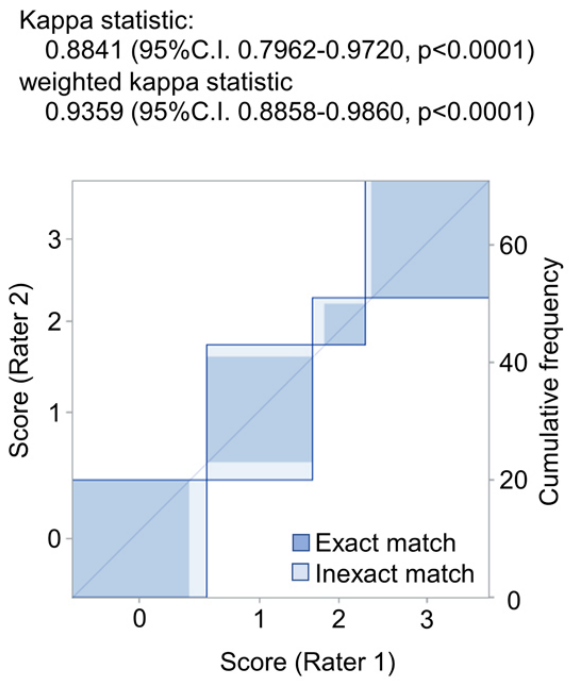


Figure S1: The definition of visual myocardial score. For visual analysis of myocardial activity, a scale of SUV was set from 0.0 g/ml to 6.0 g/ml. Myocardial uptake Visual Scores were set from 0 (minimal uptake), 1 (mostly minimum or mild uptake), 2 (mostly intense or moderate uptake) and 3 (homogeneously uptake). These 4 figures consisted with female patients.

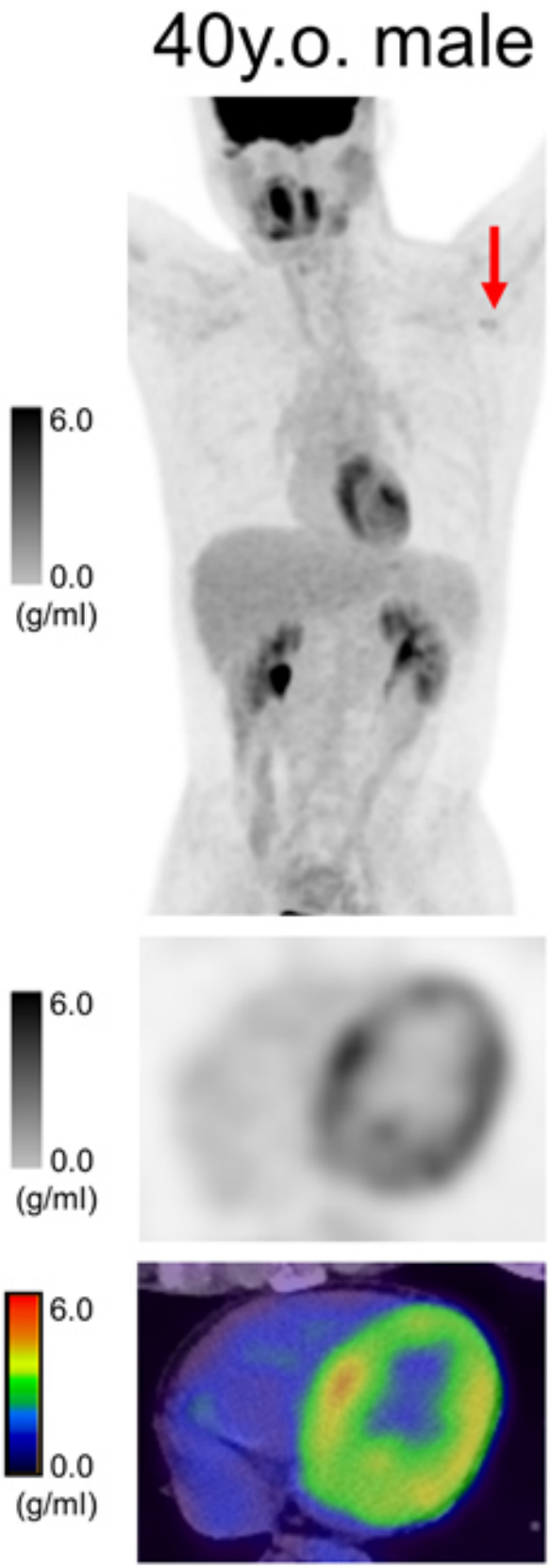


A



B

Figure S2: Myocardial heart score demonstrated excellent intra- and inter- observer reproducibility. To evaluate the reproducibility of myocardial heart score, intra- and inter-observer variability is assessed by Bland-Altman analysis. **(A)** An observer (T.N.) assessed 71 patients twice 3 months apart. The kappa statistic showed excellent inter-observer agreement (Kappa statistic: 0.96 [95%C.I. 0.91-1.00], p<.001) and weighted kappa statistic: 0.98 [95%C.I. 0.95-1.00], p<.001)]. **(B)** Two observers (T.N. and Y.I.) assessed the same 71 patients independently. The kappa statistic showed excellent inter-observer agreement (Kappa statistic: 0.88 [95%C.I. 0.80-0.97], p<.001 and weighted kappa statistic: 0.94 [95%C.I. 0.89-0.99], p<.001).



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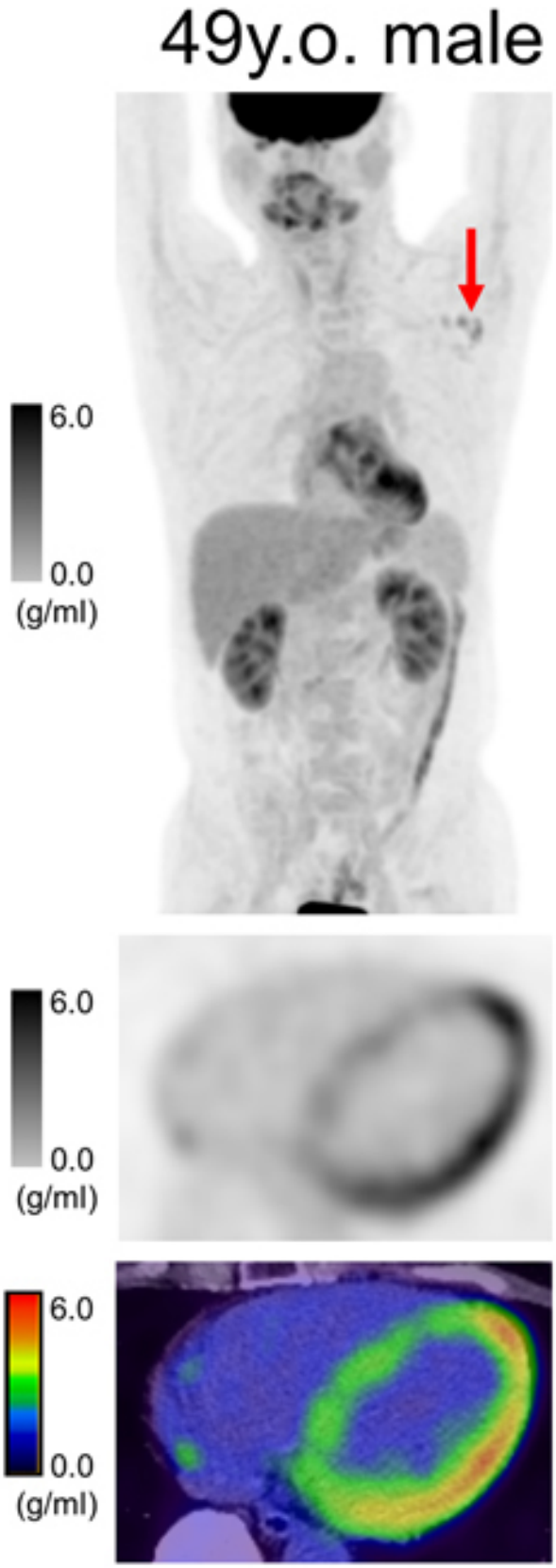

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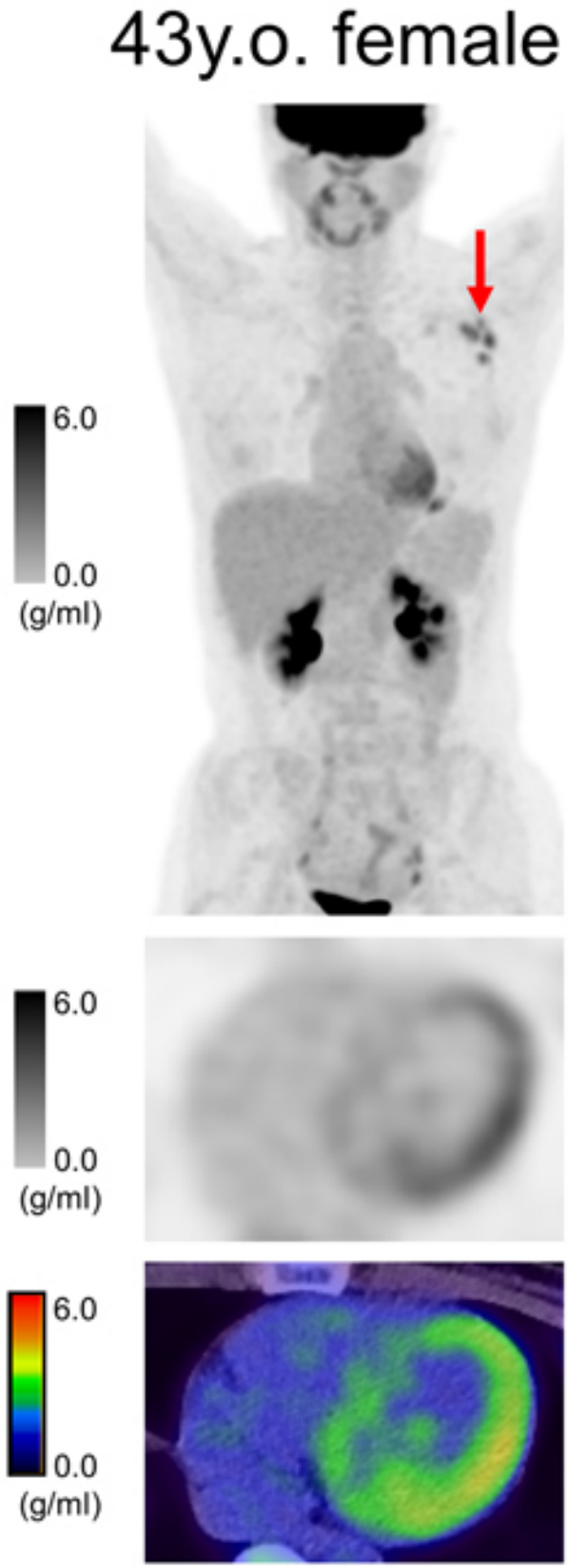

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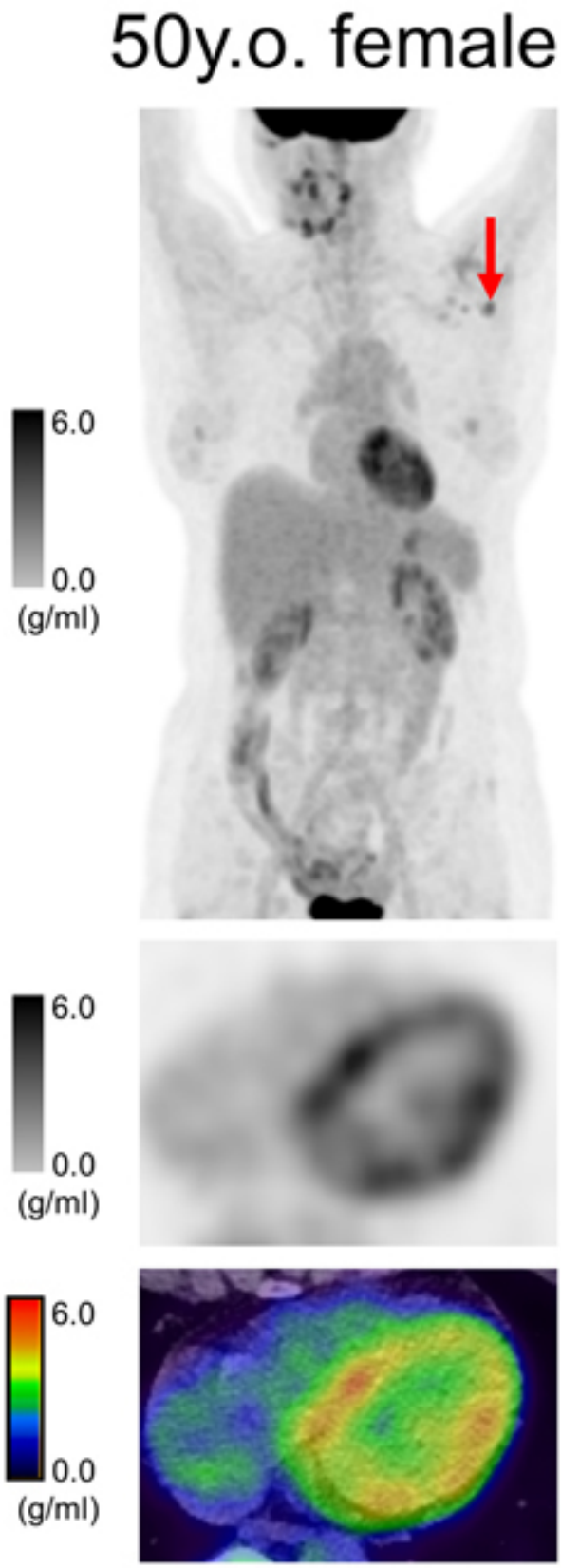
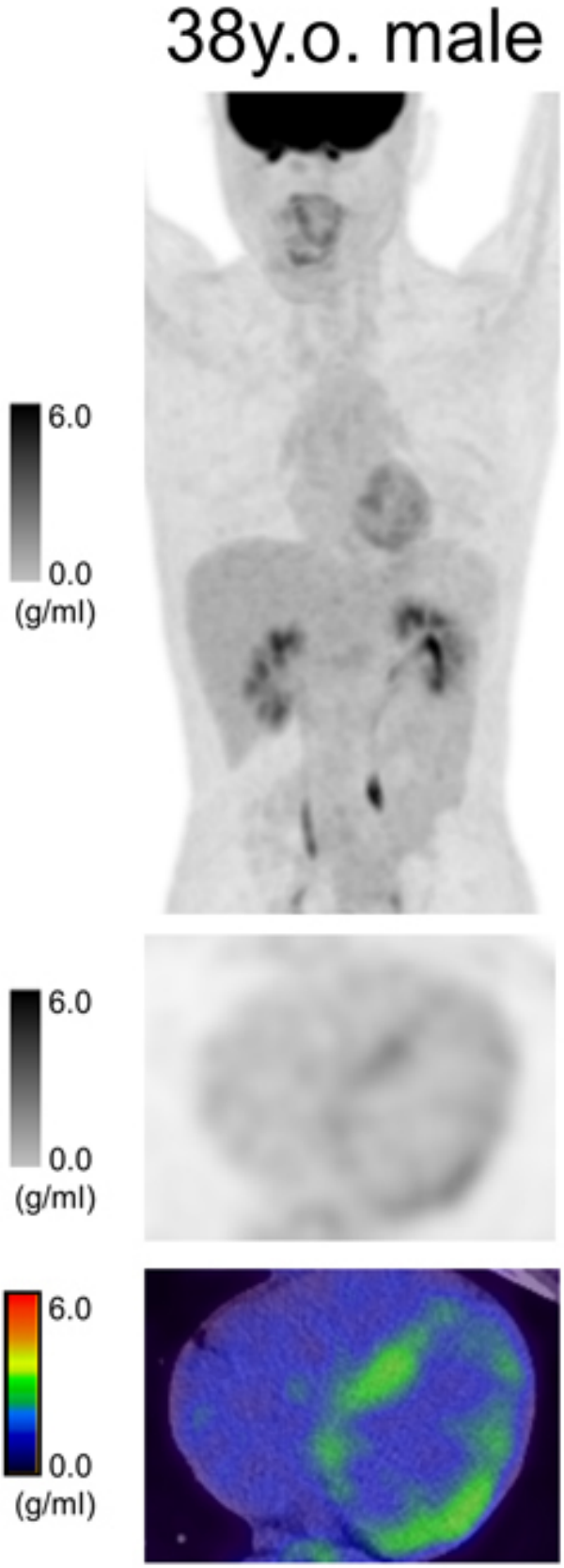


D

Figure S3: Representative cases of moderate myocardial uptake in vaccinated group. **(A)** 40-years-old male patient who received ^{18}F-FDG PET-CT for comprehensive medical checkup after BNT16b2 vaccination at left arm (1st /2nd dose: 54/33 days before). A high uptake of left axilla (arrow) and myocardium were observed. Myocardial score/SUVmax: 2/ 5.6, axillary SUVmax: 1.9, liver SUVmax: 2.1, spleen SUVmax: 1.6. **(B)** 49-years-old male patient who received ^{18}F-FDG PET-CT for comprehensive medical checkup after mRNA-1273 vaccination at left arm (1st dose: 27 days before). A high uptake of left axilla (arrow) and myocardium were observed. Myocardial score/SUVmax: 2/ 6.5, axillary SUVmax: 2.6, liver SUVmax: 2.2, spleen SUVmax: 1.7. **(C)** 43-years-old female patient who received ^{18}F-FDG PET-CT for comprehensive medical checkup after BNT16b2 vaccination at left arm (1st dose: 13 days before). A high uptake of left axilla (arrow) and myocardium were observed. Myocardial score/SUVmax: 2/ 4.1, axillary SUVmax: 4.1, liver SUVmax: 1.9, spleen SUVmax: 1.8. **(D)** 50-years-old female patient who received ^{18}F-FDG PET-CT for comprehensive medical checkup after BNT16b2 vaccination at left arm (1st /2nd dose: 43/22 days before). A high uptake of left axilla (arrow) and myocardium were observed. Myocardial score/SUVmax: 2/ 5.7, axillary SUVmax: 3.2, liver SUVmax: 2.0, spleen SUVmax: 2.4.



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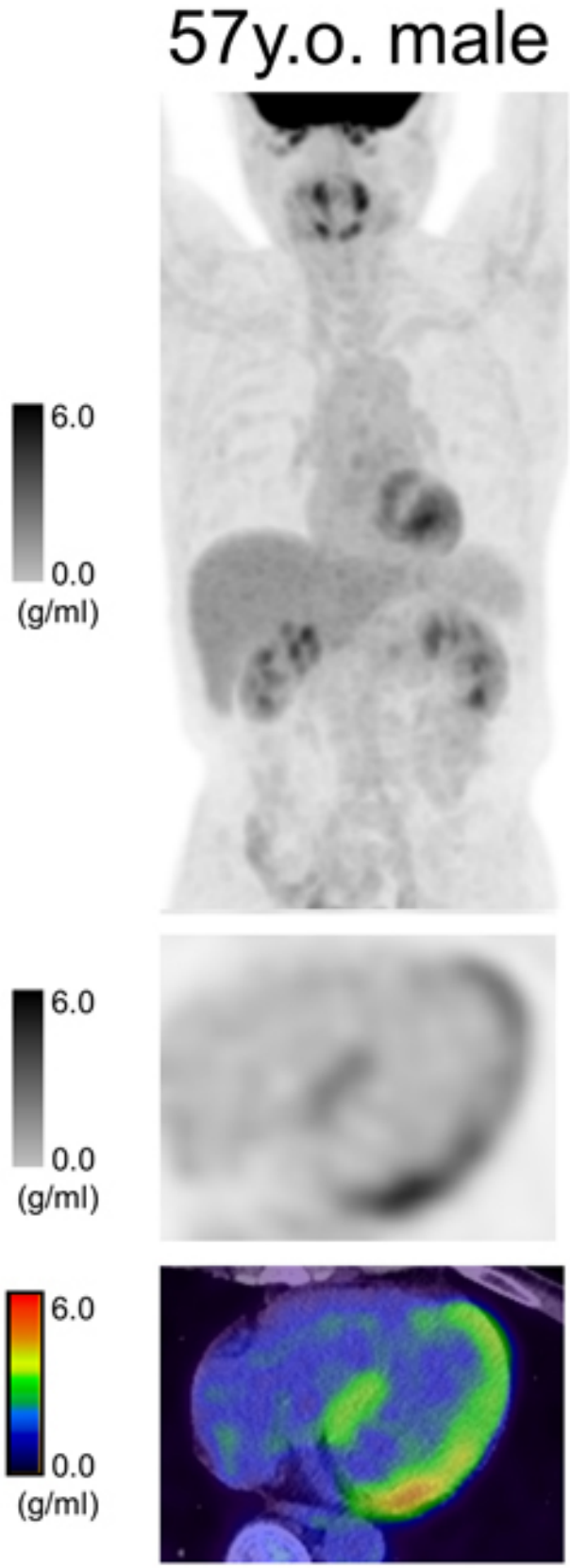

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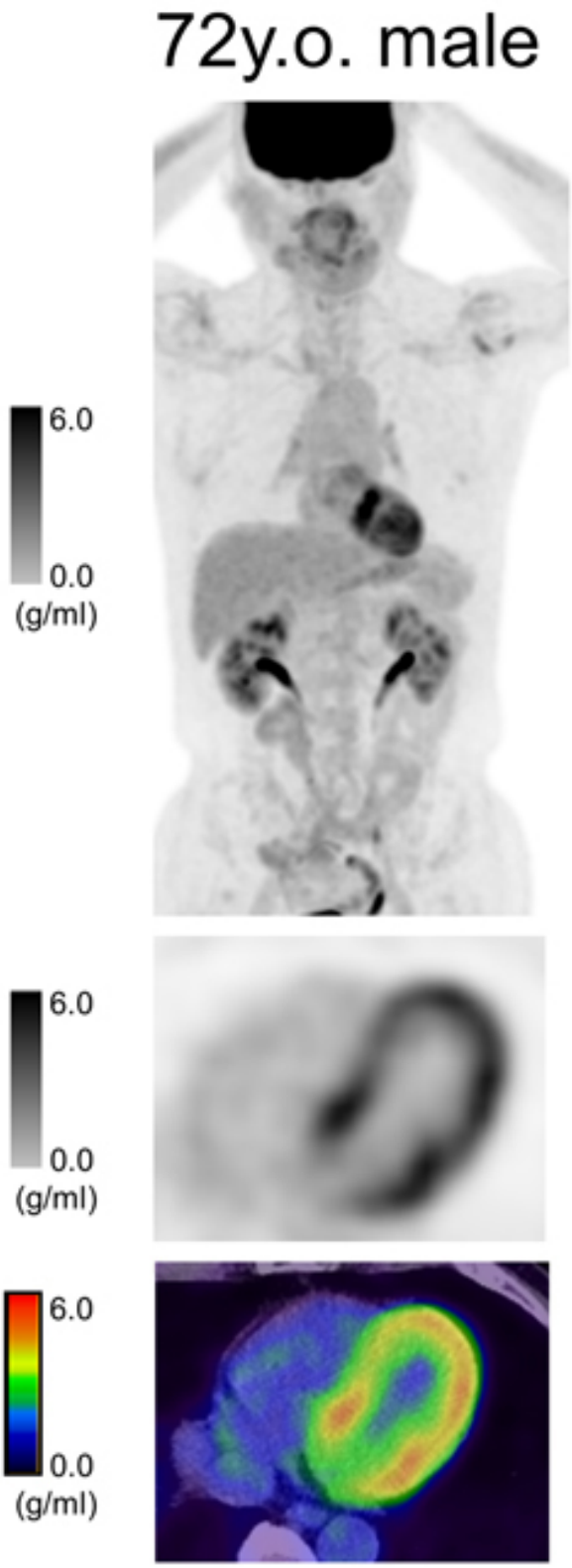
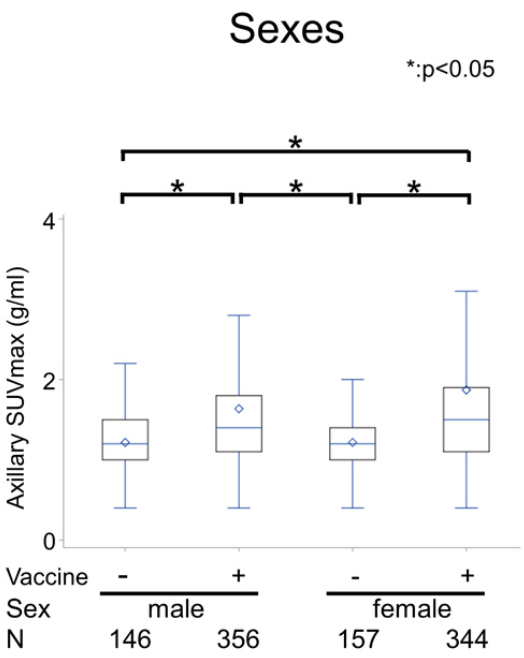


C

Figure S4: Representative cases of mild, moderate and homogeneously myocardial uptake in non-vaccinated group. Representative whole body and myocardial ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) PET/CT images (PET coronal images, PET axial images, and color blending PET-CT fusion axial images) in patients with heart score 1-3 without vaccination. **(A)** Images in a 38-year-old male who received ^{18}F-FDG PET-CT for comprehensive medical checkup after SARS-CoV-2 vaccines were available. The patient had a myocardial score of 1 and a myocardial SUVmax of 3.3. The axillary, liver, and spleen SUVmax were 0.7, 1.8, and 1.6, respectively. **(B)** Images in a 57-year-old male who received ^{18}F-FDG PET-CT for comprehensive medical checkup after SARS-CoV-2 vaccines were available. The patient had a myocardial score of 2 and a myocardial SUVmax of 5.1. The axillary, liver, and spleen SUVmax were 0.8, 2.4, and 2.6, respectively. **(C)** Images in a 72-year-old male with prostatic cancer who was underwent PET/CT during the period before SARS-CoV-2 vaccines were available. The patient had a myocardial score of 3 and a myocardial SUVmax of 7.2. The axillary, liver, and spleen SUVmax were 1.6, 2.1, and 2.5, respectively.



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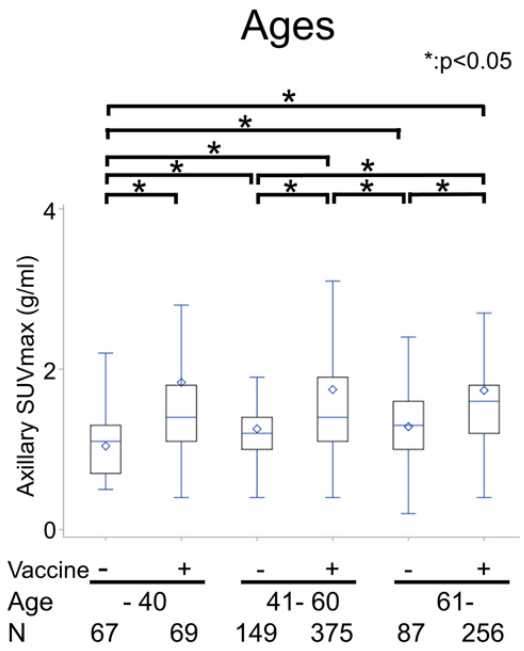

B

Figure S5: Difference of Axillary FDG uptake in sex and age. Boxplots showing axillary ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) uptake as measured by SUVmax in nonvaccinated (-) and vaccinated (+) patients stratified by **(A)** sex and **(B)** age. **(A)** For both sexes, the axillary FDG uptake were higher in the vaccinated group (males median SUVmax, 1.4 [IQR:1.1-1.8]; females median SUV max, 1.5 [IQR:1.1-1.9]) than in the non-vaccinated group (males median SUVmax, 1.2 [IQR: 1.0-1.5]; *P* <.001; females median SUVmax, 1.2 [IQR: 1.0 -1.4]; *P* <.001). **(B)** For each patient age group assessed, the axillary SUVmax was higher in the vaccinated group (<40 years median SUVmax, 1.4 [IQR: 1.1-1.8]; 41-60 years median SUVmax, 1.4 [IQR: 1.1-1.9]; >60 years median SUVmax, 1.6 [IQR: 1.2-1.8]) than in the non-vaccinated group (<40 years median SUVmax, 1.1 [IQR: 0.7-1.3]; 41-60 years median SUVmax, 1.2 [IQR: 1.0-1.4]; >60 years median SUVmax, 1.3 [IQR: 1.0-1.6] ; *P* range, <.001-<.001). For vaccinated patients, no differences in axirally SUVmax was observed between age groups. For both boxplots, horizontal bars represent the median SUVmax value and whiskers represent the interquartile range. The diamond in the box represents average. Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis was used to compare median SUVmax values between groups.

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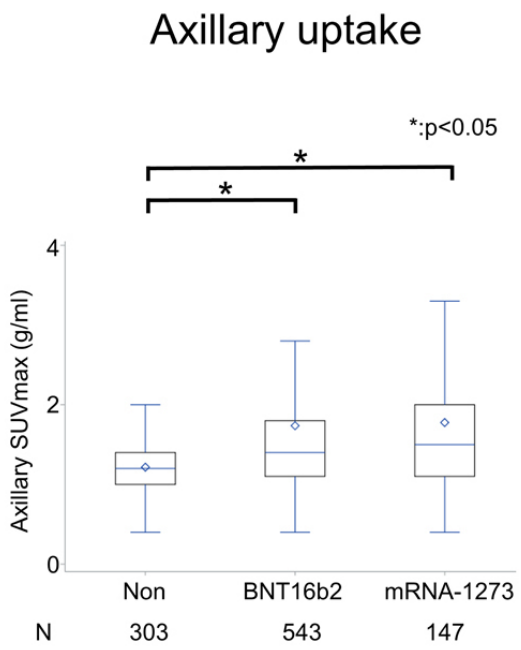
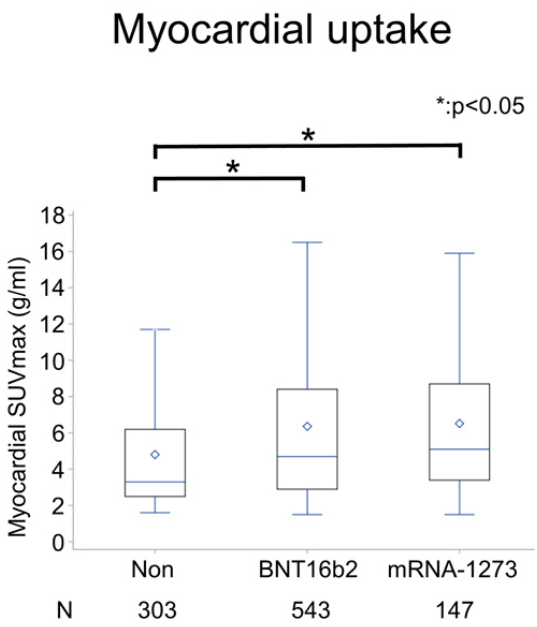


A



B

Figure S6: Difference in type of vaccine. Boxplots showing **(A)** axillary and **(B)** myocardial ^{18}Fluroine-fluorodeoxyglucose (^{18}F-FDG) uptake as measured by SUVmax in nonvaccinated (-) and vaccinated (+) patients. **(A)** For both type of vaccines, the axillary FDG uptake were higher in the vaccinated group (BNT16b median SUVmax, 1.4 [IQR:1.1-1.8]; mRNA-1273 median SUV max, 1.5 [IQR:1.1-2.0]) than in the non-vaccinated group (median SUVmax, 1.2 [IQR: 1.0-1.4]; *P* ranges <.001-<.001). **(B)** For both type of vaccines, the myocardial FDG uptake were higher in the vaccinated group (BNT16b median SUVmax, 4.7 [IQR:2.9-8.4]; mRNA-1273 median SUV max, 5.1 [IQR:3.4-8.7]) than in the non-vaccinated group (median SUVmax, 3.3 [IQR: 2.5-6.2]; *P* ranges <.001-<.001). For both boxplots, horizontal bars represent the median SUVmax value and whiskers represent the interquartile range. The diamond in the box represents average. Kruskal-Wallis test with post ad -hoc Dwass, Steel, Critchlow-Fligner multiple comparison analysis was used to compare median SUVmax values between groups.