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REVIEW

Diagnostic Imaging in Vascular Graft Infection: A Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

This meta-analysis gives an overview of the current imaging techniques used in diagnosing vascular graft infections. It shows that conventional techniques, such as CT(A), have a low accuracy and therefore seem to be obsolete in the diagnostic analysis of vascular graft infections. Nuclear imaging techniques, such as FDG-PET and WBC scintigraphy, show a higher accuracy and their diagnostic value seems to improve if combined with SPECT/CT.

Background: 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. The objective of this study was to determine the diagnostic value of various imaging techniques to diagnose VGI.

Methods: A systematic review was conducted according to the PRISMA guidelines. Data sources included PubMed/Medline, Embase, and Cochrane from January 1997 until October 2017. Observational cohort studies were included. A meta-analysis was conducted on several imaging modalities: computed tomography with or without angiography (CT(A)), ^{18}F-fluoro-D-deoxyglucose positron emission tomography with or without low dose or contrast enhanced CT (FDG-PET(/CT)), and white blood cell scintigraphy with or without single photon emission computed tomography combined with low dose CT (WBC (SPECT/CT)).

Results: Of 4259 papers, 14 articles were included, containing eight prospective and six retrospective articles. CTA (I^2 7.4%), FDG-PET (I^2 36.5%), and FDG-PET/CT (I^2 36.6%) showed negligible to moderate heterogeneity, while WBC scintigraphy ± SPECT/CT (I^2 78.6%) showed considerable heterogeneity. Pooled sensitivity for CTA was 0.67 (95% CI 0.57–0.75), in contrast to FDG-PET of 0.94 (95% CI 0.88–0.98), FDG-PET/CT of 0.95 (95% CI 0.87–0.99), WBC scintigraphy of 0.90 (95% CI 0.85–0.94), and WBC scintigraphy with SPECT/CT of 0.99 (95% CI 0.92–1.00). The pooled specificities were for CTA 0.63 (95% CI 0.48–0.76), FDG-PET 0.70 (95% CI 0.59–0.79), FDG-PET/CT 0.80 (95% CI 0.69–0.89), WBC scintigraphy 0.88 (95% CI 0.81–1.94), and WBC scintigraphy SPECT/CT 0.82 (95% CI 0.57–0.96). Pre- and post-test results showed that WBC SPECT/CT favours FDG-PET/CT, with a positive post-test probability of 96% versus 83%.

Conclusion: This meta-analysis suggests the diagnostic performance of WBC scintigraphy combined with SPECT/CT is the greatest in diagnosing VGI. However, it is a time consuming technique and not always available. Therefore FDG-PET/CT may be favourable as the initial imaging technique. The use of solitary CTA in diagnosing VGI seems to be obsolete.

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INTRODUCTION

Vascular graft infection (VGI) is a rare but severe complication in vascular surgery, associated with high morbidity and mortality rates.[1] The reported incidence of VGI at the level of the aorto-iliac tract ranges between 0.6% and 5%, with a reported mortality between 25% and 88%.[2]

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The dilemma in clinically suspected VGI is to obtain definite proof of graft infection. Positive cultures either from percutaneous aspirated perigraft fluid or from surgically obtained material are in general considered the reference standard for establishing the diagnosis of VGI, but in clinical practice are often difficult to obtain. Besides, clinical signs and symptoms are usually non-specific.[1] Early infections, defined as appearance within 4 months, usually present as high grade infections (peri-prosthetic groin abscess, sepsis, gastrointestinal bleeding). In contrast, late infections can be insidious (vague abdominal pain, general malaise, low grade fever, leukocytosis, anaemia, and increased erythrocyte sedimentation rate).[3] The grade of the infection is influenced by the virulence of the specific bacterium involved.

Early diagnosis of VGI is important for correct and early surgical and/or antibiotic treatment, which improves the outcome. In contrast, unnecessary surgery for non-infected grafts may be fatal. As a consequence, a correct diagnosis or exclusion of graft infection is essential to guide further treatment.[4]

Almost all diagnostic tests have their limitations and as a consequence a combination of physical examination, biochemical laboratory tests, microbiological cultures, and several imaging techniques is often mandatory for the adequate diagnosis of VGIs and to start the correct treatment as early as possible.

Varying imaging techniques are used in the diagnostic work up of suspected VGI. Conventional imaging techniques such as duplex ultrasound, magnetic resonance imaging (MRI), and computerised tomography, with or without angiography (CT(A)) are being used most frequently. CTA, since it can visualise the characteristic features of VGI, has for a long time been considered the reference imaging standard in diagnosing VGI and is already widely investigated.[1] However, the sensitivity and specificity of these previous mentioned imaging modalities are moderate and variable.[5] Other available imaging tools are nuclear medicine techniques, such as ^{18}F-fluoro-D-deoxyglucose positron emission tomography (^{18}F-FDG-PET) scans, accompanied by or without low dose or contrast enhanced CT and white blood cell (WBC) scintigraphy, with or without single photon emission computed tomography accompanied with low dose CT (SPECT/CT) for exact location of the infection.[1]

FDG-PET imaging is based on uptake of radioactive labeled glucose (FDG) in cells/tissue with enhanced glucose metabolism, such as inflammatory and infectious cells. WBC imaging detects sites of infection by visualizing the accumulation in time of radiolabelled white blood cells. The benefit of combining nuclear imaging and CT is that the nuclear part identifies pathophysiological processes such as infections while the CT part represents the exact anatomical location.

Although accuracy of these molecular imaging techniques seems to be improved compared with the more conventional imaging techniques, results still differ between studies and therefore the indication to use them remains uncertain. It also remains unclear which imaging technique should be used as the first option. Obviously, the diagnostic challenge for VGI lays in the fact that no single diagnostic criterion has maximum accuracy.[6]

The aim of this study was to identify the various imaging modalities being used to diagnose VGI and to compare their diagnostic performance. A systematic review and meta-analysis was carried out.

METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement and the Cochrane handbook for diagnostic test accuracy reviews.[7,8]

Study objective

The study objective of this review was to gain a full understanding of the diagnostic value of different imaging modalities used in the diagnostic work up in patients with suspected VGI. This was performed by separating the available data per imaging modality (duplex ultrasound, CTA, MRI, FDG-PET, FDG-PET/CT, WBC scintigraphy, and WBC scintigraphy with SPECT/CT) and performing a systematic review and meta-analysis per imaging modality if the volume of data allowed.

Data sources and search strategy

A systematic search in PubMed/MEDLINE, Embase, and the Cochrane library was performed by two authors on October 20, 2017. Eligible studies published between January 1997 and October 2017 were identified. Medical Subject Headings (MESH) terms were used for patient identification (vascular grafting, blood vessel prosthesis, bacterial infections, and mycoses) and for diagnostic test and reference standard (diagnostic imaging). Additionally, corresponding search terms were used to search free text. Also manual reference checks of included articles of previously published reviews were performed to compliment the electronic searches. Language restrictions were not used for the initial search in order not to miss any contributing papers and investigate potential language bias. Details of the search syntax are listed in Supplementary material 1.

Study selection

Studies were included in this review if they met the prespecified inclusion criteria in the search protocol. Studies were eligible for inclusion if the study participants were adult patients who were suspected of a VGI. All types of vascular grafts were included. The reference standard consisted of either microbiological assessment or clinical follow up with biochemical or microbiological assessments or with one of the imaging modalities. All diagnostic imaging test studies were eligible for inclusion and the studies had to describe diagnostic test accuracy measures as outcomes. Outcome measures included either the sensitivity, specificity, positive predictive value (PPV), or negative predictive value (NPV) of the diagnostic methods

used. Both prospective and retrospective observational cohort studies were included. Subsequently, studies with five patients or fewer, reviews, case reports, abstracts, and animal studies were excluded. Studies that contained patients who had cardiothoracic surgery, such as valve replacements, were excluded. Checks for duplicates and overlapping databases were performed both electronically and manually.

The initial review based on title and abstract was independently performed by two authors (E.R.F. and G.v.M.). Any discrepancies over inclusion were resolved by implementing the paper in the full text review category. The full text articles were evaluated for definite inclusion independently by two reviewers (E.R.F., M.v.d.L.). Any discrepancies over final inclusion were resolved by discussion between the reviewers and, if needed, by a third reviewer (B.S.) to reach consensus.

Data extraction

Two authors (E.R.F. and G.v.M.) performed the data extraction of the included studies. The data extracted by the two investigators were cross checked. The collected variables were study characteristics (year of publication, study design), baseline characteristics of each study (number of patients and/or number of grafts), index test used targeting VGI, reference standard, and outcome data (true positives, false positives, false negatives, true negatives). Disagreements were resolved by consensus. Authors were contacted to obtain missing data if necessary. When the authors were unable to provide missing data and/or vital information on inclusion criteria in that particular study, the study was excluded from the analysis.

Assessment of study quality

The methodological quality of the included observational cohort studies was evaluated by two authors (E.R.F. and G.v.M.). To assess the risk of bias and concerns regarding applicability of the included studies, the Quality Assessment tool for Diagnostic Accuracy Studies guidelines (QUADAS-2) was used.[9] Patient selection, the index test, the reference standard, and flow and timing were judged "low risk", "high risk", or "unclear risk" with this assessment tool.

Data synthesis and analysis

All data analysis was performed per imaging modality. RevMan version 5.3.3 was used to draw sensitivity and specificity forest plots.[10] To calculate the pooled sensitivities and specificities 2×2 contingency tables were used to show an estimation of the direction of the trend. Heterogeneity across the studies was evaluated using chi-square statistics and I^2 statistics. Using the linear regression method and funnel plot of Deeks et al.[11] publication bias was assessed. In this context, $p < .05$ indicated potential publication bias. Because there was moderate or considerable heterogeneity between studies, the pooled diagnostic odds ratios were calculated using a random effect model. Weighted estimates for each study were calculated and illustrated in a forest plot. The diagnostic odds ratio reflects on the diagnostic test accuracy of the index test and describes how many times higher the odds are of obtaining a positive test result in a diseased rather than a non-diseased person.[8] This could be calculated by dividing the positive likelihood ratio by the negative likelihood ratio. For the understanding of the meaning of a negative or positive test result the pre-test probability, and positive and negative post-test probability were calculated and drawn in a bar chart. All tests were two sided, and $p \leq .05$ was considered statistically significant. Meta-analyses were performed using STATA version 13.0.[12]

RESULTS

After excluding duplicate records, the search strategy identified a total of 4259 potential studies. Fourteen studies met all inclusion criteria for the final analysis (Fig. 1).

Study characteristics

The included articles were either prospective (8 studies) or retrospective (6 studies) observational cohort studies. No randomised controlled trials were identified. The study lengths varied from 1 to 7 years. Two studies (Liberatore et al. and Keidar et al.) did not specify their study period.[3,13] The study size was either given as included patients or as included grafts, depending on the original study.

The studies investigated different imaging techniques in diagnosing VGI: duplex ultrasound, CTA, MRI, FDG-PET, FDG-PET/CT, WBC scintigraphy, and WBC scintigraphy with SPECT/CT. Study characteristics, baseline patient characteristics, index tests, and reference standards of the included studies are provided in Table 1. Two imaging modalities, duplex ultrasound and MRI, were only investigated in one study each and therefore a meta-analysis could not be conducted with these two imaging modalities and they were excluded.

Microbiological assessment was used as a reference standard for VGI in all of the studies. Clinical follow up was used in most studies as a reference standard in and ranged (if specified) from $>$ 4 months to $>$ 36 months (Table 1). However, several studies (Bruggink, Khaja, Sah, Saleem, Tronco)[14–18] did not use clinical follow up as a reference standard, but used either solitary microbiological assessment or surgical findings.

Patient characteristics

All studies specified the number and location of the vascular grafts. Ten studies included patients with both aortic and peripheral grafts. The other four only included aortic grafts. The anatomical location of aortic grafts was nearly equal and was either limited to the abdominal region (5 studies) or the thoracic and abdominal region (7 studies). Two studies did not specify the aortic location of the grafts. Only one study also included patients with carotid grafts. In total 453 aortic, 167 peripheral and 10 combined grafts were scanned. The CTA group consisted of 141 aortic, 23 peripheral, and six combined grafts. In the FDG-PET group

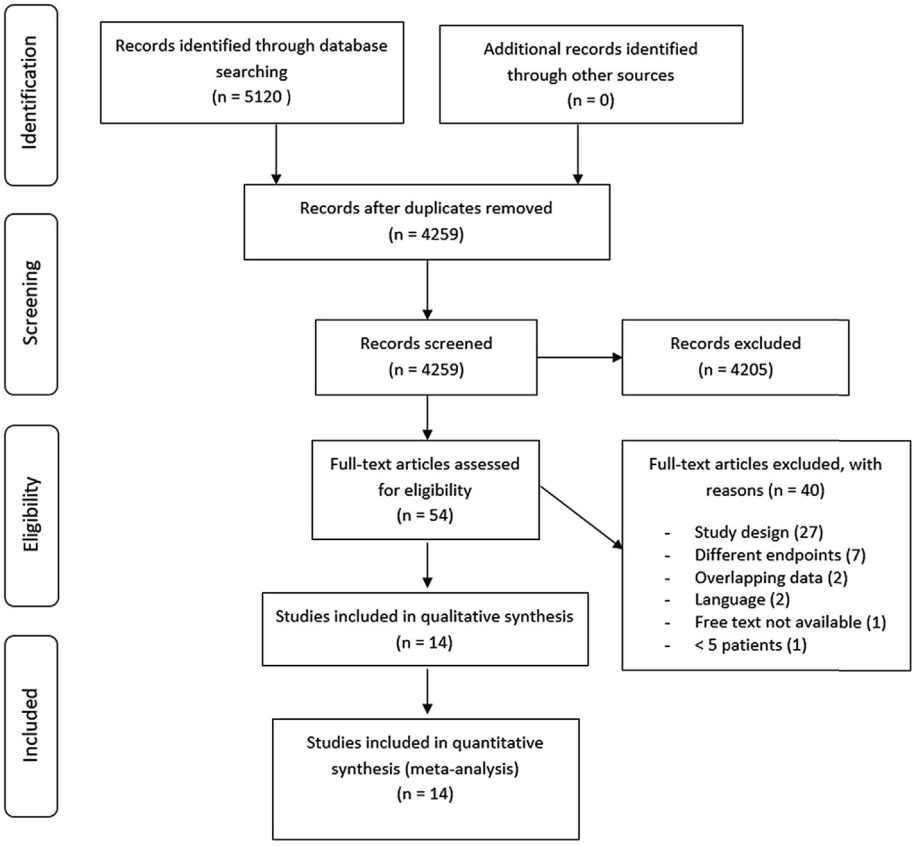

Figure 1. PRISMA flow diagram of study selection.

there were 144 aortic, 43 peripheral, and four combined grafts included. The FDG-PET/CT group included 96 aortic and 48 peripheral grafts. There were 227 aortic, 76 peripheral, and six combined grafts in the WBC scintigraphy group and the WBC SPECT/CT group consisted of 57 aortic, 23 peripheral, and six combined grafts. Table 1 provides an overview of the location of the grafts.

Only four studies mentioned the technique used, open or endovascular, during the initial operation (Chang et al., Bruggink et al., Saleem et al., Husmann et al.).[4,14,17,19] The distribution in high and low grade infection was only made in a few studies.

Study quality

The evaluation of the risk of bias and the applicability by the QUADAS-2 of all included studies is shown in Supplementary material 2. The most common reference standard used was microbiological assessment or follow up with microbiological assessments or with one of the imaging modalities. It was considered a high risk of bias if another reference standard was used other than that mentioned previously. For instance, the subjective intra-operative judgment of the presence of VGI was deemed insufficient. Almost all studies score as "high risk" of risk of bias in the category "flow and timing", since almost no study had only one reference standard. The general risk of bias and applicability was deemed sufficient not to exclude one of the studies.[20]

Heterogeneity and publication bias

The heterogeneity was evaluated per imaging modality and visually drawn in Supplementary material 3. First, the studies including CTA showed a heterogeneity chi-square statistic of 4.32 ($p = .365$) and an I^2 statistic of 7.4% and therefore showed negligible heterogeneity. Second, the FDG-PET studies showed a chi-square statistic of 4.72 ($p = .193$) and I^2 statistic of 36.5% and therefore showed negligible to moderate heterogeneity. The FDG-PET/CT studies showed a chi-square statistic of 6.31 ($p = .177$) and I^2 statistic of 36.6% and therefore showed negligible to moderate heterogeneity. Lastly, the WBC scintigraphy studies showed a chi-square statistic of 17.71 ($p = .001$) and I^2 statistic of 78.6% and therefore showed substantial to considerable heterogeneity. The WBC with SPECT/CT analysis only included three studies and therefore a HSROC or heterogeneity assessment was not possible and had to be assumed to be high.

The publication bias was also drawn per imaging modality (Supplementary material 4) by using the linear regression method of Deeks et al.[11] This showed no significant publication bias for any of the imaging modalities (CTA, $p = .53$; PET, $p = .15$; PET-CT, $p = .44$; WBC, $p = .12$; WBC-CT, $p = .09$).

Outcomes of the different imaging modalities

In Fig. 2 the forest plots of sensitivities and specificities related to the different imaging modalities are drawn. These forest plots show graphically the differences in sensitivities

Table 1. Study characteristics of the included studies.

Author	Publication year	Study design	Study size	Grafts	Imaging modality	Reference standard
Liberatore et al.[3]	1998	Retrospective cohort	162 grafts	122 Aortic (abdominal) 40 Peripheral	^{99m}Tc-HMPAO-WBC scintigraphy	Microbiological (culture graft) Follow up > 4 months
Fukuchi et al.[30]	2005	Prospective cohort	33 patients	Aortic (thoracic/abdominal)	CTA^{18}F-FDG-PET	Microbiological Surgical findings Follow up > 4 months
Keidar et al.[13]	2007	Prospective cohort	39 patients	8 Aortic (abdominal) 31 Peripheral	^{18}F-FDG-PET/CT	Microbiological (surgery) Histopathological (surgery) Follow up > 12 months
Shahidi et al.[31]	2007	Retrospective cross control	53 scans	Aortic (abdominal)	MRI Indium-111 WBC scintigraphy	Microbiological (surgery) Surgical findings Follow up > 6 months
Tronco et al.[18]	2007	Retrospective cohort	19 grafts	4 Aortic 15 Peripheral	^{99m}Tc-fanolesomab WBC scintigraphy	Microbiological Histopathological Clinical/radiological
Spacek et al.[21]	2009	Prospective cohort	96 grafts	51 Aortic 41 Peripheral 4 Combined	^{18}F-FDG-PET	Microbiological (surgery) Histopathological (surgery) Surgical findings Follow up > 6 months
Bruggink et al.[14]	2010	Prospective cohort	25 patients	23 Aortic (thoracic/abdominal) 2 Peripheral	CTA ^{18}F-FDG-PET ^{18}F-FDG-PET/CT	Microbiological (culture graft or culture perigraft fluid)
Lou et al.[32]	2010	Retrospective cohort	11 patients	9 Aortic (thoracic/abdominal) 2 Peripheral	^{99m}Tc- WBC SPECT/CT	Microbiological (culture graft or culture perigraft fluid) Presence new pseudo-aneurysm CTA (> 8 weeks after surgery) Presence gas involving the graft CTA (> 4 weeks after surgery)
Khaja et al.[15]	2013	Retrospective cohort	20 patients	12 Aortic (thoracic/abdominal) 5 Peripheral 3 Combined	CTA Indium-111 WBC scintigraphy Indium-111 WBC SPECT/CT	Microbiological (tissue culture (surgery/percutaneous)) Blood culture
Erba et al.[22]	2014	Prospective cohort	55 patients	36 Aortic (abdominal) 16 Peripheral (3 carotid) 3 Combined	US CTA ^{99m}Tc-HMPAO WBC scintigraphy ^{99m}Tc-HMPAO WBC SPECT/CT	Microbiological (culture graft or culture perigraft fluid) Blood culture Follow up >18 months
Karaca et al.[33]	2014	Retrospective cohort	17 patients	7 Aortic (abdominal) 10 Peripheral	^{18}F-FDG-PET/CT	Microbiological (surgery) Histopathological (surgery) Follow up > 36 months
Chang et al.[4]	2015	Prospective cohort	29 patients	Aortic (thoracic/abdominal)	^{18}F-FDG-PET/CT	Microbiological (surgery or image-guided drainage) Surgical findings Follow up > 11 months
Sah et al.[16]	2015	Prospective cohort	34 patients	29 Aortic (thoracic/abdominal) 5 Peripheral	^{18}F-FDG-PET/CT	Microbiological (culture graft or perigraft tissue (surgery)) Histopathological (surgery) Clinical, laboratory
Saleem et al.[17]	2015	Prospective cohort	37 patients	Aortic (thoracic/abdominal)	CTA ^{18}F-FDG-PET	Microbiological (surgery/percutaneous)

US = ultrasound, CTA = computed tomography angiography, MRI = magnetic resonance imaging, PET = positron emission tomography, WBC = white blood cell.

and specificities with their confidence intervals (CI) per included study.

CTA

To show a direction of the trend, the estimated pooled sensitivity of the CTA studies was 0.67 (95% CI 0.57—0.75) and the pooled specificity was 0.63 (95% CI 0.48—0.76). The pooled diagnostic odds ratio for all CTA studies was 2.90 (95% CI 1.21—6.98) as shown in Fig. 3.

FDG-PE

The estimated pooled sensitivity of the FDG-PET studies was 0.94 (95% CI 0.88—0.98) and the pooled specificity 0.70 (95% CI 0.59—0.79). As shown in Fig. 3 the pooled diagnostic odds ratio was 28.36 (95% CI 7.83—102.74).

FDG-PET/CT

The FDG-PET/CT studies showed an estimated pooled sensitivity of 0.95 (95% CI 0.87—0.99) and a pooled specificity of 0.80 (95% CI 0.69—0.89). The pooled diagnostic odds ratio was 38.04 (95% CI 8.49—170.44).

WBC scintigraphy

The estimated pooled sensitivity of the WBC studies was 0.90 (95% CI 0.85—0.94) and the pooled specificity 0.88 (95% CI 0.81—1.94). The pooled diagnostic odds ratio was 41.84 (95% CI 4.8—364.36).

WBC scintigraphy with SPECT/CT

The WBC SPECT/CT studies showed an estimated pooled sensitivity of 0.99 (95% CI 0.92—1.00) and, a pooled specificity of 0.82 (95% CI 0.57—0.96). The pooled diagnostic odds ratio was 73.59 (95% CI 5.35—1011.76), which is the highest diagnostic odds ratio of the five tests and therefore appears to have the best discriminative ability.

PRE- AND POST-TEST PROBABILITIES

To interpret the results of a positive or negative test result of one of the imaging modalities the pre- and post-test

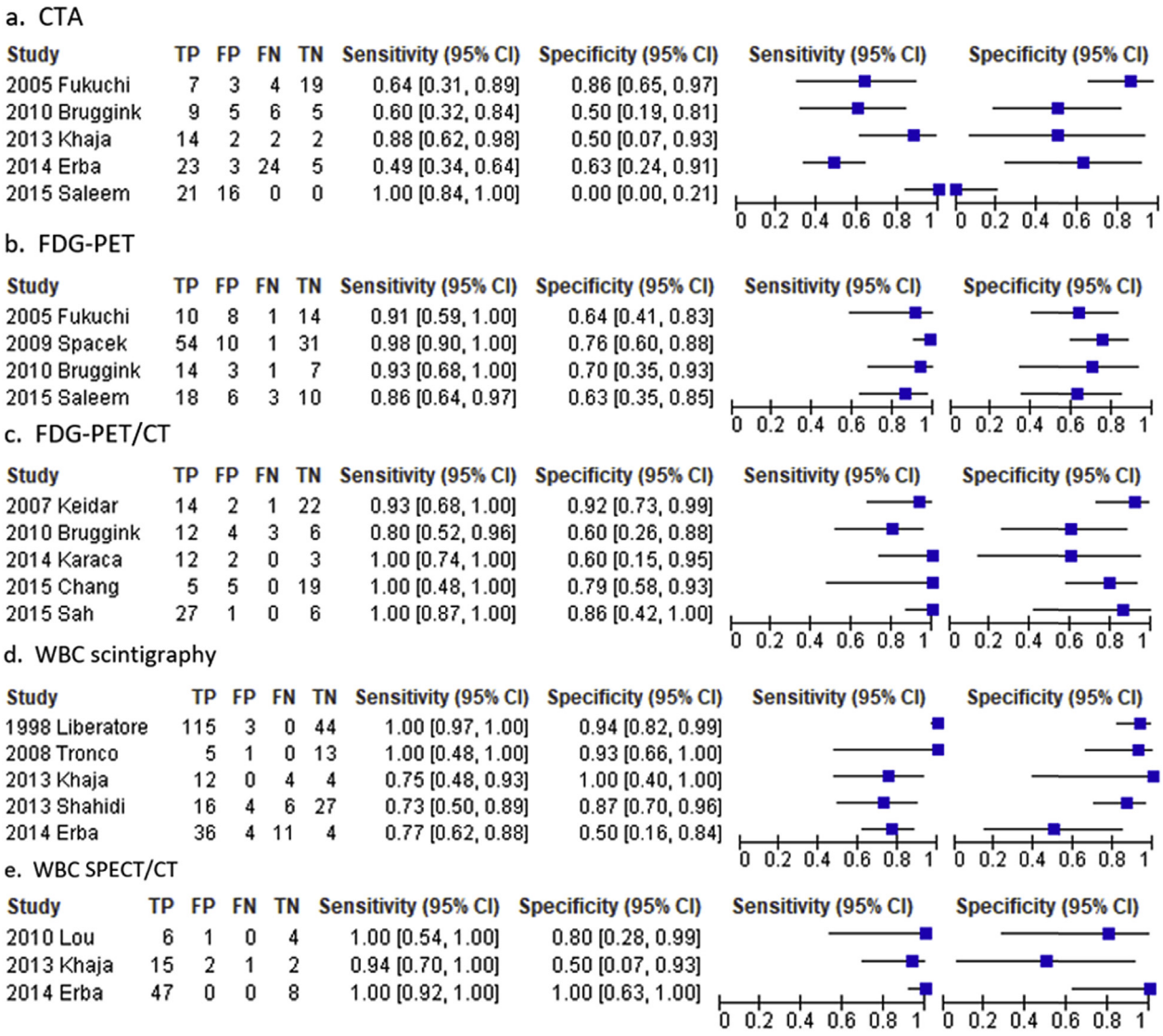

Figure 2. Forest plots of the sensitivities and specificities per imaging modality.

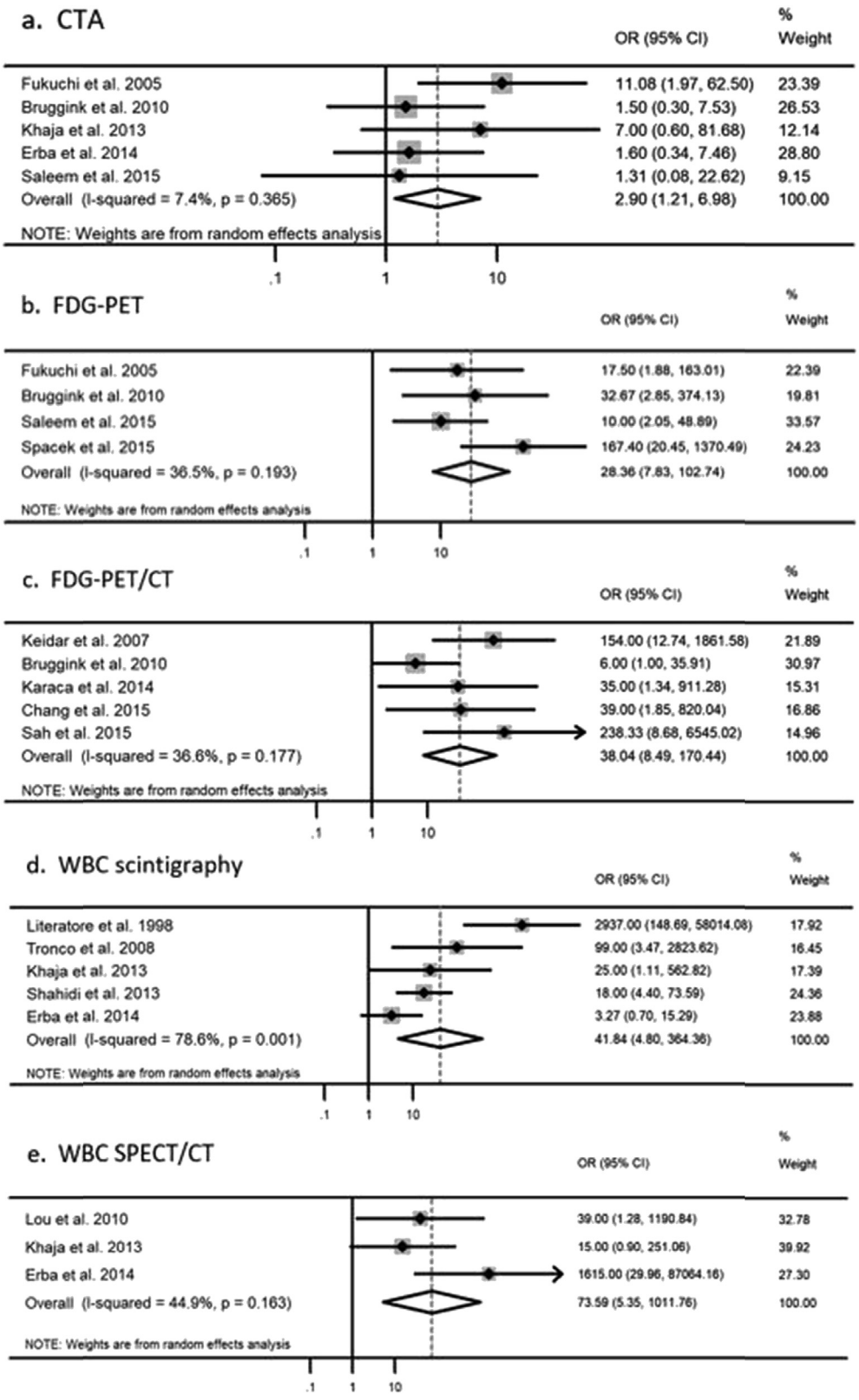

Figure 3. Pooled diagnostic risk ratios per imaging modality.

probabilities were calculated (Fig. 4). These showed the chance of having the disease prior to the test (pre-test probability) and the chance of having the disease with a positive test result (positive post-test probability) and with a negative test result (negative post-test probability). The pre-test probabilities are high, as most studies included patients who were already suspected of VGI and not a random cohort of vascular surgery patients with a vascular

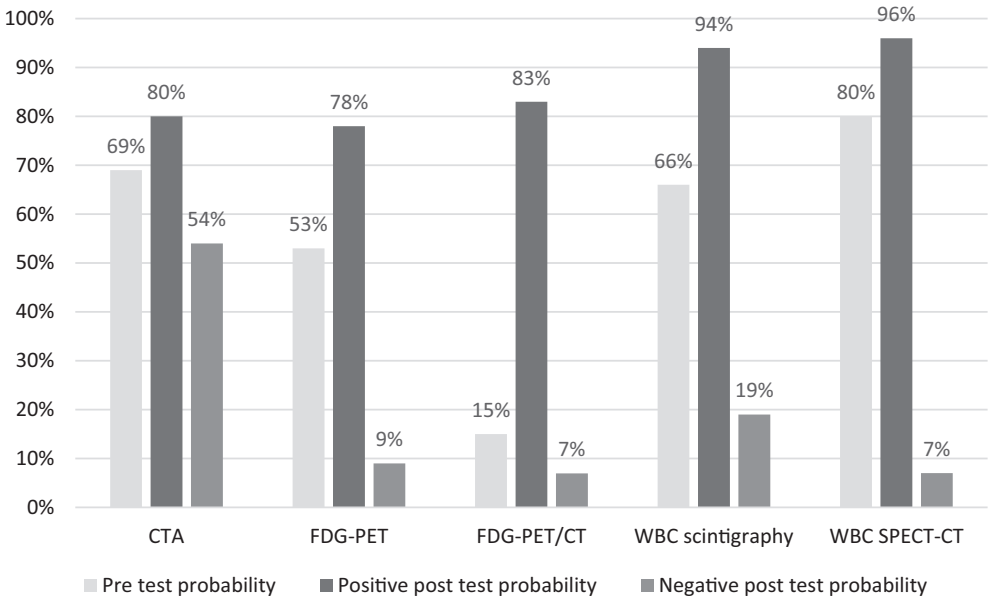

Figure 4. Pre- and post-test probabilities per imaging modality.

prosthesis in situ. For example, a patient suspected for VGI had a chance of 80% of having VGI prior to undergoing a WBC SPECT/CT scan. After a positive WBC SPECT/CT scan the chance of indeed having VGI is 96% and chance of having a VGI if the test is negative is 7%. WBC scintigraphy combined with SPECT/CT had the highest positive post-test probability with 96%, after which WBC scintigraphy without SPECT/CT followed with 94%. The positive post-test probability of CTA was 80%, of FDG-PET 78% and of FDG-PET/CT 83%. Concerning the negative post-test probability WBC scintigraphy with SPECT/CT and FDG-PET/CT scored best, both with 7%. FDG-PET and WBC scintigraphy followed with 9% and 19%. CTA showed a high negative post-test probability of 54%.

DISCUSSION

Confirming a quick and correct diagnosis to start accurate therapy in patients with VGIs is challenging. Clinical presentation, laboratory tests, and blood cultures may increase the suspicion of VGIs, but are non-specific. The recent developments in new nuclear hybrid imaging techniques are promising for diagnosing a VGI. This meta-analysis evaluated the diagnostic accuracy of several imaging modalities in a population with suspected VGI and confirms the added value of nuclear techniques.

The current meta-analysis shows that an isolated CTA in diagnosing VGIs does not provide enough distinctness, as already described in previous literature.[5] Several studies included in this meta-analysis show a high false negative rate resulting in a low specificity, especially in low grade infections.[21,22] Nuclear medicine imaging techniques evince improvement of sensitivity and specificity, even more so when combined with low dose or contrast enhanced CT or SPECT/CT. These nuclear imaging techniques incorporate anatomical and metabolic information, being able to differentiate between aortic graft infection and soft tissue infection.[23] Planar leukocyte scintigraphy at different time points is used to decide whether there is an infection or not (uptake increases in time due to an infection). A low or high dose CT (SPECT/CT) is used to determine the exact location of the infection.

The pooled sensitivity and specificity as well as the positive and negative post-test probability per imaging modality show promising results for the WBC scintigraphy combined with SPECT/CT in diagnosing VGI. Demonstrated by the highest number of true positives (positive post-test probability) and lowest number of false negatives (negative post-test probability). However, the patient population was limited, which must be taken into account. Although more false negatives are seen with WBC scintigraphy (without SPECT/CT), the number of true positives is nearly as high as in WBC scintigraphy with SPECT/CT. However, among the WBC scintigraphy patients, the heterogeneity was very high. FDG-PET/CT shows a relatively high number of true positive and low number of false negatives, whereas isolated FDG-PET seems inferior with fewer true positives and slightly more false negatives. This is in line with the literature, claiming the combination of FDG-PET/CT reduces the false positive and false negative results.[5]

The nature of VGI, being relatively rare, makes it more difficult to study. This is reflected in the available literature, where no RCTs are available on this topic. The 14 included studies were all observational cohort studies, with either a prospective or retrospective design. Although the methodology of the studies did not differ very much between the prospective and retrospective studies this could have introduced inclusion bias.

The evaluation of study quality showed a high risk of bias for all studies, except Bruggink et al.,[14] since several reference standards were used. Several studies were classified as high risk of bias, because subjective operative findings were used as the reference standard.

Many non-published abstracts were excluded in order to maintain the highest study quality and ensure completeness. No significant publication bias was seen in the linear regression method of Deeks et al.

Unfortunately two modalities could not be part of the meta-analysis, since ultrasound and MRI were both only assessed in one of the included studies. Ultrasound is non-invasive, quick, and can detect fluid collections around peripheral superficial vascular grafts or can be used for ultrasound-guided aspiration. However, no pooled data for these modalities could be found.

Diagnostic test accuracy reviews are generally limited with high heterogeneity among included studies, which is in line with this review. For example, the included patient populations vary. Although overall corresponding, the pre-test chance of a VGI differs between the studies. The variable pre-test probabilities are due to patient selection, since signs, symptoms, and biochemical analyses were interpreted differently. Also the severity of symptoms may be of influence. Differentiating between high and low grade infections was not possible, while only a few of the included studies categorised patients in these two groups. Also, the anatomical location of grafts, the technique used (open or endovascular) and materials used (Dacron, PTFE) differ.

All studies mentioned the number of central and/or peripheral grafts (Table 1). However the anatomical location was mainly mentioned in patient characteristics and therefore not linked to the outcome measures. This is a limitation of this meta-analysis, since the accuracy of the several imaging modalities used in central or peripheral locations could not be calculated. The anatomical location of the graft does influence the imaging modality used. This may have influenced the post-test probabilities. In particular in WBC scintigraphy and WBC SPECT/CT group this is a limitation, while the diagnostic value is less strong in a central location.

This also applies to the primary intervention, being open or endovascular, since diagnostic probability in these different patient groups varies and influences the diagnostic performance of the different imaging modalities. VGIs remain rare, resulting in limited patient numbers and this may explain why the included studies did not insert separated groups of the included patients.

Unfortunately it was not possible to extract the time between implementation of the graft and imaging and how this influences the outcome since none of the studies provided these data.

Concerning the included studies, the retrospective studies might have significant bias, since additional imaging was often performed when the reference imaging standard (CTA) could not establish a diagnosis. Furthermore, patients with obvious VGI diagnosis on CTA might not have undergone a nuclear scan.

Comparing the accuracy of different imaging techniques in suspected VGIs has its limitations. Regarding the nuclear imaging techniques, slightly different protocols were used. In the case of FDG-PET scans with or without CT, the quantity of administered FDG and resting time before imaging varied among the included studies. For this reason the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) guideline recommendations were published.[24] To overcome this heterogeneity between studies, a strategy was developed by the EANM to harmonise all FDG-PET studies throughout different centres EANM Research Ltd (the EARL initiative).[25] However, as most studies were performed before the introduction of this concept it remains difficult at this moment to compare the different FDG-PET(/CT) studies with each other. Also, the analysis and interpretation of the FDG-PET(/CT) studies differed, with either calculating the maximum standardised uptake value (SUV_{max}), or the tissue to background ratio (TBR), or by describing only the pattern of uptake (focal/diffuse) or the visual grading scale (VGS). Often these assessment methods were combined.

Among the WBC scintigraphy $\pm$ SPECT/CT, various compounds and isotopes are used and the dose also differed. Furthermore, different acquisition and interpretation criteria for declaring a WBC scintigraphy positive for infection were used. Although there are no guidelines for WBC scintigraphy imaging yet, there is however a guideline for the correct labelling of leukocytes and also proposals for the correct acquisition and interpretation exist.[26–28]

The studies also had various considerations according to the influence of other factors. For instance, although the exact influence of diabetes on the uptake and metabolism of FDG remains unclear, some studies measured the glucose level before administering FDG. Fukuchi et al.[30] excluded patients with diabetic mellitus, but other studies did not. However, a recent study concluded that the incidence of false negative scans in patients assessed for suspicion of an infectious or inflammatory process was not adversely affected between patients with or without diabetes and with high or normal serum glucose levels at the time of scanning.[29]

The influence of antibiotic treatment on the different imaging modalities is questionable. In a review, Bruggink et al.[5] suggested that antibiotic treatment does not adversely affect the sensitivity of leukocyte scintigraphy, but that problem is repeatedly mentioned in the insertion of the FDG-PET scan. An overview of antibiotics used during imaging could not be provided because of abundant missing data. The use of antibiotics is frequently mentioned, but not always linked to the outcome of the imaging technique used or to the final diagnosis. Also the duration of antibiotic use was scarcely mentioned. If long-term antibiotic is of influence, it could result in false negatives, affecting the diagnostic performance of the imaging technique.

On the other hand the use of long-term antibiotics could also influence the microbiological reference standard, leading to missing VGI diagnosis. Saleem et al.[17] described that patients with suspected VGI but negative cultures were treated significantly longer with antibiotics.

However, the most challenging part of diagnosing VGI is determining the reference standard, since no absolute

consensus exists on the reference standard to use for VGI. The different reference standards used, contributed to a degree of heterogeneity. Chang et al.[4] also considered operative findings, such as purulence, turbid fluid, or infected appearing thrombus to confirm VGI, whereas other studies regarded only positive (peri-)graft microbiological cultures to be evidence of the diagnosis VGI. In this meta-analysis all microbiological cultures were considered as one reference standard, regardless the material used (graft, peri-graft fluid, peri-graft tissue) or how obtained (percutaneous, surgery). Also the definition of follow up as a reference standard varied among the included papers. Besides the variety in duration of follow up, some studies used only clinical follow up, while others used biochemical, blood cultures or imaging follow up. Most studies subjected their whole (not-operated) patient group to follow up, but others only subjected the patients who had major contraindications to surgery to follow up.[22]

The diagnostic accuracy of the WBC scintigraphy including SPECT/CT was the most promising in this meta-analysis. However, the number of patients was limited and the pre-test probability was very high in that group, which might have positively influenced the positive post-test probability. Furthermore, it is a time consuming and labour intensive technique, including the dual time point imaging, resulting in higher costs. Further, these examinations are not widely available, since not all medical centres are equipped with a (GMP) laboratory and the knowledge required to perform leukocyte labelling may be lacking.

FDG-PET with low dose or contrast enhanced CT showed a high sensitivity and a reasonable specificity. This technique is less labour intensive and time consuming, which makes this technique more cost effective. Besides, the FDG-PET scan is becoming more readily accessible, since most medium-sized clinics are equipped with this technique nowadays. Therefore, FDG-PET/CT may be favourable as the initial imaging technique.

Heterogeneity in the acquisition and interpretation of scans performed in patients with VGI is known. However, this can be reduced by standardisation of scanning protocol, such as the EARL initiative for PET as mentioned before. Large prospective studies with a long follow up are necessary to compare the different imaging techniques in a multicentre setting with standardisation of all protocols. On the basis of this meta-analysis, the recommendation for future research is to compare FDG-PET/CT and WBC scintigraphy with SPECT/CT in a homogenous patient population. More data are necessary to achieve evidence based data on the interpretation of the scans. For WBC imaging this is more or less settled, but for FDG-PET, interpretation still depends on the expertise of the reader.[27,28] Criteria are needed when to declare a scan positive or negative for an infection, to better differentiate between infection and inflammation, to know exactly when the earliest time point is to acquire a scan after surgery, and to get data on the influence of, for example, antibiotics on the accumulation of the tracers. In future, we may also think of the development of more dedicated tracers, for example, tracers that are able to differentiate between infection and inflammation, or tracers that are able to visualise the bacteria involved. This is a glimpse into the future, but surely something that is really needed from an imaging point of view. Furthermore, recent developments in hybrid camera techniques such as PET/CT and SPECT/CT have already led to a significant increase in diagnostic accuracy. In recent years, PET/MRI has also been considered as a new upcoming imaging technique. Improvements in the PET system, but certainly the addition of angiography (CTA or MRA), may also further increase the sensitivity and specificity in this patient group. Moreover there is a need for a clear definition of VGI and consensus about the reference standard is of major importance to assess the diagnostic accuracy adequately and uniformly. The predictive value of the diagnostic imaging modalities for VGI should be examined in aortic and peripheral grafts separately, since their diagnostic value varies significantly according to the graft location. This meta-analysis implies that the use of solitary CTA in diagnosing VGI seems to hold no added diagnostic value over clinical evaluation and laboratory tests. WBC scintigraphy combined with SPECT/CT shows the highest accuracy in diagnosing VGI. Though, being a time consuming technique and not widely available, it might not be the technique of first choice. FDG-PET/CT may be favourable as the initial imaging technique, being less labour intensive and more accessible. However, imaging techniques are developing rapidly and new techniques such as combining nuclear techniques with MRI or MRA also seem promising in diagnosing VGI.

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CONFLICTS 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.2018.07.010.

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