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Diagnostic performance of ^{18}F -FDG PET/CT in patients with spinal infection: a systematic review and a bivariate meta-analysis

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Abstract

Purpose Diagnosis of spinal infection (SI) is challenging and usually requires multiple tests. We aimed to perform a systematic review and a bivariate meta-analysis on the diagnostic role of ^{18}F -FDG PET/CT in patients with SI.

Methods A comprehensive literature search of studies published through February 2019 in PubMed/MEDLINE and Cochrane library databases was carried out. Studies investigating the diagnostic performance of ^{18}F -FDG PET/CT in patients with SI were eligible for inclusion in the qualitative analysis. For the quantitative analysis, pooled sensitivity, specificity, positive and negative likelihood ratio (LR+ and LR−) and diagnostic odds ratio (DOR) of ^{18}F -FDG PET/CT in patients with suspected SI were calculated on a per examination-based analysis. Pooled data were presented with 95% confidence intervals (95% CI).

Results Twenty-six articles (833 patients) using ^{18}F -FDG PET/CT were eligible for the qualitative analysis. Twelve studies (396 patients) were selected for the meta-analysis. Overall, ^{18}F -FDG PET/CT demonstrated a very good diagnostic performance in patients with SI and several studies underlined the value of ^{18}F -FDG PET/CT in assessing the response to treatment. The bivariate meta-analysis on ^{18}F -FDG PET/CT in patients with suspected SI provided the following results: sensitivity 94.8% (95% CI 88.9–97.6%) and specificity 91.4% (95% CI 78.2–96.9%). The pooled LR+, LR− and DOR were 4.7 (95% CI 2.9–7.7), 0.11 (95% CI 0.07–0.16) and 63.4 (95% CI 28.9–139), respectively. No significant heterogeneity or publication bias was found.

Conclusion ^{18}F -FDG PET/CT demonstrated a very good diagnostic performance in patients with SI and can be used in patients in which MRI cannot be performed or is non-diagnostic or inconclusive. Several studies underlined the value of ^{18}F -FDG PET/CT in assessing the response to treatment in patients with SI. Overall, larger multicentre and prospective studies and cost-effectiveness analyses are warranted.

Keywords PET/CT · spinal infection · meta-analysis · systematic review · diagnosis

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Introduction

Spinal infections (SI) are a heterogeneous group of disorders that can arise from haematogenous seeding of the axial skeleton from remote infected *foci* (primary SI) or caused by direct inoculation during spinal instrumentation or contiguous spread in patients with pressure sores (secondary SI) [1].

The incidence of SI is on a steady rise and has been reported to reach 6.5/100,000 cases each year [1]. The most frequent SI is spondylodiscitis (intervertebral disc infection with associated vertebral body osteomyelitis), but other types of SI include discitis (isolated intervertebral disc infection), spondylitis (vertebral end-plate infection), septic facet joint infection and epidural abscess. Further spread of infection into adjoining soft tissues accounts for the development of secondary epidural abscesses, paravertebral muscle abscesses and prevertebral collections [1, 2].

Predisposing factors for developing SI include immunodeficiency, drug abuse, widespread use of broad-spectrum antibiotics, corticosteroids, and immunosuppressive drugs, diabetes mellitus and spinal surgery [1–3]. SI can be bacterial, fungal, parasitic or viral in origin and every effort should be made to establish a microbiological diagnosis [1–3]; in fact, diagnostic cultures are central to directing antimicrobial therapy [2].

Despite the advances in diagnosis and therapy of SI, they remain serious diseases with potentially dangerous complications; therefore, it is relevant to perform an early diagnosis of SI before massive neurologic symptoms occur [1–4]. Diagnosis of SI is challenging and usually requires multiple tests, including clinical examination, laboratory tests, a combination of imaging techniques and biopsy samples for pathogen detection [1–4].

Symptoms of SI are often non-specific and this can delay the diagnosis [4]. Constitutional symptoms such as malaise, night sweats, back pain and weight loss are common presenting symptoms; fever is a frequent but inconsistent feature present in about half of the patients with SI [1]. Range of motion of the spine is often limited due to localized spinal pain and muscle spasm [4]. Because of the low specificity of many of these clinical findings and the potential catastrophic outcomes, a high level of suspicion and a thorough diagnostic work-up is required [1, 2].

Inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are helpful in screening patients with back pain; unfortunately, they are non-specific since they can also be elevated due to other causes [1, 2].

Plain radiographs are usually normal during the early phases of an SI and become positive only in advanced stages [1, 2]. Contrast-enhanced magnetic resonance imaging (MRI) is the imaging modality of choice for diagnosis of SI if not contraindicated [1, 2, 5, 6] and is useful to evaluate the extent of the infection, providing superior imaging of paraspinal soft tissue and epidural space [2, 5, 6]. The use of gadolinium is

essential in differentiating between a phlegmon and an epidural abscess and, if possible, should always be added [1, 5, 6]. However, MRI is sometimes non-specific and cannot always differentiate infections from degenerative end-plate abnormalities or postoperative changes. Moreover, MRI interpretation is hampered by metallic implant-associated artefacts [1, 5, 6].

Nuclear medicine and radiological imaging are complementary techniques in the setting of musculoskeletal infections [7, 8]. In particular, hybrid or multimodality imaging using fluorine-18-fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) could be very useful in patients with suspected SI [6–9]. ^{18}F -FDG is a glucose analogue that usually shows a high uptake in SI. Several factors may influence ^{18}F -FDG uptake in infection: there are both an increased number and a raised expression of glucose transporters in activated inflammatory cells, as well as an increased affinity of these transporters for glucose [6]. ^{18}F -FDG uptake in SI is usually higher than normal bone marrow; furthermore, degenerative bone changes generally show only faintly ^{18}F -FDG increased uptake, whereas ^{18}F -FDG uptake in traumatized bone usually normalizes within 3–4 months [6]. Compared with CT and MRI, ^{18}F -FDG uptake is minimally hampered by metallic implant-associated artefacts, especially when also looking at the non-attenuated images [6].

Previous published meta-analyses have already evaluated the diagnostic performance of ^{18}F -FDG PET in patients with spondylodiscitis; however, they were based upon mixing data coming from ^{18}F -FDG PET and ^{18}F -FDG PET/CT studies [10–12]. This systematic review and meta-analysis examines the diagnostic performance of hybrid ^{18}F -FDG PET/CT in patients with SI, including all types of SI (not only patients with spondylodiscitis) and excluding articles not performing hybrid ^{18}F -FDG PET/CT, in order to provide timely evidence-based data in this setting.

Methods

This systematic review and meta-analysis conforms to the statement on ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy studies’ (PRISMA-DTA), which describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses of diagnostic studies [13, 14].

Search strategy

Two authors (GT and MP) performed a comprehensive computer literature search of PubMed/MEDLINE and Cochrane Library databases to find relevant retrospective or prospective published articles on the diagnostic performance of ^{18}F -FDG PET/CT in patients with SI. A search algorithm was constructed using a combination of the following terms: A) ‘PET’ OR

‘positron’ OR ‘FDG’ OR ‘fluorodeoxyglucose’ AND B) ‘spondylodiscitis’ OR ‘spondylodiskitis’ OR ‘discitis’ OR ‘diskitis’ OR ‘spondylitis’ OR ‘vertebral osteomyelitis’ OR ‘spinal osteomyelitis’ OR ‘spinal infection*’ OR ‘spine infection*’ OR ‘vertebral infection*’. The search was carried out from inception to February 28, 2019 without language restriction. To expand the search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets of studies were only included in the qualitative analysis (systematic review) if investigating the diagnostic performance of ^{18}F -FDG PET/CT in human patients with known or suspected SI. Criteria for excluding studies were as follows: (a) articles not within the field of interest of this review (including those who evaluated ^{18}F -FDG PET only); (b) review articles, editorials or letters, comments and conference proceedings; (c) case reports. Articles with insufficient data to reassess the diagnostic performance or with possible patient overlap were also excluded from the quantitative analysis (meta-analysis). In case of possible patient overlap, the most complete article was selected. Two researchers (GT and MP) independently reviewed titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. Then, the same two researchers individually examined the full text of the remaining potentially eligible articles to assess their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data extraction

For each included study, information was collected concerning basic study data (authors, year of publication, country of origin, study design), patient characteristics (type and number of patients undergoing PET/CT, mean or median age, sex ratio), indication of ^{18}F -FDG PET/CT (diagnosis or assessment of treatment response), technical aspects (hybrid imaging modality, mean injected activity, time interval between radiotracer injection and image acquisition, image analysis and other imaging modalities used for comparison) and diagnostic performance data on ^{18}F -FDG PET/CT.

Quality assessment

Critical appraisal of the overall quality of the studies included in the systematic review was based on the revised ‘Quality Assessment of Diagnostic Accuracy Studies’ tool (QUADAS-2) [15]. This tool evaluates four domains—patient selection, index test, reference standard and flow and timing—in terms of risk of bias. The first three domains are also assessed in terms of concerns regarding applicability [15].

Statistical analysis

Extraction of data regarding sensitivity and specificity, positive and negative likelihood ratio (LR+ and LR−) and diagnostic odds ratio (DOR) of ^{18}F -FDG PET/CT in patients with suspected SI was carried out from individual studies on a per examination-based analysis. A bivariate random effects statistical model was used to calculate pooled data, which were presented with 95% confidence intervals (95% CI). Furthermore, a summary receiver operating characteristic (sROC) curve was constructed. Estimations of heterogeneity and publication bias were determined by using the I-square index (I^2) [16] and Egger’s test [17], respectively. Statistical analyses were performed using OpenMetaAnalyst software that is based on R as the underlying statistical engine. OpenMetaAnalyst is funded by the Agency for Healthcare Research and Quality (AHRQ).

Results

Literature search

The comprehensive computer literature search from PubMed/MEDLINE and Cochrane Library database yielded a total of 319 articles. After reviewing titles and abstracts, 294 articles were excluded as follows: 209 were not in the field of interest of this review; 43 were reviews, editorials or letters and 42 were case reports. Finally, twenty-five articles were selected and retrieved in full-text version [18–42]. One additional study was found screening the references of these articles [43]. Therefore, 26 articles (833 patients) on the diagnostic performance of ^{18}F -FDG PET/CT were identified as eligible for the qualitative analysis [18–43]. Of them, 14 articles were excluded from the quantitative analysis: 12 for insufficient data to reassess the diagnostic performance [21, 26, 30–33, 35, 38–42] and two for possible patient data overlap [25, 34]. Finally, 12 studies including 396 patients with suspected SI were selected as relevant for the meta-analysis on the diagnostic performance of ^{18}F -FDG PET/CT [18–20, 22–24, 27–29, 36, 37, 43] (Fig. 1).

The characteristics of the studies included in the systematic review are summarized in Tables 1, 2, 3 and 4. Overall quality assessment of the studies is reported in Fig. 2.

Qualitative analysis (systematic review)

Basic study and patient characteristics

Twenty-six full-text articles published between 2007 and 2019 were selected for the systematic review. Several countries from Europe, North America and Asia were represented.

Fig. 1 Flowchart of the search for eligible studies on the diagnostic performance of ^{18}F -FDG PET/CT in patients with spinal infection

About half of the studies were prospective and most of them were single-centre studies.

The patient population included individuals with known or suspected spondylodiscitis or other SI. Mean age and sex ratio were quite heterogeneous amongst the included studies (Table 1). As shown in Table 1, ^{18}F -FDG PET/CT was always performed for diagnostic purpose and in about one-third of the studies was used also for evaluating treatment response.

Technical aspects

Closer inspection of the Table 2 showed heterogeneous technical aspects amongst the included studies. ^{18}F -FDG PET/CT was performed using a low-dose CT acquisition in most cases. The reported mean injected activity of ^{18}F -FDG ranged between 185 and 555 MBq (in absolute values) and between 3 and 5.7 MBq/kg. The time interval between radiotracer injection and image acquisition was highly variable ranging from 30 to 90 min after radiopharmaceutical injection.

The PET image analysis was performed by using qualitative (visual) analysis in all studies: a patient was usually considered positive for SI at ^{18}F -FDG PET/CT when the uptake in the spinal target region was higher than bone marrow uptake in adjacent vertebrae and/or the uptake in soft tissue was present. As can be seen from the Table 2, the visual score was used as imaging analysis in all studies, except one not reporting data [31] and was mainly performed considering intensity, site and pattern of radiopharmaceutical uptake. Additional semi-quantitative analysis was carried out in almost all studies and the most frequent semi-quantitative parameter was the maximal standardized uptake value (SUV_{max}) of the target region [18, 19, 21, 23–30, 32, 33, 35–42]. Moreover, the semi-quantitative evaluation was performed using other parameters (i.e. $\text{SUV}_{\text{ratio}}$: ratio between ^{18}F -FDG uptake in the target region and uptake in a reference region) in nine studies [18, 23, 26, 27, 36–38, 41, 42]. Finally, in almost half of the studies [18, 20–27, 29, 33, 34, 36, 37, 42], the diagnostic performance of ^{18}F -FDG PET/CT was compared also with other imaging tests, mostly MRI.

Table 1 Basic study and patient characteristics

Authors	Year	Country	Study design	Type of patients evaluated	No. of patients undergoing ¹⁸ F-FDG PET/CT	Age (years)	Male (%)	Number of patients with diagnosis of spinal infection	¹⁸ F-FDG PET/CT performed for diagnosis	¹⁸ F-FDG PET/CT performed for treatment response assessment
Follenfant et al. [18]	2019	France	Retrospective single centre	Patients with suspected chronic spinal implant infections	44	Median 65	50	22 (50%)	Yes	No
Yu et al. [19]	2018	Canada	Prospective single centre	Patients with suspected spinal infection	149	Median 59	64	NR	Yes	Yes
Kouijzer et al. [20]	2018	The Netherlands	Prospective bicentric	Patients with suspected vertebral osteomyelitis	32	Mean 67 Range 43–92	69	20 (63%)	Yes	No
Bassetti et al. [21]	2017	Italy	Retrospective single centre	Patients with spondylodiscitis	30	Mean 57	50	30 (100%)	Yes	Yes
Smids et al. [22]	2017	The Netherlands	Retrospective multicentric	Patients with suspected spondylodiscitis	68	Median 64 Range 10–88	51	49 (72%)	Yes	No
Dauchy et al. [23]	2016	France	Prospective single centre	Patients with suspected spinal infection relapse	30	Median 61.5	30	7 (23%)	Yes	No
Gunes et al. [24]	2016	Turkey	Retrospective single centre	Patients with suspected spondylodiscitis	32	Mean 57 Range 22–84	59	32 (100%)	Yes	No
Riccio et al. [25]	2015	Canada	Prospective single centre	Patients with suspected spinal infection	28	Mean 56 Range 39–79	64	20 (71%)	Yes	Yes
Niccoli Asabella et al. [26]	2015	Italy	Retrospective single centre	Patients with spondylodiscitis	15	Mean 65 Range 38–83	80	15 (100%)	Yes	Yes
Fuster et al. [27]	2015	Spain	Prospective single centre	Patients with suspected haematogenous spondylodiscitis	26	Mean 59 Range 19–86	54	18 (69%)	Yes	No
Inanami et al. [28]	2015	Japan	Retrospective multicentric	Patients with suspected spinal infection after surgery	14	Mean 67 Range 40–86	64	8 (57%)	Yes	No
Nakahara et al. [29]	2015	Japan	Retrospective single centre	Patients with suspected spinal infection	9	Mean 65 Range 40–84	89	8 (89%)	Yes	No
Dureja et al. [30]	2014	India	Prospective single centre	Patients with uncomplicated spinal tuberculosis	33	Mean 41 Range 22–81	42	33 (100%)	Yes	Yes
Fransen et al. [31]	2014	The Netherlands	Retrospective single centre	Patients with spondylodiscitis	12	Mean 69	NR	12 (100%)	Yes	No
Bagrosky et al. [32]	2013	USA	Retrospective single centre	Patients with suspected spinal fusion hardware infection	20	Mean 16.3 Range 6–31	45	6 (30%)	Yes	No
Ioannou et al. [33]	2013	Greece	Prospective single centre	Patients with brucellar spondylodiscitis	10	Median 58.5 Range 37–87	70	10 (100%)	Yes	Yes
Fuster et al. [34]	2012	Spain	Prospective single centre	Patients with suspected spondylodiscitis	34	Mean 59 Range 19–86	56	18 (53%)	Yes	No
Nanni et al. [35]	2012	Italy	Prospective single centre	Patients with spondylodiscitis	38	Mean 64	47	38 (100%)	Yes	Yes
Seifen et al. [36]	2012	Austria	Retrospective single centre	Patients with suspected spondylodiscitis	38	Mean 67 Range 34–90	53	22 (58%)	Yes	No
Skanjeti et al. [37]	2012	Italy	Retrospective single centre	Patients with suspected or confirmed spondylodiscitis	33	Mean 57	54	14 (58%)	Yes	Yes
Kim et al. [38]	2011	Korea	Retrospective single centre	Patients with spondylodiscitis	23	Mean 58 Range 20–81	35	23 (100%)	Yes	No
Gasbarrini et al. [39]	2011	Italy	Prospective single centre	Patients with spinal infections	25	Median 64 Range 20–85	68	25 (100%)	Yes	Yes
Ito et al. [40]	2010	Japan	Retrospective single centre	Patients with spondylodiscitis	29	Mean 63 Range 27–90	48	29 (100%)	Yes	No

Table 1 (continued)

Authors	Year	Country	Study design	Type of patients evaluated	No. of patients undergoing ^{18}F -FDG PET/CT	Age (years)	Male (%)	Number of patients with diagnosis of spinal infection	^{18}F -FDG PET/CT performed for diagnosis	^{18}F -FDG PET/CT performed for treatment response assessment
Kim et al. [41]	2009	Korea	Prospective single centre	Patients with spinal infections	30	Mean 55.5 Range 19–81	37	30 (100%)	Yes	Yes
Lee et al. [42]	2009	Korea	Prospective single centre	Patients with spondylodiscitis	22	Mean 58 Range 19–81	32	22 (100%)	Yes	No
Hartmann et al. [43]	2007	Germany	Retrospective single centre	Patients with suspected chronic post-traumatic spinal infection	9	Mean 61 Range 17–80	78	7 (78%)	Yes	No

^{18}F -FDG, fluorine-18 fluorodeoxyglucose; NR, not reported; PET/CT, positron emission tomography/computed tomography

Main findings

Table 3 presents the diagnostic accuracy data of ^{18}F -FDG PET/CT in patients with known or suspected SI from each study. Overall, ^{18}F -FDG PET/CT demonstrated a good diagnostic accuracy in the diagnosis of SI (from 75 to 100%).

At visual assessment of PET images, inter-observer agreement was good with a kappa coefficient ranging from 0.75 to 0.76 [18, 23].

In patients with spinal hardware infection, ^{18}F -FDG PET/CT showed intense, confluent and increased radiopharmaceutical uptake in the soft tissues and bone immediately adjacent to the spine hardware at multiple contiguous levels, with or without additional increased ^{18}F -FDG uptake at the bone-hardware interface of one or more interpedicular screws [32]. Conversely, PET/CT findings of non-infectious hardware complications as hardware loosening/bone remodelling consisted of focal ^{18}F -FDG uptake adjacent to one or two hooks, screws or anchors usually at the upper or lower portion of the spinal hardware construct [32].

The most common causes of false-positive findings for SI at ^{18}F -FDG PET/CT were inflammatory or degenerative spondyloarthropathy, recent vertebral fractures, postoperative inflammation in previously operated patients or bone tumours. By contrast, false negatives can be due to some cases of infection with low-virulence bacteria, previous antimicrobial therapy, epidural abscesses or extensive instrumented arthrodesis in previously operated patients.

In several articles, multilevel SI and/or additional extra-spinal sources of infection or inflammation were identified by ^{18}F -FDG PET/CT in some patients [19, 20, 22, 27, 30, 32–34, 36, 40].

In one article performing dual-time PET/CT acquisition protocols, no statistical difference was found between early and delayed SUV_{max} results in patients with SI [24].

In most of the articles comparing ^{18}F -FDG PET/CT and MRI, the diagnostic accuracy of ^{18}F -FDG PET/CT in patients with SI was found higher than MRI [18, 22–24, 27, 29, 36], whereas only two articles reported a superiority of MRI compared with ^{18}F -FDG PET/CT without a statistically significant difference [20, 37]. Furthermore, ^{18}F -FDG PET/CT showed higher sensitivity in diagnosing paravertebral and psoas abscesses compared with MRI, but the latter was more valuable in detecting epidural and spinal abscesses than ^{18}F -FDG PET/CT [20, 22].

Additionally, a prospective study demonstrated a superior diagnostic accuracy of ^{18}F -FDG PET/CT compared with planar bone scintigraphy plus Gallium-67 single-photon emission computed tomography (^{67}Ga -SPECT)/CT in this setting [34].

Only one study described the clinical impact of ^{18}F -FDG PET/CT in patients with SI showing that this examination

Table 2 Technical aspects of ^{18}F -FDG PET/CT in the included studies

Authors	Hybrid imaging modality	Mean injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Other imaging modalities used for comparison
Follenfant et al. [18]	PET/CT (low-dose CT)	NR	60 min	Visual and semi-quantitative (SUV_{max} , SUV ratio)	MRI
Yu et al. [19]	PET/CT (low-dose CT)	550 MBq	60 min	Visual and semi-quantitative (SUV_{max})	-
Kouijzer et al. [20]	PET/CT (low-dose CT)	3.3 MBq/kg	60 min	visual	MRI
Basseti et al. [21]	PET/CT (low-dose CT)	5.5 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max})	MRI
Smids et al. [22]	PET/CT (low-dose CT)	200 MBq	60 min	visual	MRI
Dauchy et al. [23]	PET/CT (low-dose CT)	NR	60 min	Visual and semi-quantitative (SUV_{max} , SUV ratio)	MRI
Gunes et al. [24]	PET/CT (low-dose CT)	370–740 MBq	90 min (dual-time imaging)	Visual and semi-quantitative (SUV_{max})	MRI
Riccio et al. [25]	PET/CT (low-dose CT)	350 MBq	at least 30 min	Visual and semi-quantitative (SUV_{max})	MRI
Niccoli Asabella et al. [26]	PET/CT (low-dose CT)	3.7 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max} , MTV, TLG)	MRI
Fuster et al. [27]	PET/CT (low-dose CT)	4.1 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max} , SUV ratio)	MRI
Inanami et al. [28]	PET/CT (low-dose CT)	370 MBq	60 min	Visual and semi-quantitative (SUV_{max})	-
Nakahara et al. [29]	PET/CT (low-dose CT)	400 MBq	60 min	Visual and semi-quantitative (SUV_{max})	MRI
Dureja et al. [30]	PET/CT (contrast-enhanced CT)	5.5 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max})	-
Fransen et al. [31]	PET/CT (low-dose CT)	NR	NR	NR	NR
Bagrosky et al. [32]	PET/CT (low-dose CT)	5.2 MBq/kg	50 min	Visual and semi-quantitative (SUV_{max})	-
Ioannou et al. [33]	PET/CT (low-dose CT)	370–555 MBq	60 min	Visual and semi-quantitative (SUV_{max})	MRI
Fuster et al. [34]	PET/CT (low-dose CT)	4.1 MBq/kg	60 min	visual	bone scintigraphy and ^{67}Ga -SPECT/CT
Nanni et al. [35]	PET/CT (low-dose CT)	3–5.7 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max})	-
Seifen et al. [36]	PET/CT (low-dose CT)	4 MBq/kg	60 min	Visual and semi-quantitative (SUV_{max} , SUV ratio)	MRI, bone scintigraphy
Skanjeti et al. [37]	PET/CT (low-dose CT)	222–370 MBq	60 min	Visual and semi-quantitative (SUV_{max} , SUV_{mean})	MRI
Kim et al. [38]	PET/CT (low-dose CT)	NR	60 min	Visual and semi-quantitative (SUV_{max} , spleen-to-liver and spleen-to-bone marrow ratios)	-
Gasbarrini et al. [39]	PET/CT (low-dose CT)	NR	NR	Visual and semi-quantitative (SUV_{max})	-
Ito et al. [40]	PET/CT (low-dose CT)	185–370 MBq	60 min	Visual and semi-quantitative (SUV_{max})	-
Kim et al. [41]	PET/CT (low-dose CT)	NR	60 min	Visual and semi-quantitative (SUV_{max} , SUV_{mean})	-
Lee et al. [42]	PET/CT (low-dose CT)	370 MBq	60 min (dual-time imaging)	Visual and semi-quantitative (SUV_{max} , SUV_{mean})	MRI
Hartmann et al. [43]	PET/CT (low-dose CT)	340–400 MBq	50–60 min	Visual	-

^{18}F -FDG, fluorine-18 fluorodeoxyglucose; CT, computed tomography; MBq, megabecquerel; min, minutes; MRI, magnetic resonance imaging; MTV, metabolic tumour volume; NR, not reported; PET, positron emission tomography; SPECT, single-photon emission computed tomography; SUV_{max} , maximal standardized uptake value; SUV_{mean} , mean standardized uptake value; SUV ratio, lesion to background uptake ratio; TLG, total lesion glycolysis

Table 3 Diagnostic performance of ^{18}F -FDG PET/CT in patients with suspected spinal infection

Authors	Reference standard for diagnostic performance assessment	True positive	False positive	True negative	False negative	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy of ^{18}F -FDG PET/CT	Diagnostic accuracy of MRI
Follenfant et al. [18]	Clinical or lab and follow-up	19	5	22	3	86.4%	81.5%	79.2%	88%	83.7%	71.4%
Yu et al. [19]	Clinical or lab or other imaging and follow-up	42	0	22	1	97.7%	100%	100%	95.7%	98.5%	NA
Kouijzer et al. [20]	Clinical or lab or other imaging and follow-up	20	2	10	0	100%	83.3%	90.9%	100%	93.8%	96.9%
Basseti et al. [21] ^o	NA	30	NA	NA	0	100%	NA	NA	NA	NA	NA
Smids et al. [22]	Clinical or lab and follow-up	47	1	18	2	95.9%	94.7%	97.9%	90%	95.6%	72%
Dauchy et al. [23]	Clinical or lab and follow-up	6	4	19	1	85.7%	82.6%	60%	95%	83.3%	63%
Gunes et al. [24]	Clinical or lab or other imaging	32	0	0	0	100%	NA	100%	NA	100%	96.9%
Riccio et al. [25] [*]	Clinical or lab and follow-up	20	0	6	0	100%	100%	100%	100%	100%	NA
Niccoli Asabella et al. [26] ^o	NA	15	NA	NA	0	100%	NA	NA	NA	NA	NA
Fuster et al. [27]	Clinical or lab and follow-up	15	1	7	3	83.3%	87.5%	93.8%	70%	84.6%	76.9%
Inanami et al. [28]	Clinical or lab	8	0	6	0	100%	100%	100%	100%	100%	NA
Nakahara et al. [29]	Lab	8	0	1	0	100%	100%	100%	100%	100%	88.9%
Dureja et al. [30] ^o	NA	33	NA	NA	0	100%	NA	NA	NA	NA	NA
Fransen et al. [31] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bagrosky et al. [32] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ioannou et al. [33] ^o	NA	10	NA	NA	0	100%	NA	NA	NA	NA	NA
Fuster et al. [34] [*]	Clinical or lab and follow-up	16	2	14	2	88.9%	87.5%	88.9%	87.5%	88.2%	NA
Nanni et al. [35] ^o	NA	38	NA	NA	0	100%	NA	NA	NA	NA	NA
Seifen et al. [36]	Clinical or lab and follow-up	18	0	16	4	81.8%	100%	100%	80%	89.5%	74.1%
Skanjeti et al. [37]	Clinical or lab or other imaging and follow-up	13	5	5	1	92.9%	50%	72.2%	83.3%	75%	81.3%
Kim et al. [38] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gasbarrini et al. [39] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ito et al. [40] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kim et al. [41] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lee et al. [42] ^o	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hartmann et al. [43]	Lab	7	0	2	0	100%	100%	100%	100%	100%	NA

^{*}Excluded from the meta-analysis for possible patient overlap^oExcluded from the meta-analysis for missing data to reassess sensitivity and specificity; *Lab*, laboratory data (microbiological or histological data); *NA*, not available or calculable; *MRI*, magnetic resonance imaging; *NPV*, negative predictive value; *PET*, positron emission tomography; *PPV*, positive predictive value

Table 4 Role of ^{18}F -FDG PET/CT for treatment response assessment in patients with spinal infections

Authors	Sensitivity	Specificity	PPV	NPV	Main findings
Yu et al. [19]	NR	100%	NR	97%	Pattern-based interpretation of ^{18}F -FDG PET/CT was accurate in differentiating persistent spinal infection from nonseptic causes of persistent symptoms with high NPV.
Basseti et al. [21]	NR	NR	NR	NR	^{18}F -FDG PET/CT could contribute to the early determination of the response to therapy in patients with spondylodiscitis. All treated patients showed a significant reduction of SUV_{max} over time.
Riccio et al. [25]	NR	NR	NR	NR	The ^{18}F -FDG uptake pattern was critical for accurate interpretation of treatment response in patients with spinal infection. Patients with a poor clinical response had persistent ^{18}F -FDG uptake in bone and/or soft tissue on follow-up. Patients with good clinical response had ^{18}F -FDG uptake confined to the margins of the destroyed disc.
Niccoli Asabella et al. [26]	NR	NR	NR	NR	^{18}F -FDG PET/CT was useful to detect the early response to therapy in patients with spondylodiscitis. All treated patients showed a reduction of semi-quantitative PET/CT parameters (responders) and this reduction was relevant also in patients with positive post-treatment MRI. This could be probably due to the tissue remodelling in the early post-treatment phase, resulting positive at MRI and negative at ^{18}F -FDG PET/CT.
Dureja et al. [30]	NR	NR	NR	NR	^{18}F -FDG PET/CT could have a potential role for noninvasive evaluation of treatment response in patients with spinal tuberculosis. Changes of ^{18}F -FDG uptake (SUV_{max}) correlated well with clinical markers of response and provided more objective evidence of response rather than the non-specific biochemical markers.
Ioannou et al. [33]	NR	NR	NR	NR	^{18}F -FDG PET/CT could be a complementary method for determining the efficacy of treatment in patients with brucellar spondylitis. Successful treatment was associated with a significant decrease in SUV_{max} .
Nanni et al. [35]	82%	82%	NR	NR	^{18}F -FDG PET/CT could be useful for the early identification of treatment responders amongst patients with spondylodiscitis, in particular in those with a non-informative biochemical test for inflammatory markers at diagnosis. Change of SUV_{max} provided the highest sensitivity and specificity values for identifying treatment responders.
Skandjati et al. [37]	90%	81.8%	81.8%	90%	^{18}F -FDG PET/CT was an accurate imaging method in the assessment of treatment response in patients with spondylodiscitis. Specificity and accuracy values of ^{18}F -FDG PET/CT in treatment response assessment were significantly higher compared to those of MRI.
Gasbarrini et al. [39]	NR	NR	NR	NR	^{18}F -FDG PET/CT could be useful for the early identification of treatment responders amongst patients with spondylodiscitis, in particular in those with a non-informative biochemical test for inflammatory markers at diagnosis.
Kim et al. [41]	100%	76.9%	NR	NR	^{18}F -FDG PET/CT could be useful for discrimination of residual and non-residual spinal infection after treatment. Amongst the various semi-quantitative PET indexes, change of SUV_{max} was a powerful predictor of residual spinal infection.

CT, computed tomography; NR, not reported; MRI, magnetic resonance imaging; PET, positron emission tomography; PPV, positive predictive value; SUV_{max} , maximal standardized uptake value

provided additional information in 72% of cases and changed the clinical management in 52% of patients with SI [40].

Finally, the role of ^{18}F -FDG PET/CT in evaluating the treatment response in patients with SI was assessed in just over a third of the articles [19, 21, 25, 26, 30, 33, 35, 37, 39, 41] and the main findings are summarized in Table 4. Overall, ^{18}F -FDG PET/CT was useful to detect the early response to therapy in patients with SI. Change of SUV_{max} provided the highest sensitivity and specificity values for identifying treatment responders [19, 21, 25, 26, 30, 33, 35, 37, 39, 41]. Some prospective studies calculated the diagnostic performance of delta- SUV_{max} ((SUV_{max} before treatment— SUV_{max} after treatment)/ SUV_{max} before treatment) in discriminating patients with SI who responded to the treatment [35, 41]. Nanni et al. showed that a cutoff of delta- SUV_{max} of 34% demonstrated a sensitivity of 82% and a specificity of 82% in differentiating treatment responders from non-responders

[35]. Kim et al. found that using a cutoff of delta- SUV_{max} of 43% the patient-based sensitivity and specificity was 100% and 76.9%, respectively [41].

Quantitative analysis (meta-analysis)

Twelve studies including 396 patients were selected for the meta-analysis on the diagnostic performance of ^{18}F -FDG PET/CT in patients with suspected SI by using visual analysis [18–20, 22–24, 27–29, 36, 37, 43]. Histological and/or microbiological findings or clinical follow-up were used as reference standard. Results of the meta-analysis are presented in Figs. 3, 4, 5 and 6.

The sensitivity of ^{18}F -FDG PET/CT in patients with suspected SI ranged from 81.8 to 100%, with a pooled estimate of 94.8% (95% CI 88.9–97.6%). The specificity of ^{18}F -FDG PET/CT in patients with suspected SI varied from 50 to

Fig. 2 Overall quality assessment graphs of the included studies according to QUADAS-2 domains for risk of bias and applicability concerns, respectively

100%, with a pooled estimate of 91.4% (95% CI 78.2–96.9%). The sROC curve demonstrated a very good diagnostic performance of ^{18}F -FDG PET/CT in detecting SI (Fig. 3). The pooled LR+, LR– and DOR were 4.7 (95% CI 2.9–7.7), 0.11 (95% CI 0.07–0.16) and 63.4 (95% CI 28.9–139), respectively (Figs. 4, 5 and 6).

No statistically significant heterogeneity amongst the studies was found for all the metrics evaluated ($I^2 < 50\%$). No significant publication bias was detected by Egger's test ($p = 0.1$).

Discussion

Several studies have performed ^{18}F -FDG PET/CT in patients with suspected SI reporting different values of diagnostic performance [18–43]. However, most of these studies have limited power, due to the relatively small numbers of patients enrolled. Therefore, we have pooled data reported in the published studies increasing the statistical power to obtain more robust estimates on the diagnostic performance of ^{18}F -FDG PET/CT in this setting [44].

Previous systematic reviews and meta-analyses evaluating the diagnostic performance of ^{18}F -FDG PET and PET/CT in patients with spondylodiscitis [10–12] pooled together results from studies performing both ^{18}F -FDG PET alone and PET/CT, which are expected to yield different diagnostic accuracies with higher values for hybrid PET/CT [45, 46]. As hybrid imaging methods are the current state of the art for PET imaging [46], we performed a systematic review and meta-analysis including only articles performing PET/CT and excluding those performing PET alone in order to provide timely evidence-based data. Furthermore, we have broadened the population with respect to the previous meta-analyses, including other patients with SI beyond spondylodiscitis. For all the reasons mentioned above, our results should not be compared with prior published meta-analyses.

The current study found that ^{18}F -FDG PET/CT has a very good diagnostic performance in patients with suspected SI with high values of sensitivity (94.8%) and specificity (91.4%).

One interesting finding is that some key elements may be useful to guide the visual assessment of ^{18}F -FDG PET/CT in cases of suspected SI, including the topography of hypermetabolic areas (pattern analysis) and the intensity of the uptake

Fig. 3 Summary receiver operating characteristic (sROC) curve demonstrating a good diagnostic accuracy of ^{18}F -FDG PET/CT in patients with suspected spinal infection

[18, 19]. Furthermore, the semi-quantitative analysis may support the visual analysis for the diagnosis of SI. Lastly, morphological abnormalities at co-registered CT images may reinforce the PET analysis [18, 19].

A recent diagnostic flowchart on imaging methods in patients with suspected SI have highlighted the predominant role of MRI in patients with suspected SI of haematogenous origin and the predominant role of ^{18}F -FDG PET/CT in patients with post-surgical SI [9]. Based on available literature data, ^{18}F -

FDG PET/CT appears to be helpful in particular in those cases in which MRI cannot be performed or is non-diagnostic and as an adjunct in patients in whom the diagnosis is inconclusive [9].

Although ^{18}F -FDG PET/CT has demonstrated an overall higher diagnostic performance compared with MRI for SI detection based on data retrieved by the articles included in our systematic review (Table 3), a possible selection bias cannot be excluded as in some studies only patients with

Fig. 4 Plots of individual studies and pooled positive likelihood ratios (LR+) of ^{18}F -FDG PET/CT in patients with suspected spinal infection, including 95% confidence intervals (95% CI). The size of the squares is

related to the weight of each study. The horizontal lines indicate the 95% CI values for each study, whereas the horizontal diameter of the rhombus indicates the 95% CI value for the pooled LR+

Fig. 5 Plots of individual studies and pooled negative likelihood ratios (LR-) of ^{18}F -FDG PET/CT in patients with suspected spinal infection, including 95% confidence intervals (95% CI). The size of the squares is

related to the weight of each study. The horizontal lines indicate the 95% CI values for each study, whereas the horizontal diameter of the rhombus indicates the 95% CI value for the pooled LR-

inconclusive MRI underwent ^{18}F -FDG PET/CT (Table 1). ^{18}F -FDG PET/CT showed higher sensitivity in diagnosing paravertebral and psoas abscesses than MRI, whereas the latter was more valuable in detecting epidural and spinal abscesses [20, 22]. Clear advantages of ^{18}F -FDG PET/CT over MRI are the absence of contraindication and severe artefacts in patients with metallic implants as well as the possibility to detect alternative or additional sources of infection or inflammation outside the spine [20, 22].

^{18}F -FDG PET/CT can also contribute to the early assessment of the response to therapy in patients with SI [47], in particular in identifying the responders by change in the SUV_{max} . Consistent with this finding, some studies demonstrated that ^{18}F -FDG PET/CT is more accurate and specific than MRI in this setting (Table 4), suggesting that ^{18}F -FDG PET/CT should be preferred over MRI for determining when treatment can be safely discontinued, especially in those patients with a non-informative biochemical test for inflammatory markers at diagnosis.

Notably, a recent interdisciplinary and evidence-based consensus document on imaging of SI have highlighted the role of ^{18}F -FDG PET/CT in patients with suspected SI [9]. The most relevant recommendations of this consensus document about ^{18}F -FDG PET/CT in SI are the following: (a) in patients with suspected SI and elevated ESR and/or CRP and doubtful MRI, ^{18}F -FDG PET/CT should be performed (level of evidence: 1); (b) in primary and post-surgical SI, if MRI is contraindicated, ^{18}F -FDG PET/CT is the imaging modality of choice (level of evidence: 2); (c) in post-surgical SI, ^{18}F -FDG PET/CT can detect both bone infection and soft tissue infection (level of evidence: 2); (d) in patients with SI diagnosed by ^{18}F -FDG PET/CT, a second ^{18}F -FDG PET/CT scan can be performed to evaluate the response to antibiotic therapy (level of evidence: 4) [9].

^{18}F -FDG PET/MRI, that is now becoming increasingly available [48], could be another promising diagnostic tool in SI. In contrast to PET/CT, the advantages of PET/MRI are less radiation exposure and higher soft tissue contrast [48].

Fig. 6 Plots of individual studies and pooled diagnostic odds ratio (DOR) of ^{18}F -FDG PET/CT in patients with suspected spinal infection, including 95% confidence intervals (95% CI). The size of the squares is related to

the weight of each study. The horizontal lines indicate the 95% CI values for each study, whereas the horizontal diameter of the rhombus indicates the 95% CI value for the pooled DOR

Unfortunately, only one study assessed the role of ^{18}F -FDG PET/MRI in patients with suspected SI reporting a sensitivity, specificity, PPV and NPV of 100%, 88%, 86% and 100%, respectively; interestingly, the use of ^{18}F -FDG PET/MRI significantly increased the diagnostic accuracy for the detection of SI compared with MRI alone [49]. This finding suggests the potential role of ^{18}F -FDG PET/MRI as ‘one-stop-shop’ hybrid imaging modality in patients with SI, but further investigations should be undertaken on this topic in future research.

Given that ^{18}F -FDG is a not specific tracer for infection, other radiopharmaceuticals have been preliminary used in the work-up of patients with SI. Experimental radiotracers such as radiolabelled antibiotics or vitamins are being developed and tested in preliminary studies with encouraging results but large-scale studies are needed [9]. ^{68}Ga -citrate is another PET radiopharmaceutical that has been investigated in patients with inflammatory or infectious diseases, including SI [50]. In a preliminary study on the use of ^{68}Ga -citrate PET/CT in patients with suspected bone infections, including SI, sensitivity, specificity, PPV, NPV and accuracy of ^{68}Ga -citrate PET/CT were 100%, 76%, 85%, 100% and 90%, respectively [51]. To the best of our knowledge, there are no studies comparing the diagnostic performance of ^{68}Ga -citrate PET/CT and ^{18}F -FDG PET/CT in patients with suspected SI, but this may be a topic for future research.

Some limitations of our systematic review and meta-analysis should be underlined. A major limitation was the lack of laboratory data (histopathological or microbiological) as gold standard in all patients with suspected SI; therefore, some uncertainty remains in the cases with clinical follow-up.

Another potential source of bias in the meta-analyses on the diagnostic performance of ^{18}F -FDG PET/CT in infectious and inflammatory diseases may be the heterogeneity amongst studies [52], which can be explained by baseline differences amongst patients (Table 1), various methodological aspects (Table 2) and different study quality. However, no significant statistical heterogeneity nor a significant publication bias was detected amongst the studies included in our meta-analysis.

Diagnostic performance of a test is not a measure of clinical effectiveness and improved accuracy does not necessarily result in improved patient outcomes. Unfortunately, only one article included in our systematic review assessed the clinical impact of ^{18}F -FDG PET/CT in patients with SI reporting additional information in 72% of cases and change of clinical management in 52% of patients [40].

Overall, our systematic review and meta-analysis demonstrated that ^{18}F -FDG PET/CT is an accurate diagnostic method in patients with suspected SI and could be used for evaluating the early response to treatment. Despite these promising results, larger prospective and multicentre studies, in particular cost-effectiveness analyses are warranted to strengthen the role of this imaging modality in this setting. Therefore, further studies will need to be undertaken, for both diagnosis and

assessment of treatment response, to develop a full picture of the role of ^{18}F -FDG PET/CT and ^{18}F -FDG PET/MRI in patients with known or suspected SI.

Conclusions

Based on current available literature data, ^{18}F -FDG PET/CT demonstrated a very good diagnostic performance in patients with suspected SI and can be used in patients in which MRI cannot be performed or is non-diagnostic or inconclusive. Indeed, several studies underlined the value of ^{18}F -FDG PET/CT in evaluating the response to treatment in patients with SI. Larger multicentre and prospective studies and cost-effectiveness analyses in this field would be of great help in strengthening the role of ^{18}F -FDG PET/CT in this setting.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any study with human participants or animals performed by any of the authors.

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