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REVIEW

18F-FDG PET in the Diagnosis of Vascular Prosthetic Graft Infection: A Diagnostic Test Accuracy Meta-Analysis

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WHAT THIS PAPER ADDS

The diagnosis of vascular prosthetic graft infection is often confirmed by a peri-graft biopsy, which is both invasive and time consuming. A false positive result can lead to prolonged antibiotics and unnecessary surgery, while a false negative result can put the patient at potential risk of amputation or death. There have been multiple studies evaluating the use of 18-fluorine-fluorodeoxyglucose positron emission tomography (18F-FDG PET) as a diagnostic tool for vascular graft infections. The aim of this study was to assess the accuracy and efficacy of 18F-FDG PET which can potentially impact the diagnosis of vascular graft infections in future clinical practice.

Background: For the diagnosis of vascular prosthetic graft infection (VPGI), an intra-operative peri-graft biopsy is often required. Controversy exists regarding the use of imaging techniques in the diagnostic process. This study aimed to evaluate the diagnostic accuracy of 18-fluorine fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) in VPGI.

Methods: A systematic search of electronic databases was conducted, applying a combination of free text and controlled vocabulary searches adapted to thesaurus headings, search operators, and limits to identify studies assessing the use of 18F-FDG PET in the diagnosis of VPGI. A meta-analysis was conducted using a mixed effects logistic regression bivariate model.

Results: Twelve studies were identified reporting a total of 433 prostheses, of which 202 were proven to be infected. Analysis of PET scan was performed using five different methods: graded uptake, focal uptake, maximum standardised uptake value (SUVmax), tissue to background ratio (TBR), and dual time point (DTP). The pooled estimates for sensitivity and specificity for graded uptake were 0.89 (95% CI 0.73—0.96) and 0.61 (95% CI 0.48—0.74), respectively; they were 0.93 (95% CI 0.83—0.97) and 0.78 (95% CI 0.53—0.92) for focal uptake; 0.98 (95% CI 0.42—0.99) and 0.80 (95% CI 0.70—0.88) for SUVmax; 0.57 (95% CI 0.39—0.73) and 0.76 (95% CI 0.64—0.85) for TBR; and 1.00 (95% CI 0.48—1.00) and 0.88 (95% CI 0.68—0.97) for DTP. Sensitivity analysis including studies that investigated the diagnostic accuracy of PET combined with computed tomography (CT) showed higher sensitivity and specificity for focal uptake, graded uptake, and SUVmax than 18F-FDG PET alone.

Conclusions: This meta-analysis suggests that 18F-FDG PET has a high sensitivity in diagnosing VPGI and its accuracy can be further increased by combining PET with CT.

Keywords: Vascular graft, Infection, Positron-emission tomography, PET, Diagnostic accuracy
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INTRODUCTION

Vascular prosthetic graft infection (VPGI) is the infection of the synthetic material used for reconstructive vascular surgery. It can occur at any point after surgery and has an incidence of 15% and a prevalence of 1—6%.[1,2] Diagnosis of VPGI in a precise and timely manner is essential as a false

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positive result may lead to unnecessary surgery or long courses of antibiotics, whereas a false negative result may lead to an amputation or even death. Clinical presentation can be vague and depend on the graft location and the timing of the infection.

Clinically suspected graft infections are confirmed with bacterial cultures of explanted graft or tissue surrounding the graft. This technique, although reliable, is quite inefficient in terms of time and resources.[2] Imaging techniques such as ultrasonography (US), computed tomography (CT), 99m Tc-HMPAO labelled leukocyte scintigraphy, or magnetic resonance (MR) imaging are commonly used to investigate graft infections but are associated with a high number of false negatives in low grade infections.[3]

18-fluorine-fluorodeoxyglucose (18F-FDG) is a radioactive glucose isotope which can be detected by positron emission tomography (PET). 18F-FDG PET is a useful diagnostic modality for detecting graft infections.[4] The uptake of glucose is higher in cells with a higher than average metabolic demand. It is widely used in oncology, as cancerous cells have a high metabolism.[3] Infections and inflammations also lead to activated leukocytes having a high glucose uptake, and the use of 18F-FDG PET in cases of suspected graft infection relies on the fact that these leukocytes aggregate around the infected graft.[5] The use of PET in VPGI has been assessed by multiple studies with variable results. A study comparing PET and CT in the diagnosis of vascular graft infection showed that PET had a higher sensitivity and lower specificity (91% and 64%, respectively) compared with CT (64% and 86%, respectively).[6] However, because of the high risk of false positives shown in other studies,[5] the accuracy and efficacy of PET is yet to be proven. The present objective was to investigate the accuracy of 18F-FDG PET in the diagnosis of VPGI.

METHODS

Design

The review objectives, inclusion criteria, and methods of analysis were pre-specified in a study protocol. The review was reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) of diagnostic test accuracy studies.[7]

Criteria for considering studies for this review

Types of studies. Retrospective observational, cohort or cross sectional and prospective studies that assessed the use of 18F-FDG PET in the diagnosis of VPGI were included. Case studies and reports of less than five patients, review articles, conference abstracts, and commentaries were excluded.

Participants. Patients of any age and gender who had undergone non-cardiac vascular or endovascular surgery with prosthetic graft insertion and had a suspected post-operative/interventional VPGI were considered. Any type of prosthetic graft used for open reconstructive vascular surgery, including polytetrafluoroethylene (PTFE) or Dacron, and any type of covered or uncovered stent for endoluminal treatment of vascular disease were considered.

Index test. 18F-FDG PET imaging is a PET scan done after the injection of radioactively labelled glucose, 18F-FDG. In VPGI, the infected tissues release inflammatory cells including macrophages and neutrophils, which have more glucose transporters in their membranes, hence increasing the uptake of 18F-FDG compared with surrounding healthy tissues. This is reflected with a brighter appearance on the scan result. During the early post-operative stages, this method resulted in many false positive cases as the number of activated leukocytes is increased in inflammatory tissue for reparative purposes.[3] Hence in some studies, it has been used together with CT or MR images to improve its diagnostic accuracy, known as hybrid PET/CT or PET/MR scans.[8]

Target conditions. VPGI is the bacterial colonisation of the wound and underlying graft, which most often happens because of intra-operative contamination from the normal skin flora. It can occur at any point after vascular or endovascular surgery, and its outcome depends on the location of the surgery. It is suspected when a patient with a surgically or interventionally inserted prosthetic graft in a vessel has clinical symptoms or signs of infection, high inflammatory markers, and/or positive blood cultures. The clinical signs and symptoms are variable and not always specific. Laboratory and microbiology results are often indicative of a VPGI, such as elevated inflammatory markers (C-reactive protein [CRP] and white cell count [WCC]) in peripheral blood samples and positive blood cultures.[9]

Reference standards. The reference standard used in the selected papers to confirm the diagnosis of VPGI was the positive microbiology results of the graft biopsy after surgical resection or the bacterial culture results of the perigraft material. As vascular prosthetic graft biopsy is highly invasive, blood cultures, with other imaging modalities, combined with clinical follow up of up to 18 months, have been used.

CT, when used as the reference standard, identified irregular structural boundaries to confirm graft infection. Other less reliable CT findings were fluid collection in the graft area, fluid retention around the graft, formation of pseudoaneurysm, graft wall thickening, soft tissue swelling, and air bubbles.[3] Some of these signs are common in the early post-operative period and have a better sensitivity and specificity in cases of high grade infections.[5]

Leukocyte scintigraphy has also been used; however, it fairs better as a follow-up tool, as it is unable to detect subtle morphological changes and cannot differentiate between post-operative reparative changes and infections.[10]

Search methods for identification of studies

The literature search strategy was developed by the review author team in collaboration with clinical information specialists at the Royal Oldham Hospital. The Healthcare Databases Advanced Search (HDAS) interface by the National Institute for Heath and Care Excellence (NICE) was

used to run searches in the MEDLINE/PubMed and EMBASE/Ovid databases. The literature search was done in September 2017 over a three week period and without applying any language restriction. A combination of controlled vocabulary and text words was used to search the databases. When the full text of relevant articles could not be retrieved from local or national resources, the corresponding author was contacted to request a reprint. The search strategy is presented in Appendix 1 (supplementary material).

Data collection and analysis

Selection of studies. Eligibility assessment of identified studies was performed by two review authors (DR, NK) independently. A third author (GA) acted as an arbitrator when consensus could not be reached between the two. The titles and abstracts of the studies identified during electronic searches were screened. Relevant studies meeting the inclusion criteria for the review were selected and the full text articles were retrieved through OpenAthens.

Data extraction. Data extraction was undertaken by one review author (DR). The retrieved data were then cross-checked by a second review author (NK). The following data were extracted from the full texts of the selected articles:

- Article (author, year and journal of publication)
- Study design (sample size, type of study)
- Study population demographics (age, gender)
- Reference standard, performance of the reference standard (microbiology biopsy results, CT scans, or clinical follow up)
- Index test, performance of the index test, quantifying the index test (focal uptake, graded uptake, maximal standardised uptake value [SUVmax], tissue to background ratio (TBR), dual time point reference index [DTP RI], and interpreter)
- Information about the quality assessment using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool
- Data for two by two contingency tables (absolute numbers of true positives, false positives, true negatives, false negatives, positive predictive value, negative predictive value, sensitivity, specificity, accuracy).

Assessment of methodological quality. The methodological quality of each included study was assessed using the QUADAS-2 tool on RevMan 5.3 (Cochrane collaboration, Copenhagen, Denmark). Two review authors (DR, NK) performed the methodological quality assessment independently. Participant selection, index test, reference test, and flow and timing are the four domains assessed for risk of bias. Flow and timing refers to patient flow and an appropriate interval between index test and reference standard. Applicability was also assessed for the first three domains, namely participant selection, index text, and reference test. Within each domain, the questions were answered with "yes," "no," or "unclear," and the bias risk for each domain was classified as "low," "high," or "unclear."

Statistical analysis and data synthesis. In the included studies, the reference standard and the index tests have dichotomous outcomes. Two by two contingency tables were constructed for all included studies, and true positives, false positives, false negatives, and true negatives based on the study authors' pre-specified and recommended thresholds were enumerated. Different studies used different imaging interpretation techniques for the 18F-FDG PET scan; therefore, sensitivity and specificity with 95% CI were calculated for each method in each study with RevMan 5.3. Forest plots were produced to show the variation of sensitivity and specificity estimates together with their 95% CI. The imaging test results were also plotted on a receiver operating characteristic (ROC) plot of true positive rate (sensitivity) against false positive rate (1 - specificity). A meta-analysis for each index test interpretation was performed separately using a mixed effects logistic regression bivariate model, where the logit transformed sensitivities and specificities were modelled.[11] The summary sensitivity and specificity (summary operating point) with their 95% CIs were then calculated, from which the diagnostic odds ratio (DOR), positive (LR+) and negative (LR-) likelihood ratios were obtained. Hierarchical summary ROC (HSROC) curves were developed presenting the summary points, 95% confidence regions and 95% prediction regions. The analyses were undertaken using the "metandi," "xtmelogit," or "gllamm" commands in Stata (Stata-Corp, College Station, TX, USA).

Investigations of heterogeneity. Because of the insufficient number of available studies, variation in sensitivity and specificity by adding covariables to the meta-analysis models was not investigated.

Sensitivity and subgroup analyses. The meta-analysis was repeated including only studies that combined results for PET and CT scan.

Assessment of reporting bias. The number of included studies was also inadequate to assess reporting bias by funnel plot.[12]

RESULTS

Results of the search

In the literature search on MEDLINE/PubMed for "vascular graft infection," 57,916 results were obtained and for "18F-FDG PET scan," 129,823 reports were found. A combination of both terms yielded 390 papers. During a similar search on EMBASE/Ovid, 15,845 results were obtained for "vascular graft infection" and 203,532 results were obtained for "18F-FDG PET scan." A combination of both results retrieved 385 papers. The final comprehensive search identified 775 studies, one of which had to be

obtained from the author contacted via Research Gate. Of the 775 articles, 37 articles were selected based on the title and abstract. Twenty-four studies were irrelevant and discarded, and the remaining 13 studies were selected for review based on the inclusion criteria. Two studies had a patient selection overlap of 2 years and the smaller study was hence excluded. This left the 12 studies reviewed in this paper. The literature search process is detailed in the PRISMA flow diagram (Fig. 1).

Characteristics of included studies

The characteristics of the included studies are presented in Table 1. A total of 433 prostheses were analysed, of which 202 were proven to be infected. The mean age range for patients was 63—73 years. The identified studies used one or more different methods of interpretation to assess the efficiency of 18F-FDG PET scan in the diagnosis of VPGI, and the scan results were evaluated by one or two experienced physicians, in a blinded manner.

The images were interpreted either semi-quantitatively using SUVmax, TBR, and DTP RI, or visually using a focal uptake or graded uptake scale. SUVmax is defined as the maximum concentration of 18F-FDG divided by injected dose and corrected for the body weight of the patient, and the threshold was set using the area under the curve (AUC) method. The threshold varied between studies depending on findings. Focal uptake is a three point scale used to assess the uptake of 18F-FDG in the graft; namely focal/very strong, inhomogeneous/moderate, and zero uptake. Inhomogeneous uptakes and intense uptakes were used as positive findings, whereas minimal or zero uptake was considered as a negative result. The graded uptake is a five point visual grading scale as follows:

1 Zero, 18F-FDG uptake similar to background uptake
2 Low, comparable to muscle and fat
3 Moderate, clearly visible and higher than inactive muscle and fat
4 Strong, but distinctly less than physiological urine bladder activity
5 Very strong, comparable to physiological urinary activity of bladder.

The visual grading scale, or graded uptake, was the most uniform way of assessing the usefulness of the index test across the studies. The grading scales 2—4 were considered as positive results in the studies that used this scale.

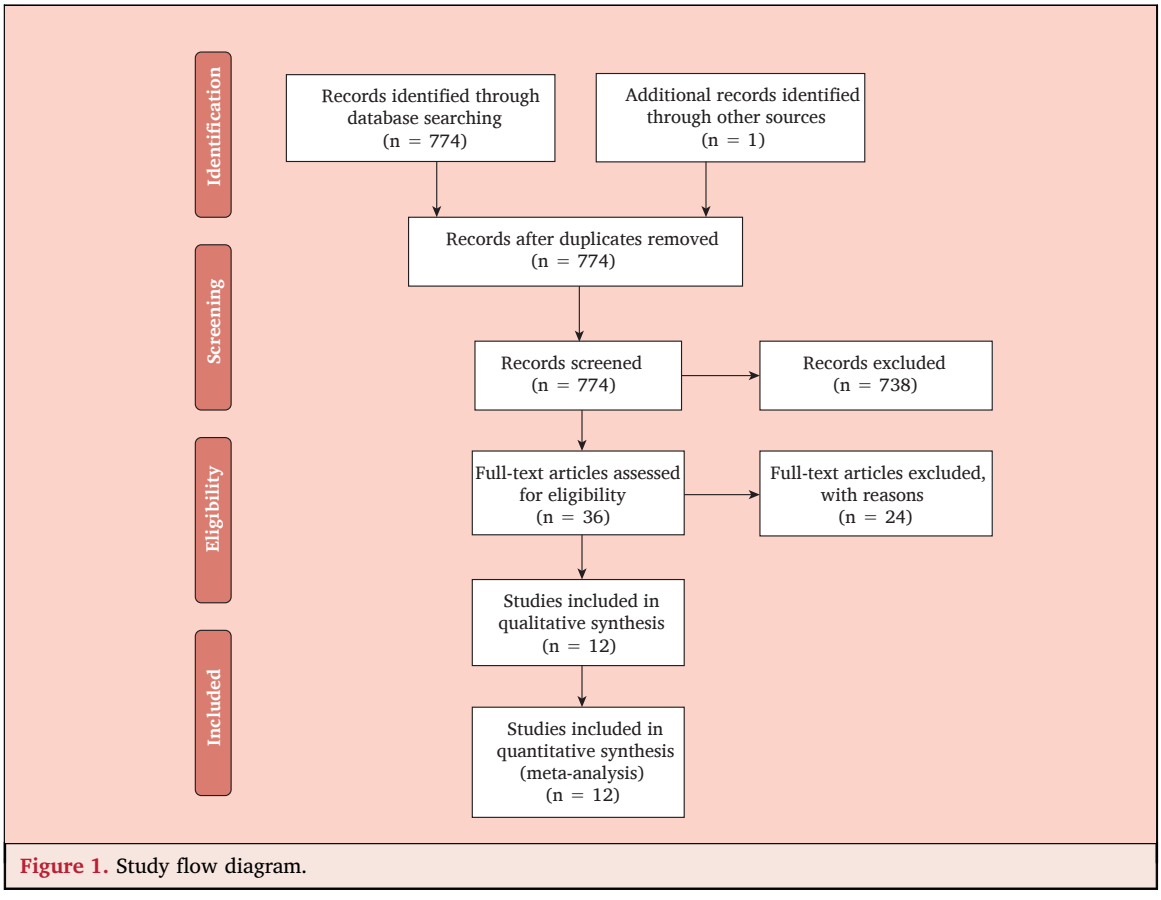

Figure 1. Study flow diagram.

Table 1. Characteristics of the studies

Author	Year	Type of study	Location of graft	Mean patient age	P	IP	UP	CC	Interpretation of 18F-FDG PET scans	Reference standard
Fukuchi et al.[17]	2005	Prospective	Aortic and peripheral	71	33	11	15	7	Graded uptake Focal uptake	Surgical and microbiological findings; in cases in which no surgical treatment or no microbiological samples, clinical follow up for >4 months
Keidar et al.[19]	2007	Prospective	Aortic and peripheral	68	69	15	54	29	Focal uptake	Histopathological/microbiological findings obtained at surgery or by decision of the referring clinical team based on further imaging work up and clinical follow up
Lauwers et al.[20]	2008	Prospective	Aortic and peripheral	63	9	4	5	0	Focal uptake (Intense) Focal Uptake (Intense + Inhomogeneous)	Operative/histopathological finding or a clinical follow up of >6 months
Spacek et al.[21]	2008	Retrospective	Aortic	68	96	55	41	0	Focal uptake	Microbiological examination of graft and peri-graft tissue culture
Wassélius et al.[6]	2008	Retrospective	Aortic	73	16	1	15	0	Graded uptake	Blood cultures; CT/leukocyte scintigraphy
Bruggink et al.[18]	2010	Prospective	Aortic and peripheral	67	25	15	10	0	Graded uptake	Positive staining of the prosthesis after exploration (irrespective of antibiotic therapy) and positive staining of peri-graft fluid obtained by puncture
Tokuda et al.[15]	2012	Retrospective	Aortic	65	9	4	5	0	SUVmax (>8)	Surgical, microbiological, and clinical follow up
Berger et al.[13]	2015	Retrospective	Central	69 (uninfected) 66 (infected)	59	32	9	18	SUVmax (>5.5) TBR (>3) Graded uptake Focal uptake	Clinical or biochemical signs with positive cultures, or based on a combination of clinical, biochemical, and imaging parameters (other than PET scan data)
Chang et al.[5]	2015	Prospective	Aortic	67	29	5	24	0	SUVmax (>5) DTP RI (>20%)	Surgical findings and microbiological exams derived directly from surgical specimens and fluids, or image guided drainage
Saleem et al.[14]	2015	Prospective	Aortic	66	37	21	16	0	Graded uptake SUVmax (>8) TBR (>6) Focal uptake	Positive culture of material obtained by puncture or after surgery
Sah et al.[16]	2015	Prospective	Aortic and peripheral	67	34	27	7	0	SUVmax (>3.8) Graded uptake Focal uptake	Intra-operative findings and microbiological and histological results of graft with a 6–12 month follow up
Karaca et al.[3]	2016	Retrospective	Aortic and peripheral	67	17	12	5	0	SUVmax (>3.5)	Follow up with control CT scan at 6 and 12 months post-discharge

18F-FDG = 18-fluorine-fluorodeoxyglucose; CC = control cases (patients with prostheses undergoing PET scan for other purposes); CT = computed tomography; DTP RI = dual time point reference index; IP = number of infected prostheses; P = number of prostheses analysed; PET = positron emission tomography; SUVmax = maximum standardised uptake value; TBR = tissue to background ratio; UP = number of uninfected prostheses.

Some studies used more than one of the above modalities for interpretation. DTP RI was used in only one study, TBP was used twice,[13,14] SUVmax was used in six studies,[5,10,13–16] as well as graded uptake,[6,13,14,16–18] and focal uptake was used in seven studies.[13,14,16,17,19–21] Combined PET CT scan was used in eight studies.[3,5,6,15,16,18,19,21]

Microbiological culture and histopathological results from explanted grafts or peri-graft material are the gold standard to confirm a graft infection. However, because of the invasive nature of the test and the expenses involved, clinical or biochemical signs and blood cultures combined with further imaging and follow up were used in some studies to confirm

VPGI. Nine of the 12 studies used surgical and microbiological findings as their reference standards, or a clinical follow up of a few months to a few years where no culture or histopathological sample was available.[5,14–21] Two of the studies used clinical signs and blood cultures together with imaging parameters, such as CT or leukocyte scintigraphy.[6,9] The remaining one study used follow up with a control CT scan at 6 and 12 months to diagnose graft infection.[5]

Patients with diabetes were included in seven of the 12 studies,[13–16,18–20] with pre-scan glucose level checks, and were excluded in two studies[17,21] to minimise bias. The remaining three studies[5,6,10] did not comment on the diabetic status of the patients. All the patients had a fasting period of 4—6 h before the scan.

Six studies made a distinction between high and low grade infection.[13,15,17–19,21] The numbers of patients with increased 18F-FDG uptake in patients with confirmed high and low grade infections are presented in Table S1. There are no data available on false positives/negatives to enable a subgroup analysis.

Methodological quality of included studies

Sources of bias in the accuracy of the index text were mainly related to the variability in parameters used for the PET scan interpretation, thus introducing information bias. The risk of bias and applicability concerns summary and graph are shown in Fig. 2A and B, respectively. The reference standard was also a source of limitation as some studies used peri-operative cultures whereas others used CT scans and follow ups of variable lengths of time. Aortic and peripheral grafts have different presentations and findings, and some studies had a combination of both without making clear distinctions in the analysis, which is believed to contribute to information bias. There was no specific time interval between the index test and reference standard; however, it does not impact the results of either the reference or the index test and hence was not thought to be a significant source of bias. The main reason was that emergency surgery to salvage a limb or prevent death was often needed, hence it was not possible to apply a specific time lapse between the index test and

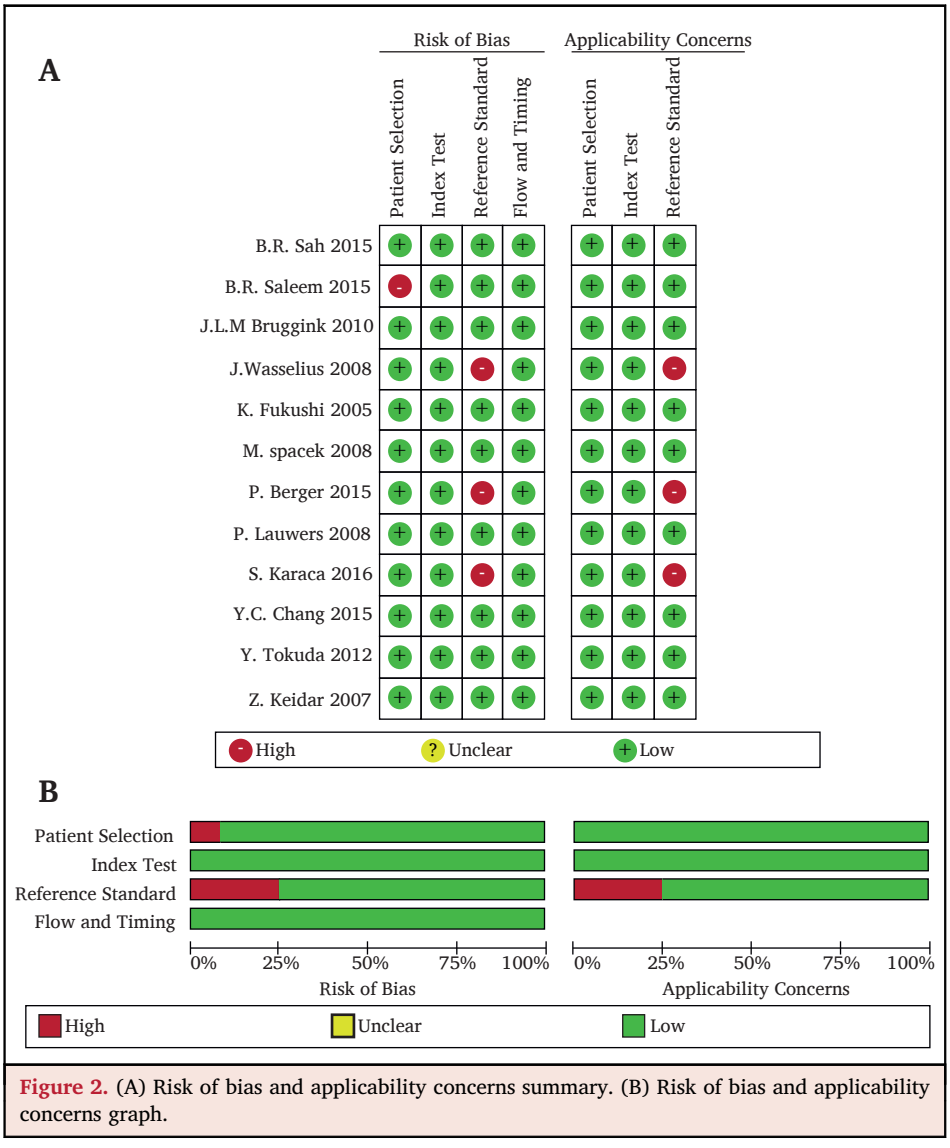

Figure 2. (A) Risk of bias and applicability concerns summary. (B) Risk of bias and applicability concerns graph.

reference standard. The most important source of bias in the study of Saleem et al.[14] was the use of antibiotics in 80% of the patients selected, but this was inevitable because of the highly virulent nature of the colonizing organism and the potential threat posed if antimicrobial therapy was to be delayed. Most studies had an acceptable risk of bias and good applicability. The characteristics of the included studies are presented in Appendix 2 (supplementary material).

Findings

The forest plots of sensitivities and specificities of the five methods of assessing the use of the index test are presented in Fig. 3. Fig. S1 presents the summary ROC plots for the methods of interpretation of 18F-FDG PET and Fig. S2 presents the summary ROC plots with paired data only. The HSROC curves for each interpretation method are presented in Fig. 4A—D.

Graded uptake. Sensitivity estimates for graded uptake ranged from 0.72 to 1.00 and the specificity estimates ranged from 0.33 to 0.86. The pooled estimates for sensitivity and specificity were 0.89 (95% CI 0.73—0.96) and 0.61 (95% CI 0.48—0.74), respectively. The DOR was 13.25 (95% CI 3.10—56.61). The LR+ and LR- was 2.32 (95% CI 1.27—4.22) and 0.17 (95% CI 0.06—0.53), respectively.

Focal uptake. Sensitivity estimates for focal uptake ranged from 0.69 to 1.00 and the specificity estimates ranged from

Graded Uptake

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
K. Fukushi 2005	10	8	1	14	0.91 [0.59,1 .00]	0.64 [0.41, 0.83]
J.Wasselius 2008	1	10	0	5	1.00 [0.03, 1.00]	0.33 [0.12, 0.62]
J.L.M. Bruggink 2010	14	3	1	7	0.93 [0.68, 1.00]	0.70 [0.35, 0.93]
P.Berger 2015	23	12	9	15	0.72 [0.53, 0.86]	0.56 [0.35, 0.75]
B.R.Saleem 2015	18	6	3	10	0.86 [0.64, 0.97]	0.63 [0.35, 0.85]
B.R. Sah 2015	27	1	0	6	1.00 [0.87, 1.00]	0.86 [0.42,1 .00]

Focal Uptake

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
K. Fukushi 2005	10	1	1	21	0.91 [0.59, 1.00]	0.95 [0.77, 1.00]
Z. Keidar 2007	14	2	1	52	0.93 [0.68, 1.00]	0.96 [0.87, 1.00]
M. Spacek 2008	54	10	1	31	0.98 [0.90, 1.00]	0.76 [0.60, 0.88]
P.Lauwers 2008	4	3	0	2	1.00 [0.40, 1.00]	0.40 [0.05, 0.85]
P.Berger 2015	22	7	10	20	0.69 [0.50, 0.84]	0.74 [0.54, 0.89]
B.R. Saleem 2015	19	12	2	4	0.90 [0.70, 0.99]	0.25 [0.07, 0.52]
B.R. Sah 2015	26	1	1	6	0.96 [0.81, 1.00]	0.86 [0.42, 1.00]

Maximal standardised uptake value

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Y. Tokuda 2012	4	1	0	4	1.00 [0.40, 1.00]	0.80 [0.28, 0.99]
B.R. Salem 2015	8	2	13	14	0.38 [0.18, 0.62]	0.88 [0.62, 0.98]
P. Berger 2015	26	5	6	22	0.81 [0.64, 0.93]	0.81 [0.62, 0.94]
Y.C. Chang 2015	5	5	0	19	1.00 [0.48, 1.00]	0.79 [0.58, 0.93]
B.R. Sah 2015	27	1	0	6	1.00 [0.87, 1.00]	0.86 [0.42, 1.93]
S. Karaca 2016	12	2	0	3	**1.00 [0.74, 1.00]**	0.60 [0.15, 0.95]

Tissue to background ratio

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
B.R. Saleem 2015	8	3	13	13	0.38 [0.18, 0.62]	0.81 [0.54, 0.96]
P. Berger 2015	23	8	9	19	0.72 [0.53, 0.86]	0.70 [0.50, 0.86]

Dual time point reference index

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Y.C. Chang 2015	5	3	0	21	1.00 [0.48, 1.00]	0.88 [0.68, 0.97]

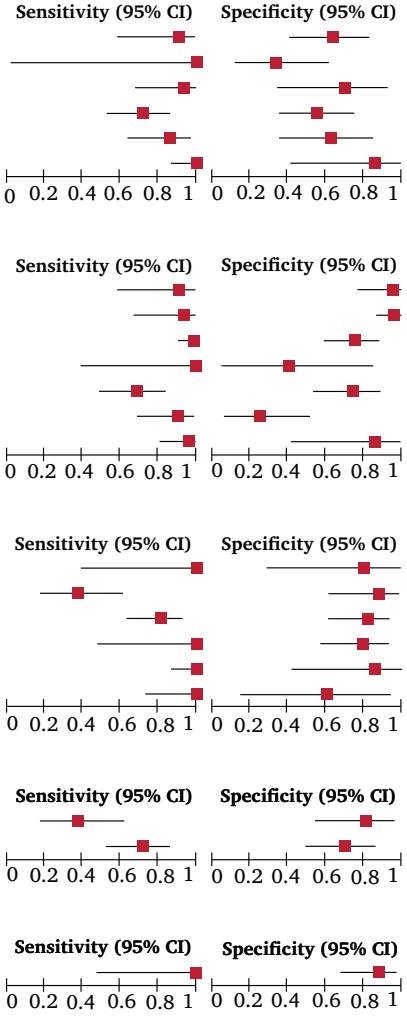

Figure 3. Forest plots of sensitivities and specificities of the five methods of assessing the use of the index test (18F-FDG PET = 18-fluorine-fluorodeoxyglucose positron emission tomography). CI = confidence interval; TP = true positive; TN = true negative; FP = false positive; FN = false negative.

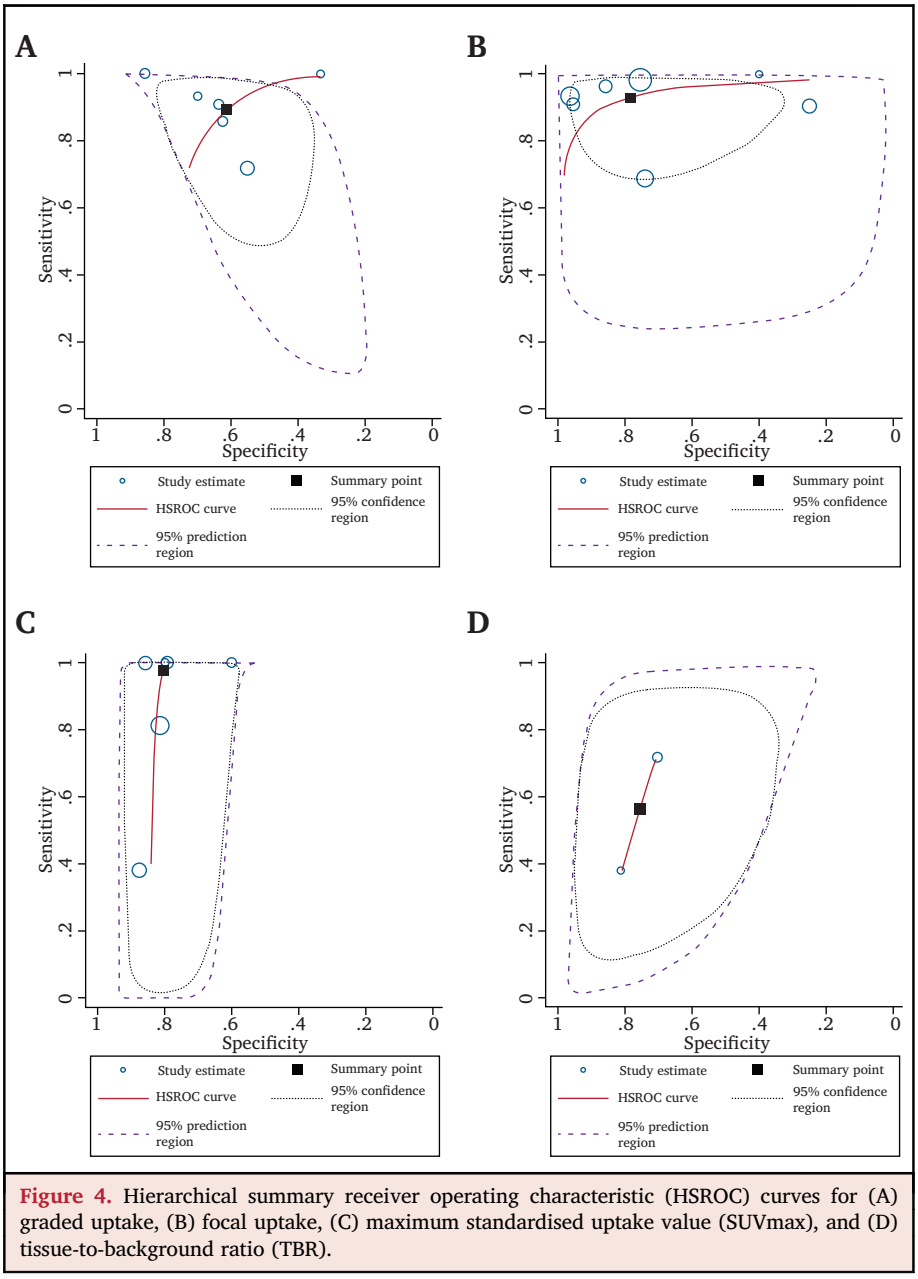

Figure 4. Hierarchical summary receiver operating characteristic (HSROC) curves for (A) graded uptake, (B) focal uptake, (C) maximum standardised uptake value (SUVmax), and (D) tissue-to-background ratio (TBR).

0.25 to 0.96. The pooled estimates for sensitivity and specificity were 0.93 (95% CI 0.83—0.97) and 0.78 (95% CI 0.53—0.92), respectively. The DOR was 48.68 (95% CI 9.61—246.65). The LR+ and LR- was 4.32 (95% CI 1.71—10.90) and 0.89 (95% CI 0.03—0.25), respectively.

SUVmax. Sensitivity estimates for SUVmax ranged from 0.38 to 1.00 and the specificity estimates ranged from 0.60 to 0.88. The pooled estimates for sensitivity and specificity were 0.98 (95% CI 0.42—0.99) and 0.80 (95% CI 0.70—0.88), respectively. The DOR was 176.73 (95% CI 2.98—10 479.27). The LR+ and LR- was 4.98 (95% CI 3.12—7.94) and 0.03 (95% CI 0.00—1.54), respectively.

TBR. Sensitivity estimates for TBR ranged from 0.38 — 0.72 and the specificity estimates ranged from 0.70 to 0.81. The pooled estimates for sensitivity and specificity were 0.57 (95% CI 0.39—0.73) and 0.76 (95% CI 0.64—0.85), respectively. The DOR was 4.04 (95% CI 1.92—8.51). The LR+ and LR- was 2.32 (95% CI 1.50—3.59) and 0.57 (95% CI 0.39—0.84), respectively.

DTP. One study only reported this method of 18F-FDG PET. The sensitivity was 1.00 (95% CI 0.48—1.00) and the sensitivity was 0.88 (95% CI 0.68—0.97).

Sensitivity analysis. Eight studies investigated the diagnostic accuracy of PET CT.[3,5,6,15,16,18,19,21] Meta-analysis showed that the pooled estimate of sensitivity and specificity for focal uptake was 0.97 (95% CI 0.89—0.99) and 0.89 (95% CI 0.70—0.96), respectively; for graded uptake 0.97 (95% 0.77—0.99) and 0.62 (0.31—0.86), respectively; and for SUVmax 0.99 (95% CI 0.95—0.99) and 0.78 (95% CI 0.68—0.86), respectively.

DISCUSSION

The search strategy identified 12 eligible papers that evaluated the efficacy of PET scans in diagnosing graft infections. In general, the 18F-FDG PET scan had a high sensitivity and a lower specificity. One of the factors influencing the 18F-FDG uptake is the time at which the PET scan was done. Karaca et al.[3] and Berger et al.[13] stated that 18F-FDG uptake reaches its peak in the first few weeks after surgery and tends towards normal values around 4 weeks post-operatively. If PET scans are performed in cases of recently implanted grafts, increased uptake can occur in uninfected grafts. This could account for the considerable number of false positives in the studies. False positive results also occurred when infections localised in the vicinity of the graft led to a high 18F-FDG uptake. In the studies performed by Keidar et al.[19] and Sah et al.,[16] infected haematoma and lymphocoele surrounding the graft led to such results. False negative results occurred mainly because of the use of antibiotics prior to imaging, thus lowering the metabolic activity expected in infections and lowering the 18F-FDG uptake.[14,16,19]

One evident finding of the present study is the remarkable variability in the parameters used among studies to analyse the PET scan images. A mix of quantitative (SUVmax, TBR, DTP), semi-quantitative (graded uptake), and qualitative variables (focal uptake) was employed. The sensitivity and specificity varied for each of these parameters. For SUVmax, there is no consensus regarding the cutoff value for a positive result. The values used in the selected studies varied between 3.5 and 8. The pooled estimates for sensitivity and specificity were 0.98 (95% CI 0.42—0.99) and 0.80 (95% CI 0.70—0.88), respectively. Focal uptake was one of the modalities that had a high sensitivity (0.90 and above) in most of the studies, with a pooled estimate of 0.93 (95% CI 0.83—0.97). Its specificity was low in some studies but generally presented an acceptable pooled estimate of 0.78 (95% CI 0.53—0.92). Focal uptake may have the disadvantage that mostly represents a qualitative variable which cannot be easily standardised. Additionally, while there is consensus that intense focal uptake indicates a high probability of VPGI, interpretation of inhomogenous/diffuse uptake is not straightforward. If this is considered a positive finding, the false negative results are reduced while the false positives increase, resulting in a higher sensitivity at the expense of a lower specificity. For example, in the study by Spacek et al.,[21] where inhomogeneous FDG uptake was considered a negative result, sensitivity and specificity were 78.2% and 92.7%, respectively; however, when inhomogeneous FDG uptake was considered a positive result, sensitivity and specificity were 98.2% and 75.6%, respectively.

Despite the abovementioned limitations, SUVmax and focal uptake seem to present the highest values of sensitivity and specificity and the higher overall diagnostic accuracy to identify vascular graft infection compared with the other variables evaluated in the studies included in this review. Specifically, TBR, although a quantitative variable, presented a pooled estimate for sensitivity and specificity of 0.57 (95% CI 0.39—0.73) and 0.76 (95% CI 0.64—0.85), respectively, thus rendering this variable inadequate to interpret the results of 18F-FDG PET scans. Moreover, regarding the graded uptake, pooled estimates for sensitivity and specificity were 0.89 (95% CI 0.73—0.96) and 0.61 (95% CI 0.48—0.74), respectively. Despite being the only modality that had consistent parameters for the interpretation of 18F-FDG uptake for all the six studies,[6,13,14,16—18] the sensitivity of this index was somewhat lower and the specificity remarkably inferior compared with SUVmax and the focal uptake. The chronic low inflammation present after surgery could have accounted for the high number of false positives, whereas infection or inflammation present outside the graft could have accounted for part of the high uptake as well.

Notably, DTP RI had a sensitivity of 1.00 (95% CI 0.48—1.00) and the specificity was 0.88 (95% CI 0.68—0.97), which compare favourably with the rest of the variables examined, but this parameter was evaluated in one study only, thus presenting very limited supportive evidence. Therefore, despite Chang et al.[5] suggesting that it could help to differentiate between prosthetic and extra-prosthetic infections leading to targeted cultures and guided antibiotic treatment, further studies are required to assess this parameter.

Low grade infections are notoriously difficult to diagnose. Only six studies[13,15,17—19,21] made a distinction between a high and low grade infection but, unfortunately, did not provide data suitable for meta-analysis. 18F-FDG PET may offer a benefit in making an accurate diagnosis in low grade infections when even the microbiological cultures can be negative and its role in this setting should be the focus of future research.

PET scan has multiple advantages; it is faster than other modalities, it has better spatial resolution and higher quality images compared with CT. However, the lack of consensus on its accuracy stems from the use of different parameters for analysis. CT improves accuracy by analysing morphological appearances of graft boundaries and by localizing pus collection enabling drainage instead of exploration. Bruggink et al.[18] showed a sensitivity for PET and CT scan of 93% and 56%, respectively, and a specificity of 79% and 57%, respectively. The study also assessed the fusion of PET and CT scans, and the sensitivity and specificity were 93% and 70%, respectively, when judged by a nuclear medicine physician and 73% and 60%, respectively, when judged by a radiologist. This emphasises that the interpreter can be a limiting factor when assessing the diagnostic accuracy of the imaging technique. The hybrid PET/CT scan has also been suggested by many of the selected papers as a better diagnostic tool as it combines morphology and metabolism, thus offering added analytical value. The combined results for PET and CT scan were specifically reported in eight studies.[3,5,6,15,16,18,19,21] Meta-analysis including those studies only showed that the sensitivity and specificity for focal uptake, graded uptake, and SUVmax were higher than those of 18F-FDG PET alone. These results suggest that fusion of these modalities should be employed whenever

feasible as it is advantageous in terms of diagnostic accuracy compared with each of these techniques alone.

The findings of the review should be interpreted in the context of its strengths and limitations. This review was conducted in accordance with the PRISMA statements standards for diagnostic test accuracy studies.[7] The literature search strategies were set in conjunction with clinical information specialists and a thorough literature search was undertaken, without time or language constraints, to identify all relevant articles. Hierarchical summary models were used, which have been proposed for meta-analysis examining the diagnostic accuracy of tests. The methodological quality of the included studies was assessed using the QUADAS-2 tool and acceptable quality was found for most of the included studies. An important limitation is the heterogeneity in the studies included in the review, which stems from different study design (retrospective or prospective), different methods used to interpret PET scans, different reference tests employed by the authors of the selected studies, and different location and type of the infected grafts. Furthermore, the length of follow up varies among the studies that used clinical follow up as part of the reference standard or not indicated at all.

CONCLUSIONS

Overall, 18F-FDG PET scan in combination with CT scan in the diagnosis of VPGI is promising. A consensus about the parameters used for interpretation of the results would lead to better diagnostic accuracy. Focal uptake and SUVmax are the two most reliable parameters used. Results from larger studies could be more supportive of the present findings. Diagnostic accuracy could be increased by performing the scan prior to antimicrobial treatment.

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CONFLICT OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvs.2018.08.040.

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