Evidence-Based PET for Infectious and Inflammatory Diseases

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12.1 Introduction

Nuclear medicine techniques are non-invasive tools that can early detect pathophysiological changes in affected tissues in patients with inflammatory or infectious diseases. These changes usually occur before clinical onset of symptoms and before the development of anatomical changes detected by radiological techniques [1, 2]. Currently, hybrid imaging techniques as positron emission tomography/computed tomography (PET/CT) may provide functional and morphological information for early diagnosis of infectious and inflammatory diseases [1, 2].

The ability of Fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT to identify sites of inflammatory and infection is mainly related to the glycolytic activity of the cells involved in the inflammatory response [3, 4]. Enough evidence in the literature already exists about the diagnostic performance of 18F-FDG PET/CT in the diagnosis and management of several infectious and inflammatory diseases [5]. The results of the selected articles, including pooled values and 95% confidence interval (95%CI), are presented in Table 12.1 and summarized here below.

12.2 Fever of Unknown Origin (FUO)

Fever of unknown origin (FUO) is commonly defined as temperature $\geq 38.3$ °C on at least two occasions, duration of illness $\geq 3$ weeks or multiple febrile episodes in $\geq 3$ weeks, not immunocompromised patient, and uncertain diagnosis despite thorough history-taking, physical examination, and obligatory investigations [6]. The diagnosis in patients with FUO is a challenging medical problem; the cause of FUO may be infectious diseases, non-infectious inflammatory diseases, or tumors, and 18F-FDG PET/CT detecting foci of increased glucose metabolism may be used for revealing the source of fever [6]. Several meta-analyses have estimated the diagnostic performance of 18F-FDG PET/CT in the assessment of FUO unidentified by conventional workup [7–13].
### Table 12.1 Characteristics and main findings of included meta-analyses on the diagnostic performance of ¹⁸F-FDG PET/CT in infectious or inflammatory diseases

| Topic                        | Authors                  | Patients included | Sensitivity (95%CI) | Specificity (95%CI) | LR+ (95%CI) | LR− (95%CI) | DOR (95%CI) |
|------------------------------|--------------------------|-------------------|---------------------|---------------------|-------------|-------------|-------------|
| Fever of unknown origin      | Dong et al. [7]          | 174               | 98.2% (93.6–99.8)   | 85.9% (75.0–93.4)   | 5.8 (3.3–10) | 0.05 (0.01–0.25) | 7.1 (0.7–67.4) |
|                              | Hao et al. [8]           | 595               | 85% (81–88)         | NR                  | NR          | NR          | NR          |
|                              | Besson et al. [9]        | 401               | NR                  | NR                  | NR          | NR          | NR          |
|                              | Takeuchi et al. [10]     | 1137              | 86% (81–90)         | 52% (36–67)         | NR          | NR          | NR          |
|                              | Bharucha et al. [11]     | 905               | NR                  | NR                  | NR          | NR          | NR          |
|                              | Kan et al. [12]          | 1927              | 84% (79–89)         | 63% (49–75)         | 2.3 (1.5–3.4) | 0.25 (0.16–0.38) | 9 (4–20)    |
|                              | Takeuchi et al. [13]     | 418               | NR                  | NR                  | NR          | NR          | NR          |
| Large vessel vasculitis      | Besson et al.a [19]      | 283               | [GCA] 80% (63–91)   | [GCA] 89% (78–94)   | [GCA] 6.73 (3.5–12.8) | [GCA] 0.25 (0.13–0.46) | NR |
|                              | Cheng et al.a [20]       | 142               | [TA] 70.1% (58.6–80) | [TA] 77.2% (64.2–87.3) | [TA] 2.3 (1.1–4.8) | [TA] 0.34 (0.14–0.82) | [TA] 7.5 (1.6–34) |
|                              | Soussan et al.a [21]     | 712               | [GCA] 90% (79–96)   | [GCA] 98% (94–99)   | [GCA] 28.7 (11.5–71.6) | NR          | NR          |
|                              |                          |                   | [TA] 87% (78–93)    | [TA] 73% (63–81)    | [TA] 4.2 (1.5–12) | [TA] 0.2 (0.1–0.5) | NR          |
|                              |                          |                   | [TA+] 84% (73–92)   | [TA+] 84% (73–92)   | [TA+] 4.6 (2.1–9.9) | [TA+] 0.2 (0.1–0.5) | NR          |
|                              | Lee et al. [22]          | 95                | 83.9% (71.7–92.4)   | 87.2% (72.6–95.7)   | 5.2 (2.4–11.2) | 0.2 (0.1–0.4) | 27.2 (8.5–86.6) |
|                              | Barra et al.a [23]       | 301               | [TA] 81% (69–89)    | [TA] 74% (55–86)    | NR          | NR          | NR          |
|                              | Gomez et al.a [24]       | 210               | NR                  | NR                  | NR          | NR          | NR          |
|                              | Lee et al.a [25]         | 298               | 88% (79–93)         | 81% (64–91)         | 4.5 (2.2–9.5) | 0.15 (0.08–0.29) | 30 (8–107) |
| Infective endocarditis       | Yan et al. [30]          | 246               | 61% (52–88)         | 88% (80–93)         | 3.24 (1.67–6.28) | 0.5 (0.32–0.77) | 6.98 (2.5–19.1) |
|                              | Mahmood et al. [31]      | 537               | 76.8% (71.8–81.4)   | 77.9% (71.9–83.2)   | NR          | NR          | NR          |
|                              | Juneau et al. [32]       | 329               | 81% (73–86)         | 85% (78–91)         | NR          | NR          | NR          |
| CIED infections              | Mahmood et al. [33]      | 492               | 85% (80–89)         | 90% (84–94)         | NR          | NR          | NR          |
|                              | Juneau et al. [34]       | 331               | 87% (82–91)         | 94% (88–98)         | NR          | NR          | NR          |
| Vascular graft infection     | Reinders Folmer et al. [36] | 144            | 95% (87–99)         | 80% (69–89)         | NR          | NR          | 38 (8.5–170) |
|                              | Rojoa et al. [37]        | NR                | 97% (89–99)         | 89% (70–96)         | NR          | NR          | NR          |
| Cardiac sarcoidosis          | Youssef et al.a [42]     | 164               | 89% (79–96)         | 78% (68–86)         | 4.1 (1.7–10) | 0.19 (0.1–0.4) | 25.6 (7.3–89.5) |
|                              | Tang et al.a [43]        | 559               | 75% (69–80)         | 81% (76–85)         | NR          | NR          | 16.9 (7.6–37.5) |
|                              | Kim et al.a [44]         | 891               | 84% (71–91)         | 83% (74–89)         | 4.9 (3.3–7.3) | 0.2 (0.11–0.35) | 27 (14–55) |
| Osteomyelitis                | Wang et al.a [46]        | 319               | 92.3% (86.7–96.1)   | 92% (87–95.6)       | 9.8 (6–16) | 0.11 (0.07–0.2) | 98 (42.8–224) |
Dong et al. firstly reported that the pooled sensitivity and specificity of 18F-FDG PET/CT for the detection of FUO were 98.2% (95% CI: 93.6–99.8) and 85.9% (95% CI: 75–93.4), respectively. Therefore, this method should be considered among the first diagnostic tools for patients with FUO in whom conventional diagnostics have been unsuccessful [7].

Hao et al. confirmed the high sensitivity of 18F-FDG PET/CT for the diagnosis of patients with FUO (pooled value: 88%; 95% CI: 81–88), but the possibility of false positive results should be kept in mind [8].

Another meta-analysis demonstrated that abnormal 18F-FDG PET/CT findings are associated with a substantially increased final diagnostic rate in FUO (pooled odds ratio: 8.94; 95% CI: 4.18–19.12, p < 0.00001). Consequently, 18F-FDG PET/CT could be considered for inclusion in the first-line diagnostic workup of FUO [9].

Tateuchi et al. reported that 18F-FDG PET/CT can be useful in identifying the source of fever in patients with classic FUO (immunocompetent patients). The summary sensitivity and specificity were 86% (95% CI: 81–90) and 52% (95% CI: 36–67), respectively. The contribution of 18F-FDG PET/CT over CT was 32% (95% CI: 22–44). The pooled proportion of

| Topic                              | Authors                  | Patients included | Sensitivity (95% CI) | Specificity (95% CI) | LR+ (95% CI) | LR− (95% CI) | DOR (95% CI) |
|------------------------------------|--------------------------|-------------------|---------------------|---------------------|-------------|-------------|-------------|
| Osteomyelitis related to diabetic foot | Treglia et al. a [47]    | 178               | 74% (60–85)         | 91% (85–96)         | 5.6 (2–15.3) | 0.37 (0.1–1.35) | 16.9 (2–139.6) |
|                                    | Lauri et al. a [48]      | 254               | 89% (68–97)         | 92% (85–96)         | 11 (4.7–25) | 0.11 (0.03–0.4) | 95 (18–504) |
| Prosthetic joint infection         | Jin et al. a [49]        | 838               | 86% (82–90)         | 86% (83–89)         | NR          | NR          | NR          |
|                                    | Verberne et al. a [50]   | 666               | 86% (80–90)         | 93% (90–95)         | NR          | NR          | NR          |
|                                    | Verberne et al. a [51]   | 179               | 70% (56–81)         | 84% (76–90)         | NR          | NR          | NR          |
| Spondylodiscitis                   | Prodromou et al. a [52]  | 224               | 97% (83–100)        | 88% (74–95)         | 8.2 (3.5–18.9) | 0.03 (0.0–0.21) | NR          |
|                                    | Yen et al. a [53]        | 191               | 96% (84–99)         | 90% (79–96)         | 9.8 (4.4–22) | 0.05 (0.01–0.19) | 124 (39–394) |
|                                    | Kim et al. a [54]        | 212               | 95% (87–98)         | 88% (73–95)         | 7.6 (3.4–17.2) | 0.05 (0.02–0.14) | 141 (44–444) |
| Rheumatic diseases                 | Descamps et al. a [57]   | 2300              | NR                  | NR                  | NR          | NR          | NR          |
| Inflammatory bowel diseases        | Treglia et al. a [59]    | 219               | 85% (81–88)         | 87% (84–90)         | 6.2 (2.9–13.4) | 0.19 (0.1–0.34) | 44.3 (11.8–167) |
|                                    | Zhang et al. a [60]      | 162               | 84% (78–89)         | 86% (81–89)         | 5.3 (1.3–22) | 0.2 (0.07–0.6) | 25.9 (2.8–238) |

LR+ positive likelihood ratio, LR− negative likelihood ratio, DOR diagnostic odds ratio, 95% CI 95% confidence interval, NR not reported, CIED cardiovascular implantable electronic device, GCA giant cell arteritis, TA Takayasu arteritis, TA+ Takayasu arteritis using National Health Institute scale

aBoth PET and PET/CT are included

LR+ positive likelihood ratio, LR− negative likelihood ratio, DOR diagnostic odds ratio, 95% CI 95% confidence interval, NR not reported, CIED cardiovascular implantable electronic device, GCA giant cell arteritis, TA Takayasu arteritis, TA+ Takayasu arteritis using National Health Institute scale

Both PET and PET/CT are included
abnormal 18F-FDG-PET/CT in patients with FUO was 69% (95% CI: 63–75); the higher proportion of abnormal scans was accounted for by a proportion of false positive abnormal scans with no contribution to the final diagnosis, with an overall result of 9% (95% CI: 5–14). The authors concluded that there is insufficient evidence to support the value of 18F-FDG PET/CT in investigative algorithms of FUO [11].

Conversely, in an updated meta-analysis on patients with FUO or inflammation of unknown origin (IUO), 18F-FDG PET/CT was demonstrated to be very helpful for recognizing and excluding diseases, directing further diagnostic decisions, and avoiding unnecessary invasive examinations. The pooled sensitivity and specificity were 84% (95% CI: 79–89) and 63% (95% CI: 49–75), respectively. Based on these findings, the authors recommended 18F-FDG PET/CT among the first-line diagnostic tools for patients with FUO and IUO [12].

Lastly, it has been recently demonstrated that patients with negative 18F-FDG PET/CT results were significantly more likely to present with spontaneous fever regression than those with positive 18F-FDG PET/CT results (summary relative risk = 5.6: 95% CI: 3.4–9.2; p < 0.001) [13].

Overall, there is not agreement among the selected meta-analyses about the added value of 18F-FDG PET/CT in patients with FUO. The main drawback of the meta-analyses evaluating the diagnostic performance of 18F-FDG PET/CT for this specific indication is that they include articles without real FUO patients or with highly variable definitions of FUO; therefore, related meta-analyses could be not accurate in this regard [14].

12.3 Large Vessel Vasculitis (LVV)

Large vessel vasculitis (LVV) is defined as an inflammatory disease mainly affecting the large arteries, with two major variants, Takayasu arteritis (TA) and giant cell arteritis (GCA). GCA often coexists with polymyalgia rheumatica (PMR) in the same patient, since both belong to the same disease spectrum [15]. 18F-FDG PET/CT may demonstrate increased radiopharmaceutical uptake in the vascular wall of large vessels in patients with LVV; therefore, this method may be used for diagnosis, monitoring of disease activity, and evaluating disease progression in LVV [15–18], and several meta-analyses have assessed the role of this imaging method in this setting [19–25].

First meta-analyses including both 18F-FDG PET and PET/CT studies reported a valuable diagnostic performance of these methods in patients with GCA with a pooled sensitivity and specificity of 80% (95% CI: 63–91) and 89% (95% CI: 78–94), respectively [19], and a moderate value of these methods in assessing TA activity, with a pooled sensitivity and specificity of 70.1% (95% CI: 58.6–80) and 77.2% (95% CI: 64.2–87.3), respectively [20].

In a meta-analysis of Soussan et al. including both 18F-FDG PET and PET/CT studies, these imaging methods showed good performances in the diagnosis of LVV, with higher accuracy in GCA patients than in TA patients. A vascular uptake equal to or higher than the liver uptake appeared to be a good criterion for the diagnosis of vascular inflammation. 18F-FDG PET or PET/CT showed high sensitivity and specificity for the diagnosis of LVV in GCA patients in comparison to controls, with pooled values of 90% (95% CI: 79–93) and 98% (95% CI: 94–99), respectively. 18F-FDG PET or PET/CT had a pooled sensitivity of 87% (95% CI: 78–93) and specificity of 73% (95% CI: 63–81) for the assessment of disease activity in TA, with up to 84% of specificity in studies using National Institutes of Health criteria as the disease activity assessment scale [21].

Another meta-analysis by Lee et al. confirmed that 18F-FDG PET/CT has good diagnostic accuracy for LVV with a pooled sensitivity and specificity of 83.9% (95% CI: 71.7–92.4) and 87.2% (95% CI: 72.6–95.7), respectively [22].

In a recent meta-analysis, the pooled sensitivity and specificity of 18F-FDG PET or PET/CT for detecting active disease in TA compared to clinical assessment were 81% (95% CI: 69–89) and 74% (95% CI: 55–86), respectively. Active disease by 18F-FDG PET or PET/CT was also associated with elevations of acute phase reactants, as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [23]. Conversely,
in another meta-analysis by Gomez et al. about the association between the CRP value and $^{18}$F-FDG PET or PET/CT vascular positivity in TA, CRP concentration only moderately reflected the $^{18}$F-FDG PET vascular positivity in TA, suggesting dissociated information [24]. More prospective studies are needed to assess the value of $^{18}$F-FDG PET/CT as an independent biomarker for subtle vascular wall inflammation detection in patients with TA [24].

Lastly, an updated meta-analysis confirmed that $^{18}$F-FDG PET or PET/CT has a good performance for the detection of active disease in patients with LVV with a pooled sensitivity and specificity of 88% (95%CI: 79–93) and 81% (95%CI: 64–91), respectively. Therefore, $^{18}$F-FDG PET/CT could be suggested as a surrogate biomarker for assessment of disease activity of LVV during or after immunosuppressive therapy, but further studies are warranted to determine if PET-based treatment of LVV can improve outcomes [25].

Several factors may significantly influence the diagnostic performance of $^{18}$F-FDG PET/CT in LVV including different PET interpretation criteria, atherosclerotic vascular $^{18}$F-FDG uptake (a possible source of false positive findings), and immunosuppressive therapy (a possible source of false findings) [15].

Overall, based on the available evidence, $^{18}$F-FDG PET/CT has demonstrated high diagnostic performance for the detection of LVV. Further studies are needed to select the most clinically relevant and reproducible criteria for defining the presence of LVV with $^{18}$F-FDG PET/CT, as well as to test the clinical impact of $^{18}$F-FDG PET/CT on the management of patients with suspected LVV [15].

### 12.4 Infectious Endocarditis and Cardiovascular Implantable Electronic Device Infections

Infectious endocarditis (IE) is a serious and potentially life-threatening condition. The current diagnosis of IE is based on the modified Duke criteria, which has approximately 80% sensitivity for the diagnosis of native valve endocarditis (NVE), with lower sensitivity for the diagnosis of prosthetic valve endocarditis (PVE) and culture-negative endocarditis [26, 27]. Non-invasive imaging modalities may improve diagnosis of infective endocarditis (IE) [26, 27]. In particular, $^{18}$F-FDG PET/CT is currently included as diagnostic tool in the diagnostic flow chart for IE [26–29] and some meta-analyses have evaluated the diagnostic performance of this method in patients with IE or CIED infections [30–34].

A first meta-analysis published in 2016 demonstrated that the overall diagnostic performance of $^{18}$F-FDG PET/CT for the diagnosis of IE was not high due to the low sensitivity: pooled sensitivity and specificity were 61% (95%CI: 52–88) and 88% (95%CI: 80–93), respectively. However, the diagnostic performance of $^{18}$F-FDG PET/CT increased in the subgroup of patients with PVE [30].

Mahmood et al. demonstrated that $^{18}$F-FDG PET/CT may be a useful adjunctive diagnostic tool in the evaluation of diagnostically challenging cases of IE, particularly in PVE. The pooled sensitivity and specificity of $^{18}$F-FDG PET/CT for diagnosis of IE were 76.8% (95%CI: 71.8–81.4) and 77.9% (95%CI: 71.9–83.2), respectively. Diagnostic accuracy was improved for PVE with pooled sensitivity of 80.5% (95%CI: 74.1–86) and pooled specificity of 73.1% (95%CI: 63.8–81.2). More recent studies published from 2015 to 2017 reported a higher pooled sensitivity of 81.3% (95%CI: 74.3–87) and specificity of 79% (95%CI: 71.2–85.5). The majority of the recent studies were prospective and used a specific protocol (i.e., a low-carbohydrate fat-allowed diet for at least 24 h prior to imaging, a prolonged fasting prior to imaging, and/or an intravenous heparin bolus prior to $^{18}$F-FDG administration). $^{18}$F-FDG PET/CT also has the potential to detect clinically relevant extra-cardiac foci of infection, malignancy, and other sources of inflammation, leading to more appropriate treatment regimens and surgical intervention. Additional extra-cardiac foci of infection were found on 17% of patients in this meta-analysis [31].

In another meta-analysis, Juneau et al. demonstrated that $^{18}$F-FDG PET/CT has a good diag-
nostic accuracy for the diagnosis of IE if adequate patient preparation for suppression of physiological myocardial \(^{18}\)F-FDG uptake was performed, including prolonged fasting at least 12 h and/or heparin injection before \(^{18}\)F-FDG administration, and/or high-fat carbohydrate-restricted protein-permitted diet (minimum two meals for 24 h). Pooled sensitivity of \(^{18}\)F-FDG PET/CT performed with adequate cardiac preparation for the diagnosis of IE was 81% (95%CI: 73–86) and pooled specificity was 85% (95%CI: 78–91). In the subgroup of patients with PVE, the pooled sensitivity was 85% (95%CI: 77–91) but specificity was 81% (95%CI: 72–88). Therefore, \(^{18}\)F-FDG PET/CT may be useful in the investigation of IE, and should be considered in cases where the diagnosis is uncertain [32].

\(^{18}\)F-FDG PET/CT may be helpful in the diagnosis of cardiovascular implantable electronic device (CIED) infections, particularly in patients with the absence of localizing signs or definitive echocardiographic findings. In a recent meta-analysis, Mahmood et al. reported a pooled sensitivity and specificity of \(^{18}\)F-FDG PET/CT in the diagnosis of CIED infections of 85% (95%CI: 80–89) and 90% (95%CI: 84–94), respectively. \(^{18}\)F-FDG PET/CT demonstrated a higher sensitivity of 96% (95%CI: 86–99) and specificity of 97% (95%CI: 86–99) for diagnosis of pocket infections. Diagnostic accuracy for lead infections or CIED-IE was lower with pooled sensitivity of 76% (95%CI: 65–85) and specificity of 83% (95%CI: 72–90). In the subgroup of studies that described the use of any myocardial suppression protocol, the pooled sensitivity was 92% (95%CI: 85–96) and the pooled specificity was 81% (95%CI: 71–89) [33].

Another recent meta-analysis confirmed the high diagnostic performance of \(^{18}\)F-FDG PET/CT for the diagnosis of CIED infections with a pooled sensitivity of 87% (95%CI: 82–91) and a pooled specificity of 94% (95%CI: 88–98). Pooled sensitivity and specificity for diagnosis of pocket/generator related CIED infections were 93% (95%CI: 84–98) and 98% (95%CI: 88–100), respectively. Pooled sensitivity and specificity for diagnosis of lead or IE-related CIED infection were 65% (95%CI: 53–76) and 88% (95%CI: 77–94), respectively [34].

Overall, \(^{18}\)F-FDG PET/CT demonstrated a good diagnostic performance in patients with IE and CIED infections with higher diagnostic accuracy if adequate patient preparation for suppression of physiological myocardial \(^{18}\)F-FDG uptake was performed.

### 12.5 Vascular Graft Infections

Vascular graft infection (VGI), a serious complication in vascular surgery, has a high morbidity and mortality rate. The diagnosis is complicated by non-specific symptoms and challenged by the variable accuracy of different imaging techniques [35, 36]. A recent meta-analysis demonstrated a good diagnostic performance of \(^{18}\)F-FDG PET/CT in patients with VGI with a pooled sensitivity and specificity of 95% (95%CI: 87–99) and 80% (95%CI: 69–89), respectively [36].

Another recent meta-analysis investigating the diagnostic accuracy of \(^{18}\)F-FDG PET/CT in VGI reported a pooled sensitivity and specificity for focal \(^{18}\)F-FDG uptake of 97% (95%CI: 89–99) and 89% (95%CI: 79–96), respectively [37].

Factors influencing the diagnostic performance of \(^{18}\)F-FDG PET/CT in VGI include the time at which \(^{18}\)F-FDG PET/CT is performed after surgery (if \(^{18}\)F-FDG PET/CT is performed in cases of recently implanted grafts, false positive \(^{18}\)F-FDG PET/CT findings for VGI are possible), the use of antibiotics prior to \(^{18}\)F-FDG PET/CT (causing possible false negative findings for VGI), and the PET interpretation criteria used [37].

### 12.6 Sarcoidosis

Sarcoidosis is a multisystem chronic inflammatory disease of unknown etiology characterized by widespread growth of non-caseating granulomas. The diagnosis of sarcoidosis is based on clinical and imaging presentation, histological confirmation, and the absence of alternative diseases. Imaging techniques may play a role in the diagnostic workup of patients with sarcoidosis to assess disease extent and activity, and treatment response evaluation [38]. The role of \(^{18}\)F-FDG
PET/CT in patients with sarcoidosis is well established [39, 40]. Based on evidence-based data, the recommendations for use of $^{18}$F-FDG PET/CT in patients with sarcoidosis could be the following: evaluation of inflammatory active disease in patients with persistent symptoms and negative serologic markers; assessment of inflammation in radiologic stage IV sarcoidosis with lung fibrosis; evaluation of inflammatory active extrathoracic sites of sarcoidosis or assessment of cardiac sarcoidosis (especially in patients with implanted pacemakers); identification of active sites for diagnostic biopsy not revealed by other methods; evaluation of treatment response in refractory sarcoidosis [39].

The role of $^{18}$F-FDG PET/CT in cardiac sarcoidosis is currently under active investigation [41] and some meta-analyses have addressed the diagnostic performance of $^{18}$F-FDG PET/CT in this setting [42–44].

In the meta-analysis of Youssef et al., the pooled sensitivity and specificity of $^{18}$F-FDG PET or PET/CT for diagnosis of cardiac sarcoidosis were 89% (95%CI: 79–96) and 78% (95%CI: 68–86), respectively [42].

Tang et al. demonstrated that the diagnostic accuracy of $^{18}$F-FDG PET/CT for cardiac sarcoidosis depends on adequate suppression of physiological cardiac glucose uptake. Overall, $^{18}$F-FDG PET/CT had a pooled sensitivity of 75% (95%CI: 69–80) and a pooled specificity of 81% (95%CI: 76–85) for the diagnosis of cardiac sarcoidosis. This modest diagnostic accuracy was attributed to the inclusion of studies in which a short fasting duration before scanning likely influenced its sensitivity. Excluding studies without adequate myocardial suppression resulted in a pooled sensitivity of 81% (95%CI: 76–86) and a pooled specificity of 82% (95%CI: 77–86). Fasting for at least 12 h before scanning or a high-fat low-carbohydrate diet given at 3–6 h before imaging or heparin infusion before imaging has shown to improve the diagnostic accuracy of $^{18}$F-FDG PET/CT in cardiac sarcoidosis [43].

Lastly, an updated meta-analysis on the diagnostic performance of $^{18}$F-FDG PET or PET/CT in cardiac sarcoidosis demonstrated a pooled sensitivity and specificity of 84% (95%CI: 71–91) and 83% (95%CI: 74–89), respectively. The presence of combined myocardial perfusion imaging improved the diagnostic accuracy of $^{18}$F-FDG PET/CT for diagnosis of cardiac sarcoidosis. Nevertheless further large multicenter studies in this setting are needed [44].

### 12.7 Musculoskeletal Infections

Timely identification and precise localization of musculoskeletal infections by imaging techniques are critical for early initiation of treatment and can have a significant impact on patient outcome. In this setting, nuclear medicine and radiological imaging are complementary techniques [45]. In particular, several meta-analyses have investigated the diagnostic performance of $^{18}$F-FDG PET/CT in patients with suspicious musculoskeletal infections [46–54].

Wang et al. calculated the diagnostic performance of $^{18}$F-FDG PET or PET/CT in patients with suspicious osteomyelitis reporting a high pooled sensitivity and specificity in this setting: pooled values were 92.3% (95%CI: 86.7–96.1) and 92% (95%CI: 87–95.6), respectively [46].

A first meta-analysis focused on the diagnostic performance of $^{18}$F-FDG PET or PET/CT in osteomyelitis related to diabetic foot reported a pooled sensitivity and specificity of 74% (95%CI: 60–85) and 91% (95%CI: 85–96), respectively [47]. An updated meta-analysis on the same topic demonstrated a pooled sensitivity of 89% (95%CI: 68–97) and a pooled specificity of 92% (95%CI: 85–96) [48].

Jin et al. calculated the diagnostic performance of $^{18}$F-FDG PET or PET/CT in detecting prosthetic infection after arthroplasty. They found a pooled sensitivity and specificity of 86% (95%CI: 82–90) and 86% (95%CI: 83–89), respectively. The pooled sensitivity of $^{18}$F-FDG PET or PET/CT in demonstrating hip and knee prosthetic infection was 88% (95%CI: 83–92) and 72% (95%CI: 58–84), respectively. The pooled specificity of $^{18}$F-FDG PET or PET/CT in demonstrating hip and knee prosthetic infection was 88% (95%CI: 84–91) and 80% (95%CI: 71–88), respectively [49].

A meta-analysis focused on periprosthetic hip infection confirmed the good diagnostic accuracy
of $^{18}$F-FDG PET or PET/CT in this setting with pooled sensitivity and specificity of 86% (95%CI: 80–90) and 93% (95%CI: 90–95), respectively, using increased $^{18}$F-FDG uptake in the bone-prosthesis interface as the criterion for infection for the index test [50].

A meta-analysis focused on periprosthetic knee infection demonstrated a nonoptimal diagnostic accuracy of $^{18}$F-FDG PET or PET/CT in this setting with pooled sensitivity and specificity of 70% (95%CI: 56–81) and 84% (95%CI: 76–90) [51].

Some factors influencing the diagnostic performance of $^{18}$F-FDG PET/CT in patients with osteomyelitis should be underlined: first of all, several interpretation criteria of $^{18}$F-FDG PET have been used in the literature, by using visual and/or semi-quantitative criteria, leading to different diagnostic accuracy values [46–51]. Furthermore, continuous physiologic $^{18}$F-FDG activity around the prostheses may be cause of false positive $^{18}$F-FDG PET/CT findings for peri-prosthetic infection [49–51].

$^{18}$F-FDG PET or PET/CT has an excellent diagnostic performance in detecting infectious spondylodiscitis [55]. A first meta-analysis on $^{18}$F-FDG PET or PET/CT in patients with suspicious spondylodiscitis reported a pooled sensitivity and specificity of 97% (95%CI: 83–100) and 88% (95%CI: 74–95), respectively [52]. In this setting, the diagnostic performance of $^{18}$F-FDG PET or PET/CT was higher compared with magnetic resonance imaging (MRI). Considering studies comparing $^{18}$F-FDG PET or PET/CT and MRI, pooled sensitivity and specificity of $^{18}$F-FDG PET or PET/CT were 96% (95%CI: 84–99) and 90% (95%CI: 79–96), whereas the pooled sensitivity and specificity of MRI were 76% (95%CI: 65–84) and 62% (95%CI: 45–77) [53].

Another recent meta-analysis confirmed the better diagnostic accuracy of $^{18}$F-FDG PET or PET/CT compared to MRI for the detection of spondylodiscitis: for $^{18}$F-FDG PET or PET/CT, pooled sensitivity and specificity were 95% (95%CI: 87–98) and 88% (95%CI: 73–95), respectively; for MRI, pooled sensitivity and specificity were 85% (95%CI: 65–95) and 66% (95%CI: 48–80), respectively [54].

Overall, based on the available evidence, $^{18}$F-FDG PET/CT has demonstrated a good diagnostic performance for the detection of musculoskeletal infections.

### 12.8 Inflammatory Rheumatic Diseases

Molecular imaging methods, including $^{18}$F-FDG PET/CT, have been proposed for a better assessment of inflammatory rheumatic diseases [56]. $^{18}$F-FDG uptake in the shoulders or hips was often reported in PMR (pooled prevalence: 76%), especially in periarticular sites (pooled prevalence: 84%). Furthermore, interspinous $^{18}$F-FDG uptake, demonstrating interspinous bursitis, is common in PMR (pooled prevalence: 67%). However, these findings are not very specific for PMR [57].

Patients with rheumatoid arthritis (RA) may also have interspinous $^{18}$F-FDG uptake (pooled prevalence: 34%) or articular $^{18}$F-FDG uptake in shoulders or hips (pooled prevalence: 66%) or in other articular regions (pooled prevalence: 78%). Articular $^{18}$F-FDG uptake is not specific for PMR or RA, as it is common in other connective tissue diseases (pooled prevalence: 70%). Overall, $^{18}$F-FDG PET/CT is helpful in diagnostic research, but the interpretation of $^{18}$F-FDG uptake at each site is not characteristic of a specific inflammatory rheumatic disease [57].

### 12.9 Inflammatory Bowel Diseases

$^{18}$F-FDG PET/CT may also be used to image areas of active inflammation, such as those occurring in patients with active inflammatory bowel disease (IBD) as Crohn’s disease and ulcerative colitis [58]. In this setting, $^{18}$F-FDG PET or PET/CT showed a good accuracy with a pooled sensitivity and specificity of 85% (95%CI: 81–88) and 87% (95%CI 84–90), respectively [59]. These findings were confirmed by another meta-analysis including prospective studies only [60]. Nevertheless, more prospec-
tive studies evaluating the role of $^{18}$F-FDG PET/CT for this indication are needed. Specific challenges for the use of $^{18}$F-FDG PET/CT in IBD are the physiological $^{18}$F-FDG uptake in the bowel and the movement of the bowel that may influence a correct co-registration of $^{18}$F-FDG PET and CT images [59].

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