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SYSTEMATIC REVIEW

COVID-19 vaccination, implications for PET/CT image interpretation and future perspectives

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Abstract

Introduction The present paper aims to systematically review the literature on COVID-19 vaccine-related findings in patients undergoing PET/CT.

Methods The search algorithms included the following combination of terms: "PET" OR "positron emission tomography" AND "COVID"; "PET" OR "positron emission tomography" AND "COVID" AND "vaccination"; "PET" OR "positron emission tomography" AND "COVID", AND "autoimmune".

Results We selected 17 articles which were assessed for quality and included in the systematic analysis. The most frequent vaccine-related signs on PET/CT were the deltoid [^{18}F]FDG uptake and axillary hypermetabolic lymph nodes, which were described in 8–71% and 7–90% of the patients, respectively. Similarly, frequency of these findings using other tracers than [^{18}F]FDG was greatly variable. This large variability was related to the variability in time elapsed between vaccination and PET/CT, and the criteria used to define positivity. In addition, vaccine-related findings were detected more frequently in young and immunocompetent patients than in elderly and immunocompromised ones.

Discussion Therefore, awareness on vaccination status (timing, patient characteristics, and concurrent therapies) and knowledge on patterns of radiopharmaceutical uptake are necessary to properly interpret PET/CT findings.

Keywords COVID-19 · Vaccination · SARS-CoV-2 · PET/CT · Inflammation · Infection

Introduction

Over time, humans have been afflicted by several pandemics of which the SARS-CoV-2 is chronologically the latest, but helpfully—at least for now—not the deadliest (https://www.visualcapitalist.com/history-of-pandemics-deadliest/). It became clearly apparent since the first wave that the SARS-CoV-2 infection does not only affect the respiratory system, but it is a systemic disease, regardless of the severity of clinical symptoms. During 2021, the number of symptomatic and severe COVID-19 patients, as well as the number of deaths caused by COVID-19, has been greatly reduced thanks to the large-scale vaccination campaigns [1].

Since the worldwide COVID-19 vaccination campaigns started, positron emission tomography (PET) findings related to the vaccine administration—typically muscular uptake at the injection site and axillar hypermetabolic lymph nodes—were reported in patients examined for other purposes. Although post-COVID-19 vaccination findings are typically reported with [^{18}F]FDG PET/CT, similar occasional reports have also been described with other tracers.

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The present paper aims to systematically review the literature about vaccine-related findings in patients performing PET/CT.

Materials and methods

A comprehensive literature search on the PubMed/MEDLINE database was performed to collect published original studies reporting PET/CT findings related to COVID-19 vaccination. The search algorithms included the following combination of terms: "PET" OR "positron emission tomography" AND "COVID"; "PET" OR "positron emission tomography" AND "COVID" AND "vaccination"; "PET" OR "positron emission tomography" AND "COVID", AND "autoimmune". Google was scanned with the same criteria, and the resulting matching manuscripts were listed in an Excel file. The literature search was performed by two authors independently (M.S. and M.B.), who excluded: (i) case reports and small case series (five or less patients), (ii) articles not in English or not available in full text, (iii) articles out of the scope of this review, (iv) reviews and meta-analyses, conference proceedings, commentaries, editorials and letters. The titles and the abstracts of the identified articles were reviewed by two authors (M.S. and M.B.) applying the aforementioned inclusion/exclusion criteria, and full-text versions of the selected articles were downloaded. References of the eligible articles and reviews on the topic were also evaluated.

For each selected article, we collected the following information: authors and country, date of publication, design of the study (retrospective or prospective), number of patients, demographics of patients (sex and mean age), radiopharmaceutical, type of vaccine administered (mRNA or DNA, and commercial name), number of vaccine injections, days between last vaccination and imaging, main findings (hypermetabolic lymph nodes, uptake at vaccination injection site, and/or others), indication for PET/CT examination.

The quality of each study was assessed independently by two reviewers (M.S. and F.G.) using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria. For each study, the risk of bias and the applicability of primary diagnostic accuracy studies were evaluated, and for both domains, we assigned qualitative measures such as "unclear", "low", or "high".

Results

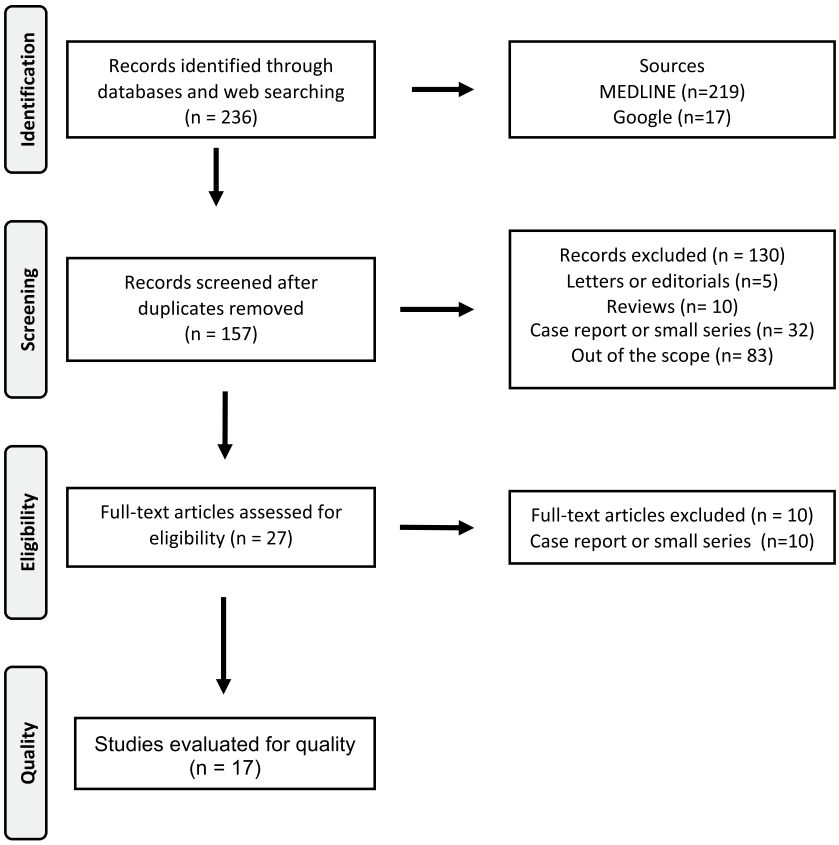
The first inquiry on PubMed and Google using the aforementioned algorithms produced 295 and 17 records, respectively. We identified 79 duplicates. Using the above-stated inclusion/exclusion criteria, we selected 17 articles which were assessed for quality and included in the systematic analysis (Fig. 1). The results of quality assessment are presented in Fig. 2. The majority of studies included in the analysis presented a high risk of bias in the domain of reference standard. Table 1 summarizes the main characteristics of selected studies.

Local signs of inflammation

Orevi et al. described PET/CT findings after COVID-19 vaccination in a large cohort of patients [2]. Images were visually and semi-quantitatively retrospectively evaluated to assess the presence of radiopharmaceutical uptake in the deltoid muscle, and/or cervical, supraclavicular, and axillar lymph nodes. Radiological criteria were used as reference standard to label lymph nodes as benign, malignant, or equivocal. Reporters were blinded to vaccination status. Patients not immunized or recovered from COVID-19 infection were used as controls. Overall, deltoid muscle increased uptake was found in 20%, 21%, and 3% of patients imaged by [^{18}F]FDG, [^{68}Ga]DOTATATE, and PSMA, respectively; the shorter the interval of time between vaccination and examination, the higher was the frequency of this finding. Nodal uptake was reported in 59% of patients imaged with [^{18}F]FDG (PPV = 86%), in 86% of [^{68}Ga]DOTATATE scans (PPV = 100%), and in 84% of PSMA images (PPV = 80%). The uptake in deltoid muscle and lymph nodes lasted for a longer period of time after the second vaccination (up to 21 and 32 days, respectively) than after the first administration (up to 10 and 22 days, respectively).

Eshet et al. [3] aimed to describe the epidemiology of [^{18}F]FDG-avid axillary lymph nodes beyond 6 weeks after the second dose of BNT162b2 vaccine. They excluded patients with conditions likely to involve the axilla (e.g., ipsilateral locally advanced breast cancer) and patients vaccinated in both arms. SUVmax ratio between the ipsilateral and contralateral axillary lymph nodes > 1.5 was selected as criterion for positivity. [^{18}F]FDG-avid axillary lymph nodes were described in 29% of cases. Interestingly, although in the majority of the cases positivity was detected earlier after vaccination (42% up to the 7th week), a consistent percentage of patients exhibited [18F]FDG-avid axillary lymph nodes even 70 days after vaccination (19% at the 10th week). [^{18}F]FDG-avid lymph nodes were not enlarged, and no correlation between [^{18}F]FDG-avid lymph nodes and ongoing immunotherapy was found. The same group [4] performed an ad hoc study to evaluate the correlation between local signs of inflammation after vaccination, age and immune status in a large cohort of patients examined with [^{18}F]FDG PET/CT. They applied the same criteria for PET interpretation mentioned above and they highlighted a negative correlation between [^{18}F]FDG-avid lymph nodes and patient age, immunosuppressive treatment, and hematologic disease; no

Fig. 1 Paper selection process



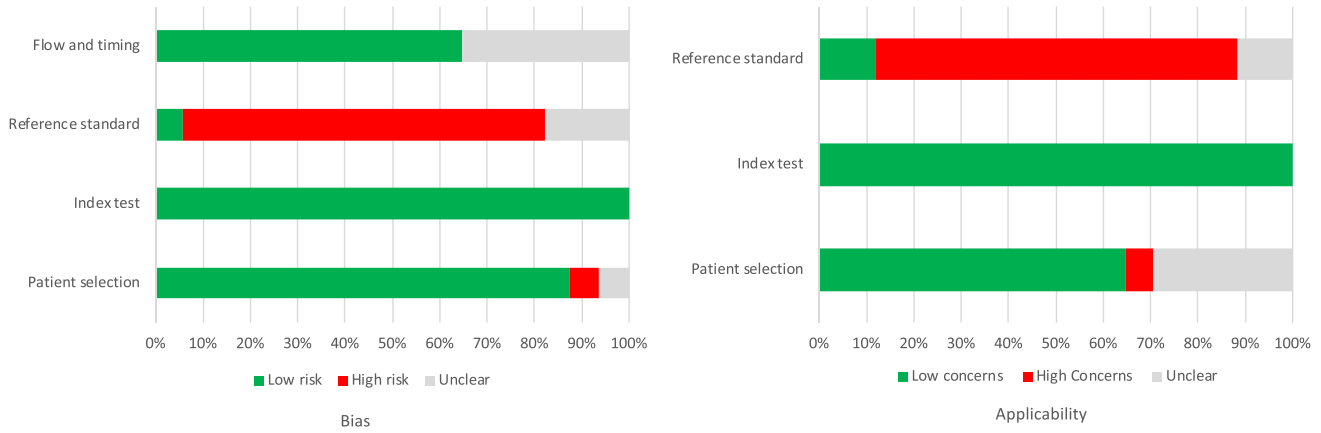


Fig. 2 Quality assessment according to QUADAS-2 of the 17 articles included in the systematic review

association was found between [^{18}F]FDG deltoid uptake and patients' characteristics [4].

Bernstine et al. [5] described the pattern and duration of vaccination-related [^{18}F]FDG activity in the axillary lymph nodes after the first and the second vaccination. They included in the analysis 650 subjects (394 vaccinated once and 256 vaccinated twice). The presence of [^{18}F] FDG uptake higher than the surrounding background was elected as criterion for positivity. The percentage of positivity was higher after the second dose both in deltoid muscle (6 and 2% of patients after the second and the first dose, respectively) and lymph nodes (43 and 14% of the cases after the second and the first dose, respectively), without any difference in terms of degree of uptake, number and size of involved lymph nodes. Nodal uptake was reported 12.3 ± 5.9 (1–22) days after the first injection, and 7.5 ± 5.4 (1–22) days after the second vaccination.

Table 1 Summary of the main characteristics of selected studies

Reference	Country	Patients, *n*	Study design	Vaccine	Reference standard	Tracer	Main findings		
							Deltoid muscle*	Lymph nodes*	Other
[2]	Israel	458	R	Pfizer-BioNTech	Radiological criteria	[^{18}F]FDG	20%	59%	–
		14				[^{68}Ga] DOTATOC	21%	86%	–
		31				[^{68}Ga]/[^{18}F] PSMA	13%	84%	–
[3]	Israel	169	R	Pfizer-BioNTech	Ipsilateral/controlateral SUVmax > 1.5	[^{18}F]FDG		29%	–
[4]	Israel	377	R	Pfizer-BioNTech	Ipsilateral/controlateral SUVmax > 1.5	[^{18}F]FDG	26%	45%	–
		11				[^{68}Ga] DOTATATE	9%	55%	–
		37				[^{68}Ga]/[^{18}F] PSMA	0	0.3%	–
		1				[^{18}F]DOPA	0	100%	–
[16]	Israel	137	R	Pfizer-BioNTech	Uptake > surrounding background	[^{18}F]FDG	–	31%	–
[5]	Israel	650	R	Pfizer-BioNTech	Uptake > surrounding background	[^{18}F]FDG	8%	26%	–
[8]	Israel	728	R	Pfizer-BioNTech	Uptake > surrounding background	[^{18}F]FDG	37%	37%	–
[17]	Israel	179	R	Pfizer-BioNTech	Uptake > surrounding background	[^{18}F]FDG	–	47%	–
[6]	UK	204	R	Pfizer-BioNTech or Vaxzevria	Uptake > surrounding background	[^{18}F]FDG		36%	
[7]	Turkey	206	R	Pfizer-BioNTech or ChAdOx1-S	Ipsilateral/controlateral SUVmax > 1.5	[^{18}F]FDG	10%	13%	–
[9]	Switzerland	140	R	Pfizer-BioNTech or Moderna	Difference between ipsilateral and controlateral SUVmax > 0.5	[^{18}F]FDG		37%	
[10]	US	262	P	Pfizer-BioNTech or Moderna	Uptake > surrounding background	[^{18}F]FDG		47%	
[11]	US	68	R	Pfizer-BioNTech or Moderna	Uptake > mediastinal blood pool	[^{18}F]FDG	12%	13%	
[12]	US	54	R	Pfizer-BioNTech or Moderna	SUVmax > SUVmax mediastinal blood pool	[^{18}F]FDG	14%	7%	
		13				[^{11}C]Choline		23%	

Table 1 (continued)

Reference	Country	Patients, *n*	Study design	Vaccine	Reference standard	Tracer	Main findings		
							Deltoid muscle*	Lymph nodes*	Other
[13]	Italy	389	R	Pfizer-BioNTech or Moderna or Vaxzevria	Uptake > surrounding background	[^{18}F]FDG	–	30%	–
		45				[^{18}F]Fluorocholine	–	7%	–
		3				[^{18}F]Fluciclovine	–	0%	–
[14]	Korea	31	R	Vaxzevria	Uptake > surrounding background	[^{18}F]FDG	71%	90%	0%
[15]	France	260	R	mRNA or viral vector	Ipsilateral/controlateral SUVmax > 1.5	[^{18}F]FDG	–	35%	–
[18]	Thailand	8	R	Vaxzevria or Sinovac	Threshold of 2.5 statistical deviations from the mean difference assessed by the MIM software between baseline and follow-up imaging	[^{18}F]FDG and [^{15}O] Water	–	–	Changes in brain perfusion (25%) and metabolism (63%)

P prospective, *R* retrospective, *SUVmax* maximum standardized uptake value

*Percentage are calculated according to each radiopharmaceutical

Positive lymph nodes were observed less frequently in elderly (≥ 64 years) patients (22 versus 37%, respectively).

El-Sayed et al. [6] evaluated the incidence and the temporal extent of vaccination-related hypermetabolic lymph nodes with two different vaccine types (Pfizer-BioNTech or Vaxzevria). They found "hot" ipsilateral lymph nodes in 36% of cases up to 10-week post-vaccination, although intensity and frequency of vaccination-related hypermetabolic lymph nodes decreased over time. A correlation between hypermetabolic lymph nodes and gender as well as age was reported, as this finding was more common in women (51 versus 35% within 6 weeks) with less than 65 years**.** Although they reported a higher percentage of positive lymph nodes after Vaxzevria compared to Pfizer-BioNTech early after vaccination (within 6 weeks), this trend did not reach significance (53 versus 33%).

Sahin [7] reported the incidence of vaccination-related findings in patients who received Pfizer-BioNTech ($n = 24$) or Vaxzevria ($n = 182$) injection before [^{18}F]FDG PET/CT. A higher number of hypermetabolic lymph nodes were observed after Pfizer-BioNTech than Vaxzevria (35 versus 10%). Similarly, [^{18}F]FDG uptake at the administration site occurred more commonly with Pfizer-BioNTech than Vaxzevria (17 versus 9%). Deltoid muscle uptake was observed within 14 days. Regardless of the type of vaccine, positive lymph nodes were less frequent in elders (> 65 years). [^{18}F]FDG nodal uptake was higher after BioNTech than Vaxzevria (mean SUVmax of 2.44 ± 1.43 versus 1.67 ± 0.75, respectively).

Cohen et al. [8] described the incidence of vaccination-related findings, the pattern of [^{18}F]FDG uptake, and patients' characteristics in a large cohort of oncological subjects. Hypermetabolic lymph nodes (i.e., uptake > surrounding background) were defined as cancer-related, equivocal or vaccine-related. "Hot" vaccination-related lymph nodes were anatomically located and graded according to a 4-point scale. Accordingly, grade 1 described a mild uptake (SUVmax < 2.2); grade 2 corresponded to a moderate uptake ($2.2 \leq$ SUVmax < 4); grade 3 and grade 4 defined high [^{18}F] FDG uptake intensity (SUVmax ≥ 4) in normal-size and enlarged (> 8 mm for oval and > 10 mm for round) lymph nodes, respectively. Positive lymph nodes were observed less frequently in elderly (≥ 64 years) patients, and although after the second injection a second peak of incidence was observed in great elders (≥ 85 years), this datum should be carefully interpreted due to the small sample size. After the second injection, [^{18}F]FDG-avid lymph nodes were hotter

and larger than after the first administration with a higher percentage of grades 3 (14 and 8%, respectively) and 4 (13 and 4%, respectively).

Skawran et al. [9] compared the inflammatory reaction observed after Pfizer-BioNTech and Moderna vaccinations in patients examined with [^{18}F]FDG PET/CT. Firstly, lymph node positivity was visually and semi-quantitatively assessed ("hot" lymph node visible at MIP image with a minimum difference of 0.5 in SUVmax compared to the contralateral side), and thereafter the risk of malignancy was evaluated based on PET/CT appearance and patients' medical history. Overall, "hot" lymph nodes were considered to be related to vaccination in 52 out of 75 patients with positive PET/CT, and equivocal in 15 cases. Patients who received Moderna presented more frequently [^{18}F]FDG-avid lymph nodes than those vaccinated with Pfizer-BioNTech (72 and 43%, respectively).

Advani et al. [10] assessed the temporal metabolic response to mRNA vaccination in 262 patients imaged by [^{18}F]FDG PET/CT. Symptoms including sore arm and flu-like symptoms were reported in 6% of cases, and 47% of patients had positive lymph nodes, rarely enlarged (short axis > 1.0 cm in about 2% of patients). [^{18}F]FDG uptake was inversely related to the time between examination and vaccination—the shorter the interval, the highest the uptake (ΔSUVmax of 2.6 and 0.8 in the first and second week after vaccination, respectively; ΔSUVmax of 0.3 > 14 days). They suggested to postpone PET/CT imaging at least 2 weeks after vaccination, if possible, to avoid equivocal findings.

Adin et al. [11] reported their initial experience with [^{18}F]FDG findings related to mRNA vaccination in 68 patients. [^{18}F]FDG uptake in lymph nodes was graded by using the 5-point scale according to the Deauville criteria. A score higher than 2 was considered reactive. They reported [^{18}F]FDG uptake in axillar lymph nodes ipsilateral to the injection site in 13% of patients, mainly after the second vaccination (6 versus 3 cases), as well as in the deltoid muscle (12%).

Schroeder et al. [12] described the frequency and characteristics of vaccination-related findings in patients examined with [^{18}F]FDG and [^{11}C]Choline. They selected and analyzed only patients scanned twice, both before and after vaccination, and their pre-vaccination scan was used as control. An elongated morphology of deltoid uptake, along the muscular striations, and an uptake higher than the mediastinal blood pool were the criteria selected to define deltoid and nodal positivity, respectively. Deltoid and nodal uptake were observed in 14 and 10% of the patients, respectively. Positive lymph nodes occurred more frequently in patients imaged with [^{11}C]Choline (3/13) than with [^{18}F]FDG (4/54). Positive lymph nodes were located in the axilla (6/7) or in the supraclavicular fossa (1/7). Notably, this study was conducted when only older patients were approved to receive the COVID-19 vaccine; this selection bias may have affected the observed incidence of positive axillary lymph nodes.

Ferrari et al. [13] assessed vaccine-related lymph nodes in a large cohort of Italian patients imaged using different tracers including [^{18}F]Fluciclovine, [^{18}F]Fluorocholine, and [^{18}F]FDG. Lymph nodes visually defined as positive were graded according to a 3-point scale based on SUVmax values (SUVmax < 2.2, 2.2 ≤ SUVmax ≤ 4, and SUVmax > 4). Vaccine-related lymph nodes were observed in 27% of the population, presenting a moderate/high uptake in the majority of cases (89%). Positivity and intensity were inversely correlated to the time elapsed between the vaccination and the scan (less frequent and faint if > 20 days; positive nodes were most frequently observed after the second injection (66 versus 34%), and in young patients (37% in patents under 65 years versus 20% in patents over 65 years). No differences were observed with regard to the different type of vaccine administered.

Shin et al. [14] investigated [^{18}F]FDG findings related to vaccination against COVID-19 in 31 healthy health-care workers, vaccinated with Vaxzevria, who underwent PET/CT within a cancer screening program. All patients imaged within 22 days from vaccination presented both deltoid and nodal [^{18}F]FDG uptake. Deltoid muscle uptake was no more visible from 24 days post-vaccination onwards.

Seban et al. [15] investigated the relationship between [^{18}F]FDG nodal uptake and lymphocyte count in 260 patients. A SUVmax ratio between the ipsilateral and contralateral axillary lymph nodes > 1.5 was selected as criterion for positivity. Age (≤ 50 years), lymphocytes count (normal) and time elapsed between the last vaccine injection and the date of PET/CT (less than 30 days) were significantly and independently associated with [^{18}F]FDG nodal uptake. In a sub-analysis focused on women affected by breast cancer ($n = 145$), the absence of lymphopenia was the only independent factor significantly associated with hypermetabolic lymph nodes. Cohen et al. [16] explored the correlation between [^{18}F]FDG-avid lymph nodes and humoral immunity in patients affected by hematological malignancies, evaluating the possible effect of B cells-depleting therapy. Nodal positivity was defined as the presence of "hot" (i.e., uptake > surrounding background) lymph nodes and was graded according to a 4-point scale. Accordingly, grade 1 described a mild uptake (SUVmax < 2.2); grade 2 corresponded to a moderate uptake (2.2 ≤ SUVmax < 4); grade 3 and grade 4 defined high [^{18}F]FDG uptake intensity (SUVmax ≥ 4) in normal-size and enlarged lymph nodes, respectively. Incidence of positive lymph nodes was not different in lymphoma and myeloma patients (35 and 30%, respectively). [^{18}F]FDG-avid lymph nodes positively correlated with antibody-mediated immune response to COVID-19 vaccine (i.e., incidence was highest in patients with high anti-spike titers), and was barely found in patients exposed

to anti-CD20 antibody-containing therapy during the last year prior vaccination.

More recently, Cohen et al. [17] evaluated PET/CT findings related to the third vaccination in a cohort of 179 patients. They used the same criteria described above for image interpretation. Interestingly, they found that the incidence and the intensity of nodal [^{18}F]FDG uptake dropped down significantly starting from the fifth day.

Other abnormal findings

Siripongsatian et al. [18] reported preliminary data on patients who experienced neurological symptoms (e.g., headache, nausea, dizziness/drowsiness, paresthesia) after COVID-19 vaccination. Brain perfusion and metabolism were assessed at baseline (i.e., during symptoms) and within 1 week (i.e., control) through [^{15}O]Water PET and [^{18}F]FDG PET/MRI. Baseline and follow-up images were analyzed and compared using the MIM software. Differences were assessed as statistical deviations—using a threshold of 2.5—from the mean difference within the whole brain. Two patients showed changes in brain perfusion between baseline and follow-up scan (increased and decreased, respectively). Visual analysis of baseline [^{18}F]FDG imaging showed hypometabolism in the bilateral parietal cortex (from moderate to marked) in all patients, associated to hypo- or hypermetabolism in the bilateral cuneus (in 6 and 2 patients, respectively). The comparison between baseline and follow-up images exhibited metabolic differences (hypo/hypermetabolism) only in the five patients in whom neurological symptoms had recovered. Normal mediastinal blood pool, spleen and/or liver uptake were reported [7, 12, 14, 15]. No other finding, including [^{18}F]FDG foci suggestive for deep vein thrombosis or pulmonary embolism, was observed after Vaxzevria vaccination [14].

Discussion

The present systematic review showed that PET findings related to COVID-19 vaccination are mainly occasional signs—deltoid and ipsilateral axillar lymph nodes tracer uptake—detected in patients imaged for other reasons. The [^{18}F]FDG deltoid sign and hypermetabolic lymph nodes were described in 8–71% and 7–90% of the patients, respectively. Similarly, frequency of both deltoid and lymph nodes uptake of other tracers was greatly variable. These data suggested that this large variability was related to the time elapsed between vaccination and examination and the criterion selected to define positivity. Although exceptional cases of diseases occurred or worsened apparently after COVID-19 vaccination have been described in PET/CT literature [19–32], none of the included studies reported findings suggestive for systemic reaction. The only exception was the study of Siripongsatian et al. [18] who specifically evaluated a small series of patients who experienced neurological symptoms after COVID-19 vaccination. All types of COVID-19 vaccine, boosting a protective immune response through the production of neutralizing antibodies targeting SARS-CoV-2 spike S membrane glycoprotein [33], safely and positively impact on individual and global health, reducing the risk of severe infections. On the contrary, evidence about a higher risk of vaccine-related harm due to a cross-reaction between anti-spike S antibodies and human proteins is currently minimal and restricted to specific cases, even in patients affected by autoimmune diseases [34, 35]. Moreover, an increasing number of positive events apparently triggered by COVID-19 vaccination, including the spontaneous regression of some types of cancers, have been described [29, 36].

Although the majority of studies included in the present review focused on [^{18}F]FDG, local signs of inflammation have been also described with other tracers [2, 4, 12, 13]. Further ipsilateral supraclavicular and/or cervical "hot" lymph nodes have been reported [2, 12]. At the co-registered CT images, lymph nodes can be normal or, less frequently, enlarged [3, 8, 10, 16]. Deltoid muscle uptake may be visible up to 23 days post-vaccination [14]. The percentage of positivity was higher after the second dose with regard to both deltoid muscle and lymph-nodal uptake. The incidence of hypermetabolic lymph nodes appeared to be higher in the first few weeks after the injection and seems to decrease over time [2, 5, 6, 10, 13–15], although they may be visible even after 10 weeks [3, 6]. Vaccine-related axillar uptake following the third vaccination usually persists just for few days (up to 5 days), rarely interfering with images' interpretation [17]. There is no evidence about frequency and duration after the fourth COVID-19 vaccination [37–40]. Recently, Win et al. [41] described kinetics and activation of muscle and lymph nodes after adjuvanted and unadjuvanted vaccines through a cross sectional approach. They found different patterns of onset and duration of [^{18}F]FDG and [^{11}C]PBR28 uptake, demonstrating a causative effect between the observed activation and the response to immunization. That being said, the exact time-course of lymph-nodal activation induced by COVID-19 vaccines remains to be defined, being influenced by a number of factors including age and immune response status. Indeed, vaccine-related findings were detected more frequently in young and immunocompetent patients than in elderly and immunocompromised [4–8, 13, 15], as already described for influenza's vaccine [42, 43]. Furthermore, the lower PET/CT findings in elderly and immunocompromised were consistent with the reduced immunogenicity and, consequently, the lower detection of neutralizing antibodies after COVID-19 vaccination in these classes of patients [44, 45]. The type of vaccine may also influence the immune

response. The frequency of hypermetabolic ipsilateral axillar lymph nodes was lower with inactivated Coronavirus vaccine than with mRNA ones [7]. A higher frequency of hypermetabolic ipsilateral axillar lymph nodes was reported after Pfizer-BioNTech than Moderna vaccination [9]. From our results, it emerged that COVID-19 vaccination induced effects similar to those observed with other intramuscular vaccines such as seasonal flu, H1N1, and human papillomavirus. Deltoid [^{18}F]FDG uptake and hypermetabolic axillary lymph nodes have been reported in subjects who, close in time before the imaging assessment, underwent H1N1, seasonal flu, and human papillomavirus vaccinations [46–48]. Positive axillar lymph nodes have been reported up to 84 and 37 days after H1N1/seasonal flu and human papillomavirus vaccination, respectively [48, 49], and as for COVID-19, patients who received two doses of H1N1 vaccine presented a boosted immune response resulting in a further increased [^{18}F]FDG avidity compared to subject vaccinated only once [49].

It should be acknowledged that in the vast majority of cases vaccine-related findings, especially when the "double sign" (i.e., tracer uptake at the injection site and in axillary lymph nodes) is present, can be easily related to the history of recent vaccinations, thus not representing an issue for experienced readers (Fig. 3A), even when evaluating diseases in which axillary lymph nodes represent a region of interest such as breast cancer or lymphoma (Fig. 3B). Some articles go as far as suggesting postponing whenever possible the PET/CT scan to at least 2 weeks after vaccination. However, we believe that this additional caution may not be needed and that the organizational and clinical disadvantages of such a practice may outweigh the benefits, also considering that experienced readers deal with these and other potential interpretative pitfalls on a daily basis (e.g., uptakes related to concomitant infection or phlogistic foci, surgical procedure; Fig. 4). Moreover, as above-mentioned COVID-19 vaccinations may induce findings similar to those observed with other vaccinations such as H1N1 or seasonal flu (Fig. 5). Therefore, in case of typical findings, further examinations such as ultrasound or biopsy result unnecessary. That being said, a thorough collection of the patient's clinical data and vaccination history definitely help in making images interpretation less tricky.

In this review, PET/CT modality has been demonstrated to effectively image inflammatory process following vaccination. Indeed, PET/CT imaging is a valuable tool for the diagnosis and monitoring of inflammatory and infectious diseases. Inflammatory cells such as macrophages or granulation tissue, especially under activated conditions, have been demonstrated to express targets that can be visualized through several radiopharmaceuticals—[^{18}F]FDG, fibroblast activation protein inhibitors (FAPI), somatostatin receptor and CXCR4—targeting tracers [50–52].

PET/CT may target lung inflammation, such as acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) using [^{18}F]FDG and non-[^{18}F]FDG radiopharmaceuticals to non-invasively assess lung cellularity, and can, therefore, evaluate the inflammatory activity thus providing critical information about disease progression, response to therapy, and prognosis [53, 54]. Furthermore,

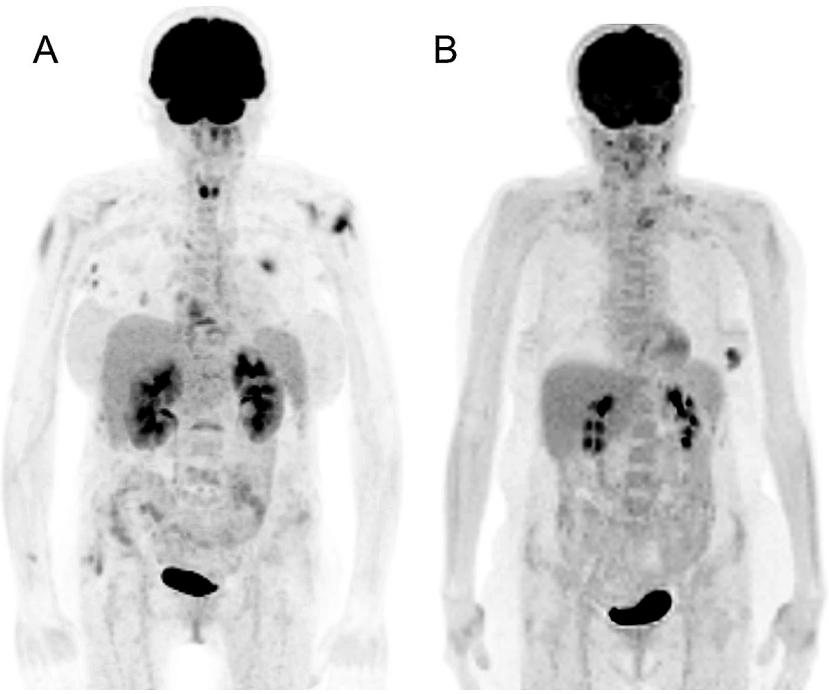


Fig. 3 Examples of vaccine-related findings in patients who underwent [^{18}F]FDG PET/CT for staging. Maximum intensity projection (MIP) image (**A**) shows the "double sign" in a multiple myeloma patient who received the third COVID-19 vaccination on the right side, 2 days prior PET/CT. MIP image (**B**) of a left breast cancer patient with omolateral "double sign", who has been injected with the fourth dose of COVID-19 vaccination on the left side, 7 days prior the scan

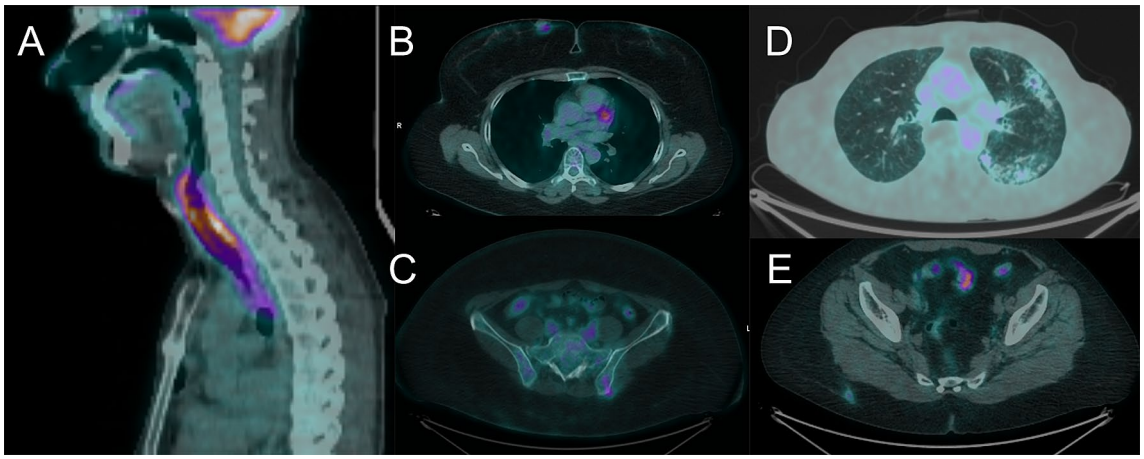


Fig. 4 Examples of potential interpretative PET/CT pitfalls in oncology. [^{18}F]FDG uptake along the trachea due to Aspergillosis in a patient with lymphoma during immunotherapy (**A**). [^{18}F]FDG uptake in the right breast related to post-bioptic hematoma in a lymphoma patient (**B**). Bone-marrow biopsy caused [^{18}F]FDG uptake in the left iliac bone in a lymphoma patient (**C**). Mild [^{11}C]Choline uptake in left lung due to pneumonitis (**D**). Moderate focal [^{68}Ga]Ga-DOTA-TOC uptake in the right gluteus related to somatostatin analogues injection in a patient with neuroendocrine tumor (**E**)

[^{18}F]FDG PET is an imaging method with growing interest for the diagnosis of sarcoidosis. In a recent metanalysis, [^{18}F]FDG PET/CT has been demonstrated to have a specificity similar to cardiac MRI in diagnosing cardiac sarcoidosis, although with a lower sensitivity [55]. Several studies assessed the role of [^{18}F]FDG PET/CT in the diagnosis of large-vessel vasculitis and in monitoring the disease's activity. Indeed, [^{18}F]FDG PET has shown good sensitivity and specificity for the diagnosis of large-vessel inflammation in giant cell arteritis and in Takayasu arteritis patients [56]. [^{18}F]FDG PET/CT is a useful diagnostic method in detecting active vascular graft infections with high diagnostic accuracy [57]. PET allows to identify infections involving valves, vessels, and devices while also spotting septic emboli and metastatic infections [58]. PET radiotracers can provide quantitative, targeted biomarkers which relate to the activity of molecular pathways and may expedite development of specific anti-inflammatory drugs.

In addition, distinct physiological conditions result from complex interactions among the various organs and systems. While PET imaging has been extensively applied in detecting focal lesions or diseases in oncology, neurology, and cardiology, its potential in the assessment of systemic abnormalities is seldom explored [59]. Long axial field-of-view PET/CT systems empowering dynamic scans hold the promise of transforming the investigation of these diseases [60]. Alternative to PET/CT, PET/MR imaging studies in infection and inflammation allow the integration of the multiparametric and functional information offered by both modalities. Synergy arising from their combination can provide further insights on multisystem alterations [61].

The combination of novel trends in radiopharmaceuticals' development, the progress in technology and new insights on the biological mechanisms that play a role in inflammation and infections, will likely provide in the near future new diagnostic and therapeutic biomarkers, advancing drug and vaccine development.

Conclusions

Awareness on vaccination status (in particular timing, patient characteristics, and concurrent therapies) and knowledge on the patterns of radiopharmaceutical uptake are necessary to avoid misinterpretation of PET/CT imaging findings. On the other hand, PET/CT using different tracers appears to be a powerful tool to investigate in vivo immune/inflammatory reactions to vaccinations and immunomodulating drugs in future studies.

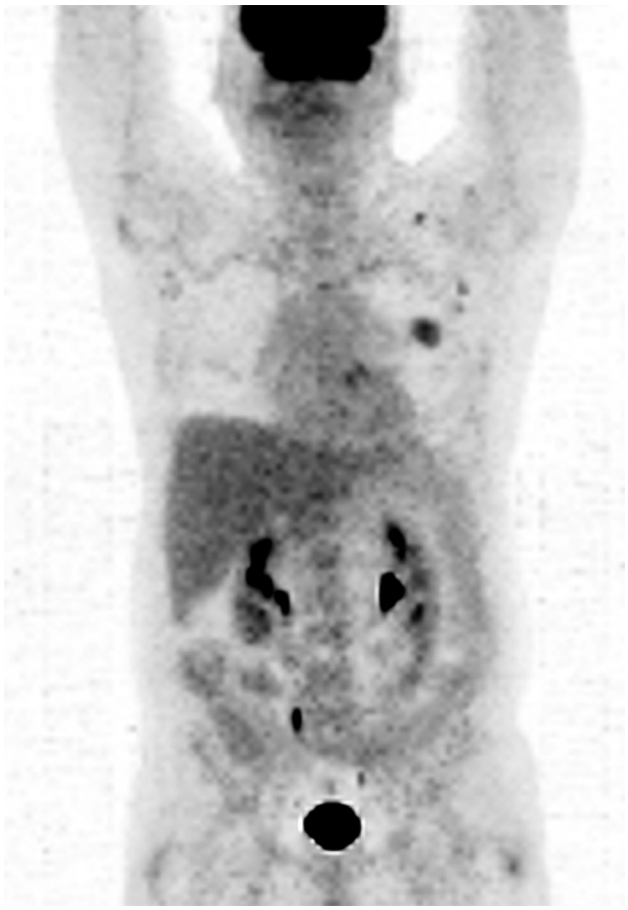


Fig. 5 [^{18}F]FDG PET/CT in a patient with a solitary pulmonary nodule in the left lung. MIP image shows high uptake in the left lung, moderate uptake in some left supraclavicular and axillary lymph nodes, and a faint "double sign" on the right side. The patient received, 5 days before the scan, the third dose of COVID-19 vaccination on the left side, and the H1N1 vaccine on the right one

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Declarations

Conflict of interest Prof. Chiti reports a fellowship grant from Sanofi, personal fees from AAA, Blue Earth Diagnostics and General Electric Healthcare, outside the submitted work. The other authors do not report any conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable for a systematic review.

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