Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis

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Received Sep 5, 2017; accepted Oct 2, 2017
doi:10.1007/s12350-017-1092-8

Background. **The current diagnosis of infective endocarditis (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. There is preliminary evidence that ^{18}F-FDG PET/CT is an adjunctive diagnostic test with high accuracy reported in small studies to date. We therefore performed a meta-analysis of studies evaluating the use of PET/CT in the diagnosis of IE to establish a more precise estimate of accuracy.**

Methods. **PubMed, Embase, Cochrane library, CINAHL, Web of Knowledge, and www.clinicaltrials.gov were searched from January 1990 to April 2017 for studies evaluating the accuracy of PET/CT for the evaluation of possible IE.**

Results. **We identified 13 studies involving 537 patients that were included in the meta-analysis. The pooled sensitivity of PET/CT for diagnosis of IE was 76.8% (95% CI 71.8–81.4%; $Q = 39.9$, $P < 0.01$; $I^2 = 69.9\%$) and the pooled specificity was 77.9% (95% CI 71.9–83.2%; $Q = 44.42$, $P < 0.01$; $I^2 = 73.0\%$). Diagnostic accuracy was improved for PVE with sensitivity of 80.5% (95% CI 74.1–86.0%; $Q = 25.5$, $P < 0.01$; $I^2 = 72.5\%$) and specificity of 73.1% (95% CI 63.8–81.2%; $Q = 32.1$, $P < 0.01$; $I^2 = 78.2\%$). Additional extracardiac foci of infection were found on 17% of patients on whole body PET/CT.**

Conclusion. **PET/CT is a useful adjunctive diagnostic tool in the evaluation of diagnostically challenging cases of IE, particularly in prosthetic valve endocarditis. It also has the potential to detect clinically relevant extracardiac foci of infection, malignancy, and other sources of inflammation leading to more appropriate treatment regimens and surgical intervention. (J Nucl Cardiol 2017)**

Key Words: Endocarditis • PET • infection • imaging • meta-analysis

Electronic Supplementary Material The online version of this article (doi:10.1007/s12350-017-1092-8) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

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1071-3581/$34.00

Published online: 30 October 2017

Abbreviations	
IE	Infective endocarditis
PET	Positron-emission tomography
CT	Computed tomography

BACKGROUND

Infective endocarditis (IE) is associated with considerable morbidity and mortality, resulting from local damage to cardiac structures, metastatic infection, embolic phenomenon, or immune-mediated damage. With early mortality in IE ranging from 10% to 30% and 1-year mortality up to 40%,[2,3] prompt diagnosis and initiation of appropriate therapy is critical. Current practice guidelines use modified Duke criteria [1,2] for the diagnosis of IE which has around 80% sensitivity for the diagnosis of native valve endocarditis (NVE), and lower sensitivity for the diagnosis of culture-negative endocarditis. [4–7] Fluorine 18 fluorodeoxyglucose (^{18}F-FDG) positron-emission tomography (PET)/computed tomography (CT) has demonstrated potential as an adjunctive diagnostic tool in the evaluation of IE, with high diagnostic accuracy reported in small studies. We therefore performed a meta-analysis of studies evaluating the use of ^{18}F-FDG PET/CT in the evaluation of possible IE to establish a more precise estimate of diagnostic accuracy.

METHODS

Literature Search

PubMed, Embase, Cochrane library, CINAHL, Web of Knowledge, and www.clinicaltrials.gov were searched from January 1, 1990 to April 30, 2017 for studies evaluating the use of PET/CT for diagnosis of possible IE. The search strategy used a combination of search terms (e.g., ''endocarditis,'' ''valve infection,'' ''valvular infection,'' ''valvular endocarditis,'' ''heart valve infection,'' ''positron-emission tomography,'' ''radionuclide imaging,'' ''PET'') as controlled vocabulary and keywords modified for the individual databases (detailed search strategy appears in appendix 1 of the supplement). Further pertinent studies were found via manual inspection of references of pertinent papers. To make our search as comprehensive as possible and include ''gray literature'' sources, we also included conference proceedings. If required, we attempted to contact corresponding authors for unpublished data. No language constraints were applied to the search. Search results were screened independently by 2 reviewers (MM and SF) based on predefined inclusion and exclusion criteria; discrepancies were resolved by a third reviewer (SA).

Inclusion and Exclusion Criteria

Studies were included if they assessed the diagnostic accuracy of PET/CT in the diagnosis of possible IE; provided detailed criteria of a reference standard for diagnosis of IE, and provided sufficient data to determine sensitivity and specificity of PET-CT. Studies were excluded if they were case reports, case series, animal studies, pediatric studies, duplicate reports, or if insufficient data were provided to calculate sensitivity and specificity values. The index test was PET/CT.

Data Extraction

Data were abstracted from the included studies using a standard form which included first author, publication year, geographical region, single-center or multicenter study, sample size, reference standard, PET/CT methods and analysis, PET-CT results, echocardiogram results, and blood and device culture results. The quality of each study was evaluated according to the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) tool by 2 independent investigators (MM and SA); any discrepancies were resolved by consensus after discussion. Review Manager Software (version 5.3, the Cochrane Collaboration) and Stata Metan package (Stata Statistical Software, Release 13; StataCorp LP, College Station, TX) were used to generate a graphical summary of the quality assessment. Accuracy of the data was verified by 2 independent reviewers (MM and SA), and any discrepancies in data extraction or quality assessment were resolved by consensus discussion with a third reviewer (SF).

Statistical Analysis

Accuracy data (true positive, false positive, true negative, and false negative) were extracted from each study to calculate estimates of pooled sensitivity and specificity weighted based on the study population size. To calculate the overall performance of the diagnostic accuracy of PET/CT, summary receiver operating curve (SROC) and area under the curve (AUC) analysis were done. Heterogeneity was evaluated with the Cochrane Q test and I^2 test. Possible sources of heterogeneity were further explored by subgroup analyses and sensitivity analyses. Threshold effect was assessed with the Spearman correlation. Meta-DiSc 1.4 software (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain) and Stata Metan package (Stata Statistical Software, Release 13; StataCorp LP, College Station, TX) were used to perform statistical analysis.

RESULTS

A total of 529 articles were identified through the electronic database search; 388 articles remained after removal of duplicate records. After screening of the title and abstract, 49 full text articles were reviewed. Following full text screen, 13 studies involving 537 patients were included in the meta-analysis (Figure 1).

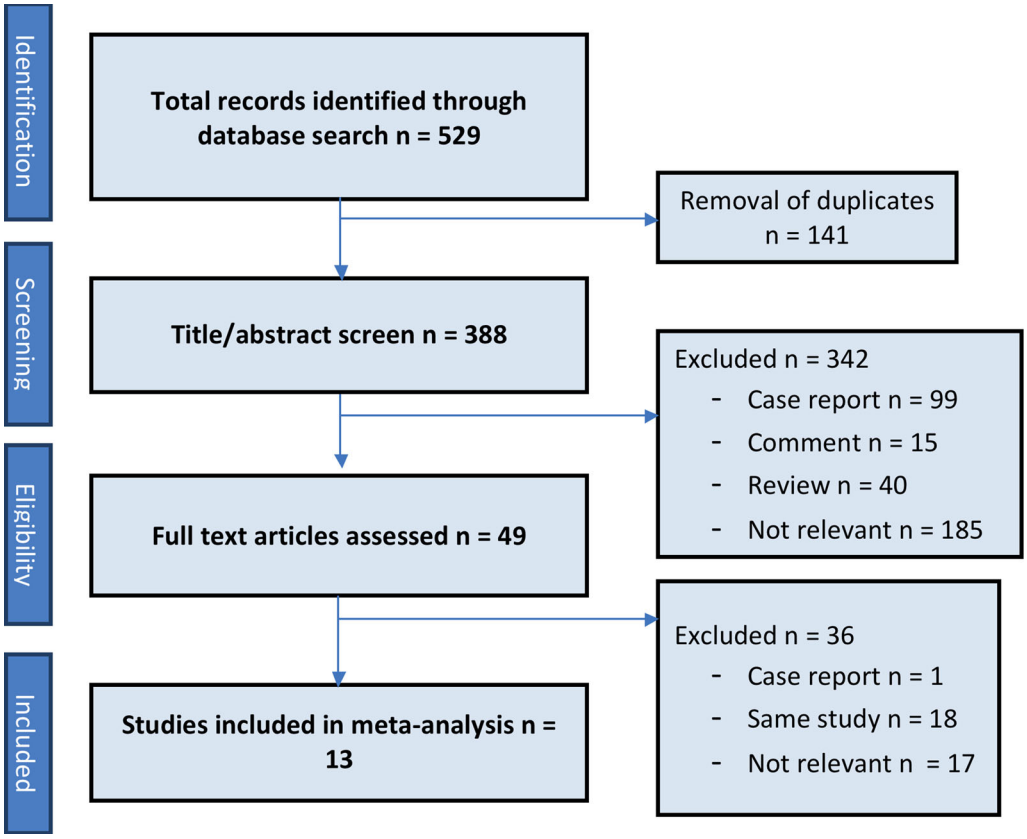

Figure 1. Flowchart of study selection and search results.

Characteristics of Included Studies

Table 1 summarizes the main characteristics of each of the included studies. The majority of the included studies were from Europe; 75% of participants were male. Five of the 13 studies involving 203 patients included both native and prosthetic valve endocarditis;[8–12] five studies with 227 patients included only prosthetic valve endocarditis;[13–17] the remaining 3 studies with 107 patients included valvular endocarditis and cardiac implantable electronic device-related infective endocarditis.[18–20] Eight of the included studies were retrospective and 5 were prospective. Three of the included studies were abstracts from conference proceedings. [8,10,18] Specific PET/CT protocols were reported by 9 studies; all involved at least 6 hours of fasting prior to imaging. Of those studies that described their PET/CT protocol, 7 used a low-carbohydrate diet;[11–14,16,17,20] 3 used intravenous heparin 50 IU/kg bolus 15 minutes prior to FDG administration [9,14,15] and 6 blinded clinical information from interpreting physicians.[9,11,13,16,17,20] Most studies used a combination of visual and semi-quantitative analysis methods for PET/CT interpretation (summarized in Table 2).

Presence of fever was reported in 63% ($N = 150/237$); echocardiogram findings suggestive of endocarditis in 40% ($N = 168/418$); and blood cultures were positive in 51% ($N = 181/355$). The most common organisms from blood cultures were *Staphylococcus aureus* ($N = 38$), coagulase-negative *Staphylococcus* ($N = 27$), *Streptococcus* species ($N = 26$), and *Enterococcus* species ($N = 21$). Most (138/184, 75%) patients received antibiotic therapy prior to PET/CT with median duration of antibiotic therapy prior to imaging ranging from 4 to 20 days. Findings of metastatic infection were found in 17% ($N = 34/198$), with the most common reported sites being spinal vertebrae ($N = 12$), spleen ($N = 11$), and extremities ($N = 5$).[12,15–17] Two studies described the detection of malignancy or other sources of infection; these included colon cancer ($N = 2$), pneumonia ($N = 5$), and prostatitis ($N = 3$).[12,20]

Diagnostic Accuracy of PET-CT

The pooled sensitivity of PET/CT for diagnosis of IE was 76.8% (95% CI 71.8–81.4%; $Q = 39.9$, $P < 0.01$; $I^2 = 69.9\%$) and the pooled specificity was 77.9% (95% CI 71.9–83.2%; $Q = 44.42$, $P < 0.01$;

Table 1. Summary of characteristics of studies

Study	Setting	Patients	Inclusion criteria	Reference standard	PET/CT protocol	Presentation	Sensitivity/ specificity (95% CI)
Salomaki[12]	Prospective, single center, Finland	23	Valvular endocarditis	Modified Duke Criteria by expert team, blinded to PET/CT results	MS† diet for 24 hours, 10-hour fast, mean FDG uptake time 72 minutes (range 52–98), interpretation blinded to clinical scenario	Positive blood cultures 74% Positive echocardiogram 52%	56% (31–79) 80% (56–94)
Granados 2016[9]	Retrospective, single center, Spain	80	Valvular endocarditis	Modified Duke Criteria by expert team, 6-month follow-up	12-hour fast, 50 IU/kg heparin bolus 15 minutes prior to FDG, FDG uptake time 60 minutes, interpretation blinded to clinical scenario	Definite IE ($N = 31$): Positive blood cultures 61%, positive echocardiogram 71%	61% (36-83) 94% (80-99)
Jimenez-Ballve[14]	Prospective, single center, Spain	41	Prosthetic valve endocarditis	Histopathology & culture of surgical specimens, or expert team opinion with 4-month follow-up	High-fat, low-carbohydrate diet for 48 hours, 12-hour fast, 50 IU/kg heparin bolus 15 minutes prior to FDG, FDG uptake time 45-60 minutes	Not stated	100% (86-100) 28% (10-53)
Pate[10]	Prospective, single center, India, abstract only	16	Valvular endocarditis	Modified Duke criteria	Low-carbohydrate, high-fat diet for 48 hours, 12-hour fast	Not stated	50% (19-81) 83% (36-100)
Zhang-Yin[20]	Retrospective, single center, France	35	Valvular endocarditis, CIED-IE*	Histopathology & culture of surgical specimens, or modified Duke criteria, 6-month follow-up	MS diet for 24 hours, 6-hour fast, FDG uptake time 60 minutes	Positive blood cultures 23% Positive echocardiogram 14%	92% (64–100) 77% (55–92)
Fagman[13]	Retrospective single center, Sweden	11	Prosthetic valve endocarditis	Modified Duke criteria, expert team review	18-hour fast, blinded interpretation, FDG uptake time 60 minutes	Positive blood cultures 73%	67% (30–93) 100% (16-100)

Table 1. continued

Study	Setting	Patients	Inclusion criteria	Reference standard	PET/CT protocol	Presentation	Sensitivity/ specificity (95% CI)
Pizzi[15]	Prospective, single center, Italy	92	Prosthetic valve endocarditis, CIED-IE	Expert team review based on echocardiogram, culture and clinical data	Gated cardiac PET and ECG gated cardiac CTA, 12-hour fast, heparin bolus, FDG uptake time 60 minutes	Positive blood cultures 72% Positive echocardiogram 51%	89% (77-96) 84% (69-94)
Chirillo[18]	Single center, Italy, abstract only	45	Valvular endocarditis, CIED-IE	Modified Duke criteria, 6-month follow-up	Not stated	Not stated	87% (69-96) 67% (38-88)
Grazios[19]	Prospective, single center, Italy	27	CIED-IE	Modified Duke criteria, expert team review, mean follow-up time 11 months	FDG uptake time 45-60 minutes	Positive blood cultures 37% Positive echocardiogram 41%	67% (35-90) 87% (60-98)
Ricciardi[11]	Retrospective, single center, Italy	27	Valvular endocarditis	Modified Duke criteria	MS diet, 6-hour fast, FDG uptake time 60 minutes, blinded interpretation	Positive blood cultures 81% Positive echocardiogram 52%	64% (43-82) 100% (16-100)
Rouzet[16]	Retrospective, single center, France	39	Prosthetic valve endocarditis	Expert team review based on clinical & echocardiographic data, 3-month follow-up	MS diet (1 meal), 12-hour fast, FDG uptake time 60 minutes, blinded interpretation	Positive blood cultures 62% Positive echocardiogram 54%	83% (59-96) 71% (48-89)
Camargo[8]	Retrospective, single center, Brazil, abstract only	29	Valvular endocarditis	Modified Duke criteria	Not stated	Positive echocardiogram 28%	83% (59-96) 73% (39-94)

Table 1. continued

Study	Setting	Patients	Inclusion criteria	Reference standard	PET/CT protocol	Presentation	Sensitivity/specificity (95% CI)
Saby[17]	Prospective, single center, France	72	Prosthetic valve endocarditis	Modified Duke criteria, expert team review, 3-month follow-up	MS diet (1 meal), 12-hour fast, FDG uptake time 60 minutes, blinded interpretation	Positive blood cultures 38% Positive echocardiogram 67%	62% (47–75) 80% (56–94)

CI, confidence interval; *IE*, infective endocarditis; *MS diet*, myocardial suppression diet (low-carbohydrate, fat-allowed diet); *CIED-IE*, cardiac implantable electronic device infection-related infective endocarditis; *CTA*, computed tomography angiography

$I^2 = 73.0\%$) (Figure 2). Summary receiver operating characteristic curve (SROC) analysis demonstrated moderate overall accuracy with an area under the curve (AUC) value of 0.86 and Q^* 0.79 (Figure 3).

A sensitivity analysis of 8 studies involving only prosthetic valve endocarditis demonstrated pooled sensitivity of 80.5% (95% CI 74.1–86.0%; $Q = 25.5$, $P < 0.01$; $I^2 = 72.5\%$) and specificity of 73.1% (95% CI 63.8–81.2%; $Q = 32.1$, $P < 0.01$; $I^2 = 78.2\%$), with AUC of 0.88 and Q^* of 0.81 on SROC analysis.

More recent studies published from 2015 to 2017 reported a higher pooled sensitivity of 81.3% (95% CI 74.3–87.0%; $Q = 26.53$, $P < 0.01$; $I^2 = 77.4\%$) and specificity of 79.0% (95% CI 71.2–85.5%; $Q = 40.88$, $P < 0.01$; $I^2 = 85.3\%$). Comparison studies published prior to 2015 reported sensitivity of 72.3% (95% CI 64.5–79.1%; $Q = 9.81$, $P = 0.08$; $I^2 = 49.1\%$) and specificity of 76.2% (95% CI 65.7–84.8%; $Q = 3.30$, $P = 0.65$; $I^2 = 0.0\%$). More of the recent studies published from 2015 to 2017 were prospective [10,12,14,15] and described using a low-carbohydrate, fat-allowed diet for at least 24 hours prior to imaging.[10,12,14,20] In addition, more of the recent studies described using a prolonged fast prior to imaging and used an intravenous heparin bolus prior to FDG administration.[9,14,15]

Additional sensitivity analysis of 9 studies that included a myocardial suppression protocol as part of the PET/CT methodology demonstrated a sensitivity of 76.7% (95% CI 70.9–81.9%; $Q = 33.59$, $P < 0.01$; $I^2 = 76.2\%$) and specificity of 78.3% (95% CI 71.4–84.2%; $Q = 42.39$, $P < 0.01$; $I^2 = 81.1\%$).

There was no significant difference in diagnostic accuracy among studies that blinded interpreting physicians. Overall, 6 of the 13 studies blinded clinical information from physicians interpreting PET/CT; in this group, sensitivity was 70.9% (95% CI 62.9–78.1%; $Q = 8.57$, $P = 0.128$; $I^2 = 41.7\%$) and specificity was 85.3% (95% CI 77.6–91.2%; $Q = 11.23$, $P = 0.04$; $I^2 = 55.5\%$). In comparison, the 7 studies that did not blind interpreting physicians had a sensitivity 80.9% (95% CI 73.8–86.8%; $Q = 24.64$, $P < 0.01$; $I^2 = 75.6\%$) and specificity of 69.9% (95% CI 59.5–79.0%; $Q = 28.51$, $P < 0.01$; $I^2 = 79.0\%$).

Threshold Effect and Heterogeneity

Visual inspection of forest plots and SROC curves, as well as Spearman's correlation of 0.318 ($P = 0.289$) suggested the presence of a threshold effect to some extent. The I^2 values and Cochran Q values of the pooled sensitivity and specificity also suggested the presence of heterogeneity between studies. Sensitivity analysis through omission of single studies

Table 2. Summary of PET analysis methods

Study	Visual analysis method	Semi-quantitative analysis method	PET/CT findings
Salomaki[12]	Increased FDG uptake at the valve or prosthesis area on AC and NAC images	SUV_{max} at valve/prosthesis area	NVE: 1 of 7 positive on visual analysis Median SUV_{max} 2.7 (range 2.4-8.3) for NVE vs. 2.5 (1.4-3.5) for uninfected valves PVE: 6 of 6 positive on visual analysis Median SUV_{max} 5.8 (range 4.1-9.0) for PVE vs. 4.8 (range 2.9-7.8) for uninfected valves
Granados[9]	Increased focal or heterogeneous FDG uptake at the valve in the AC and NAC images	SUV_{max} at valve area SUV_{mean} = blood pool (SVC, liver) $SUV_{ratio} = SUV_{max}/ SUV_{mean}$	91% sensitivity & 94% specificity for IE at an $SUV_{max} \geq 3.485$
Jimenez Ballve[14]	Increased FDG uptake at the PV area on AC and NAC images	SUV_{max} at PV area SUV_{max} at MBP, liver 5-point scale (0 = no uptake; 1 = PV lower than MBP; 2 = PV higher than MBP, lower than liver; 3 = PV higher than liver, less than twice liver value; 4 = PV more than twice liver value)	100% sensitivity & 73% specificity of AC + NAC images More true positive in focal uptake (62%) vs. diffuse uptake (44%) ($P = 0.02$) Mean SUV_{max} of 5.9 ± 2.4 for IE vs. 3.6 ± 2.1 for uninfected valves
Patel[10]	Increased FDG uptake	Not stated	Focal increased uptake in 37.5%
Zhang Yin[20]	Increased FDG uptake at valve area	SUV_{max} at valve area $SUV_{ratio} = SUV_{max}$ at valve/SUV_{max} at atria	All true positive PET/CTs had focal FDG uptake (vs. diffuse uptake) Mean SUV_{max} of 6.9 (range 3.5-8.4) for IE vs. 3.5 (range 2.9-5.1) for uninfected valves Mean SUV_{ratio} of 2.8 ± 0.5 for IE vs. 1.5 ± 0.2 for uninfected valves
Fagman[13]	Focal increased FDG uptake at PV on AC and NAC images	SUV_{max} at PV SUV_{max} at MBP $SUV_{ratio} = SUV_{max}$ at PV/SUV_{max} at MBP	Visual analysis positive in 6 of 8 patients with IE Mean SUV_{max} of 5.8 (interquartile range [IQR] 3.5-6.5) for PVE vs. 3.3 (IQR 3.1-3.5) for uninfected valves Mean SUV_{ratio} of 2.4 (IQR 1.7-3.0) for PVE vs. 1.5 (IQR 1.3-1.7) for uninfected valves

Table 2 continued

Study	Visual analysis method	Semi-quantitative analysis method	PET/CT findings
Pizzi[15]	Focal or heterogeneous increased FDG uptake at valves on AC and NAC images	SUV_{max} at valve SUV_{max} at MBP SUV_{ratio} = SUV_{max} at valve/SUV_{max} at MBP	True positive visual analysis of PET/CT in 86% with definite IE, 40% with possible IE, 40% with no infection True positive visual analysis of PET/CTA in 92% with definite IE, 40% with possible IE, 20% with no infection Median SUV_{max} of 7.36 (IQR 5.41–10.49) for PVE vs. 0.5 (IQR 0.5–3.74) for uninfected valves Median SUV_{max} of 5.56 (IQR 5.16–7.72) for CIED-IE vs. 0.5 (0.5–2.9) for uninfected CIED
Graziosi[19]	Increased FDG uptake along the CIED lead course	Not stated	67% sensitivity and 87% specificity of visual analysis
Ricciardi[11]	Increased FDG uptake at valve, AC and NAC images used for suspected PVE	Not stated	64% sensitivity and 100% specificity of visual analysis
Rouzet[16]	Focal or diffusely increased FDG uptake at PV on AC and NAC images	SUV_{mean} at PV = Average of SUV_{max} on 3 adjacent axial slices with the highest FDG uptake at the PV SUV_{mean} of blood pool = Average of SUV_{max} on 3 adjacent axial slices within the right atrium in areas without activity from adjacent tissue PV-to-background ratio = SUV_{mean} at PV/ SUV_{mean} of blood pool	Mean SUV_{mean} of 6.5 (range 3.9–14.7) for PVE vs. 4.9 (range 3.3–6.2) for uninfected valves Mean PV-to-background ratio of 4.1 (range 2.3–7.8) for PVE vs. 3.4 (range 2.4–4.4) for uninfected valves
Camargo[8]	Not stated	Not stated	Not stated
Saby[17]	Increased FDG uptake at PV on AC and NAC images	SUV_{max} at PV SUV_{max} at right atrium PV-to-background ratio = SUV_{max} at PV/ SUV_{max} at right atrium	Significantly higher SUV_{max} for PVE vs. uninfected valves, values not stated ($P < 0.05$) No significant difference in PV-to-background ratio for PVE vs. uninfected valves

AC, attenuation correction; *NAC*, non-attenuation correction; *SUV*, standardized uptake value; *IE*, infective endocarditis; *NVE*, native valve endocarditis; *PVE*, prosthetic valve endocarditis; *PV*, prosthetic valve; *MBP*, mediastinal blood pool; *ABP*, aortic blood pool; *CIED*, cardiac implantable electronic device

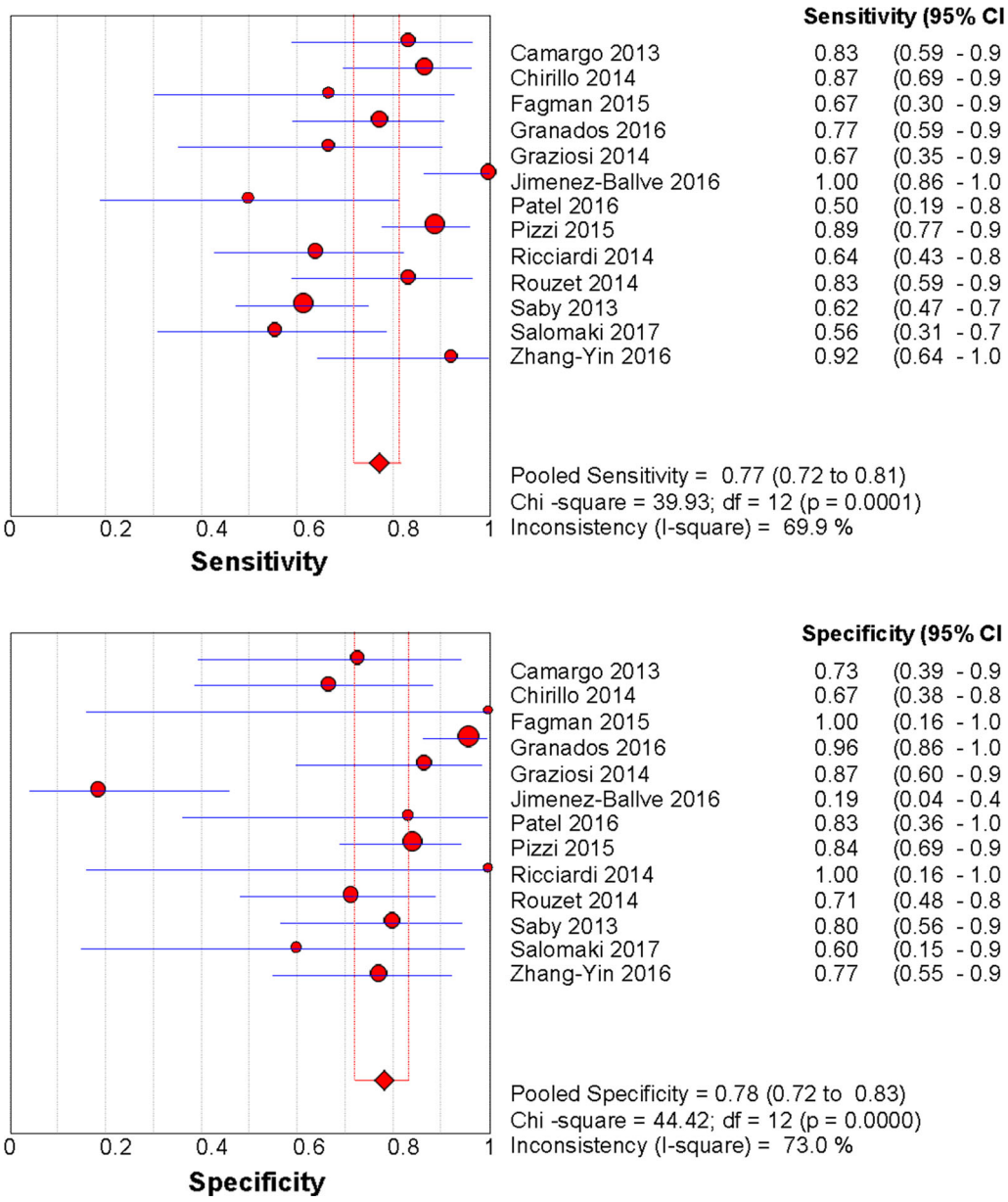

Figure 2. Pooled sensitivity and specificity of 18F-FDG PET/CT in evaluation of IE.

demonstrated somewhat less heterogeneity with exclusion of Jimenez-Ballve [14]; pooled sensitivity was 73% (95% CI 67–78%; $Q = 23.83$, $P = 0.013$; $I^2 = 53.8\%$) and specificity of 82% (95% CI 75–87%; $Q = 13.64$, $P = 0.254$; $I^2 = 19.4\%$). The characteristics of included patients, methods, definition of infection, and described image interpretation in this study were not substantially different from the other included studies. It is possible that the heterogeneity noted in these results reflects threshold effect, a primary concern when pooling diagnostic test accuracy studies in a meta-analysis. Threshold effect occurs when different cut-off values are used to define a positive test result in different studies, affecting the reported sensitivity and specificity of the test. Interpretation of PET/CT involves assessing the degree and distribution of FDG uptake. As there are no specific diagnostic criteria for interpretation of PET/CT in the evaluation of endocarditis, it is possible that variability in interpreting PET/CT is contributing to heterogeneity. In addition, many studies did not blind radiologists to the clinical scenario, which may have affected the interpretation of the PET/CT findings. There

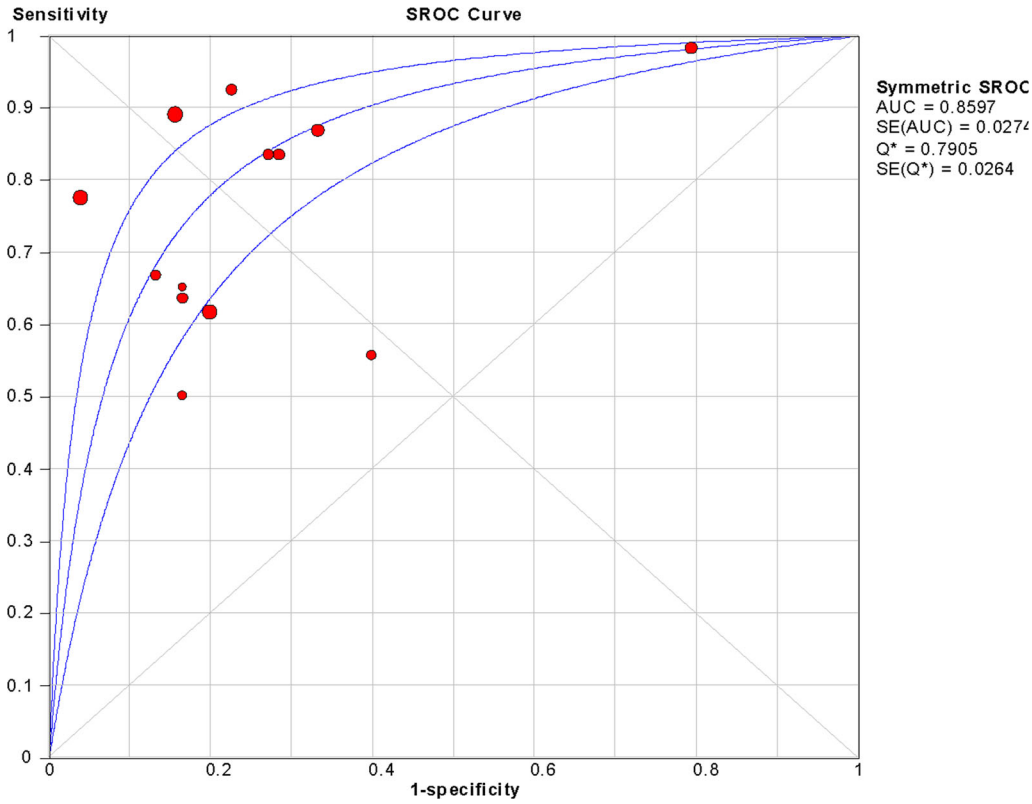

Figure 3. SROC curve of pooled sensitivity and specificity of 18F-FDG PET/CT in evaluation of IE.

is also a possibility of partial verification bias as the clinical providers were aware of the PET/CT results, which may have influenced their clinical decision making. Further potential sources of heterogeneity include the different settings or different variety of patients in the included studies. Meta-regression analyses demonstrated publication bias (Figure 4) without other significant findings.

Quality of Evidence

The QUADAS-2 summary plot (Figure 5) demonstrates the overall adequacy of the methodological quality of the included studies. Risk of bias was related to the lack of random sequence generation, and lack of blinding for imaging technique or outcome assessment in the majority of studies. Additionally the absence of a gold standard for diagnosis of IE was a consistent concern across all studies.

DISCUSSION

In this meta-analysis of 13 studies involving 537 patients, PET/CT had a moderate sensitivity of 76.0% and specificity of 78.5% for the diagnosis of IE. In the evaluation of patients with suspected prosthetic valve endocarditis, the sensitivity improved to 80.5%. These data suggest that PET/CT has the potential for use as an adjunctive diagnostic modality in challenging cases of possible IE. The rapid turnaround time of around 2 hours combined with an excellent spatial resolution allows for precise definition of valvular infection and associated complications. It can provide information on the extent of cardiac infection, potentially before substantial damage to heart valves occurs, and detect indications for surgical intervention such as cardiac abscess or paravalvular extension of infection.

Whole body PET/CT is also a rapid means of assessing sites of extracardiac infection including clinically unsuspected distant foci, guiding more appropriate and timely intervention, as well as duration of antibiotic therapy.[21–24] Use of whole body PET/CT lead to treatment modification in up to 35% of patients with IE in one study [25] and was associated with a lower risk of relapse of infection in another investigation.[26] Use of PET/CT in the evaluation of gram positive bacteremia has reduced morbidity and mortality, as well as being cost effective.[27] Moreover, PET/CT can detect

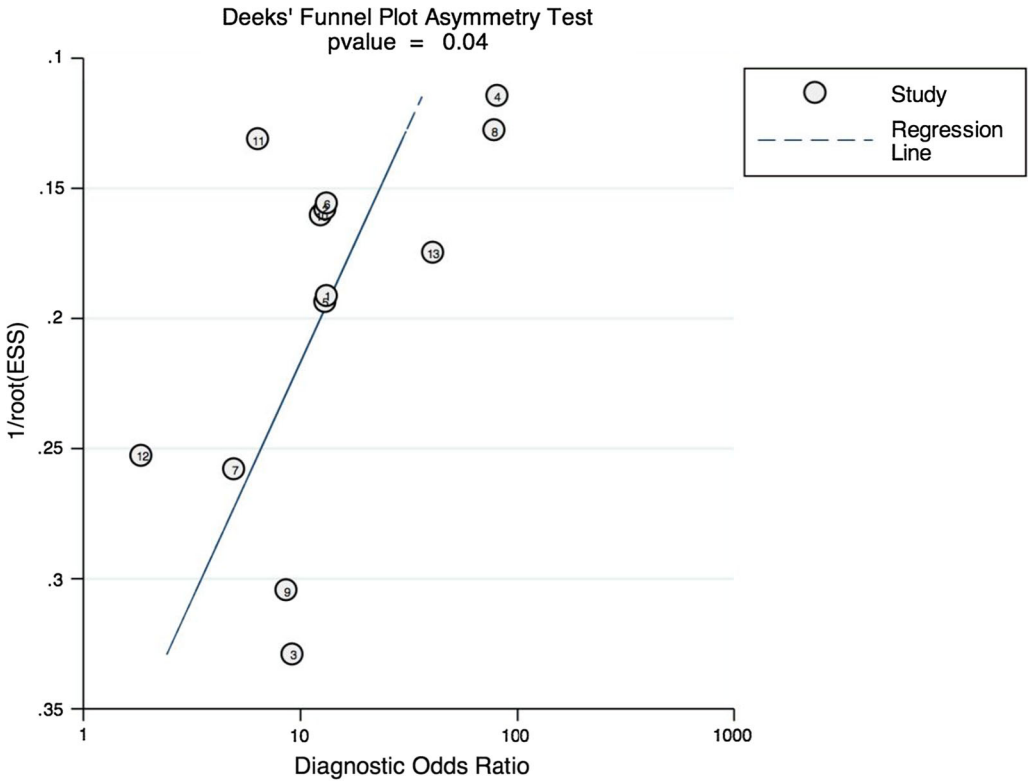

Figure 4. Deeks funnel plot—publication bias.

alternative sources of infection or inflammation, avoiding unnecessary antibiotic therapy or surgical intervention for presumed IE.

Certain factors, such as prior antimicrobial therapy, small vegetation size, and elevated blood glucose may impact the sensitivity and specificity of PET/CT. False negative findings have been reported with prior administration of antimicrobial therapy.[28,29] In addition, it can be challenging to detect FDG uptake in small vegetations, below the spatial resolution of PET (less than 4–5 mm), particularly when there is high FDG uptake in the surrounding myocardium. Imaging performed shortly after cardiac procedures, such as valve replacement surgery or cardiac device implantation, can also be challenging to interpret, as some degree of inflammation will be present at cardiac prostheses or devices for weeks to months following a procedure.[30,31] Protocols to suppress physiologic myocardial FDG utilization have improved detection of cardiac foci of infection and inflammation. These myocardial suppression protocols include patient preparation with the use of a low-carbohydrate and fat-permissive diet, fasting for at least 6 hours, and use of heparin prior to imaging. Prolonged fasting and low-carbohydrate, high-fat diets lead to decreased blood glucose and insulin levels, and increased free fatty acid levels. These methods all lead to a relative decrease in myocardial glucose utilization and improved image quality.[32] Heparin induces lipolysis and leads to an increase in free fatty acid levels; however, its utility in suppressing physiologic myocardial activity in clinical settings remains unclear. [33,34] Our findings indicate higher pooled sensitivity of 81.3% and specificity of 79.0% in studies published after 2015; these studies were more likely to include myocardial suppression methods such as prolonged fasting, administration of heparin, and use of a low-carbohydrate, fat-allowed diet. Our institution utilizes a PET/CT protocol that avoids physiologic myocardial uptake in the heart by using a low-carbohydrate, high-fat diet for 24 hours prior to imaging, fasting for at least 6 hours before imaging and a blood glucose level of less than 200 mg/dL immediately prior to imaging.

Use of CT angiography for the cardiac portion, instead of routine CT, may also improve diagnostic accuracy, particularly in prosthetic valve endocarditis.[15,35,36] Motion compensation methods, such as cardiac and respiratory gating, may also improve spatial resolution and diagnostic accuracy in the evaluation of small cardiac vegetations; however, these methods have not been adequately validated in the diagnosis of IE.[37]

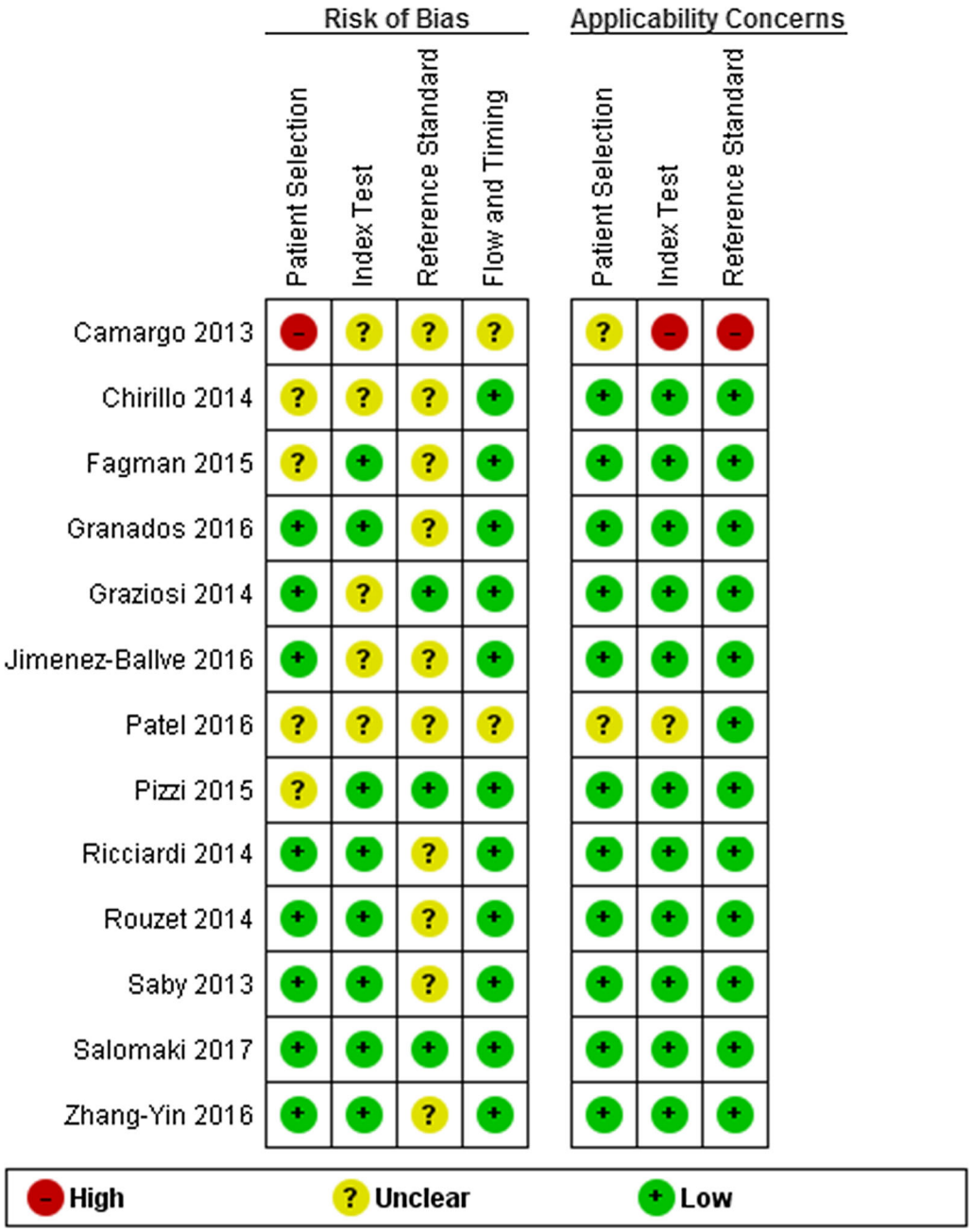

Figure 5. Summary of quality assessment of individual studies.

A previous meta-analysis on this topic included 6 studies with 246 patients with reported sensitivity of 61% and specificity of 88%.[38] The methodology of this previous study does not elaborate specific inclusion and exclusion criteria; however it included fewer studies and patients than our meta-analysis. We believe our findings to be more accurate given our comprehensive search strategy and inclusion of more studies.

LIMITATIONS

Our results suggest that there is a moderate amount of heterogeneity between studies, which likely impacted on the pooled estimates of diagnostic accuracy. Imaging protocols, data acquisition processes, blinding of interpreting providers, and blinding of PET results to clinical providers were not consistent across studies, all of which

may have contributed to heterogeneity. A threshold effect was also noted in our results which may have been due to non-blinded interpretation of images and the semi-qualitative nature of PET/CT. In this meta-analysis, 6 of the 13 included studies involved non-blinded interpretation of PET/CT, and only 1 of them included studies that blinded clinical providers to PET/CT results which may have influenced their clinical decision making.[12] As there are no validated diagnostic criteria for the interpretation of PET/CT for IE, a combination of qualitative values such as the pattern and intensity of FDG uptake, as well as semi-quantitative values such as SUVmean, SUVmax, and SQR is utilized by interpreting providers. There are as yet insufficient data to establish a cut-off value for SUV or SQR that would confidently differentiate infection from inflammation. It is also unclear whether the sensitivity of PET/CT differs based on the pathogen; its utility in gram positive bacteremia has been demonstrated, however, it is unclear whether it will consistently have the same utility in the evaluation of more indolent pathogens.[27,39]

Further uncertainty exists due to the impact of prior antibiotic treatment on the sensitivity of PET/CT for diagnosing IE. Timing and duration of prior antimicrobial therapy can affect the microbial burden at the infection site and reduce inflammatory response, leading to false negative PET/CT results. It is also unclear whether this can be a useful modality for monitoring response to therapy, particularly in challenging cases involving prosthetic valves and vascular graft material. Many of the included studies are small, single-center, retrospective series limiting their applicability to a broader setting. Larger, well-designed prospective studies, where the methodology involves consistent attempts at suppression of physiologic myocardial activity, are needed to define the role of PET/CT in the diagnosis of IE. Finally, our analysis also suggests the presence of publication bias where negative studies may not have been published.

CONCLUSION

Our findings support the utility of PET/CT as an adjunctive diagnostic tool in the evaluation of challenging cases of IE, particularly in patients with suspected prosthetic valve endocarditis. PET/CT has the potential to detect IE before structural cardiac damage occurs and can detect clinically relevant extracardiac foci of infection leading to more appropriate management interventions.

NEW KNOWLEDGE GAINED

PET/CT demonstrates promise as an adjunctive diagnostic tool for infective endocarditis, particularly in the diagnosis of prosthetic valve endocarditis.

Disclosures

LMB received royalty payments for authorship duties from UpToDate, Inc. MRS received honoraria/consulting fee from Medtronic Inc., Spectranetics, and Boston Scientific Corporation (All < US$10 K). MM, PC, SA, SF, ATK, and JCO received research grants from Medtronic Inc. They had no relationship with industry. The authors affirm that all institutional or corporate affiliations, financial disclosures, and conflicts of interest have been disclosed above.

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