

F-18 FDG PET for assessment of disease activity of large vessel vasculitis: A systematic review and meta-analysis

Sang-Woo Lee, MD, PhD,^a Seong-Jang Kim, MD, PhD,^{b,c} Youngduk Seo, MD, PhD,^d Shin Young Jeong, MD, PhD,^a Byeong-Cheol Ahn, MD, PhD,^a and Jaetae Lee, MD, PhD^a

^a Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Taegu, South Korea

^b Department of Nuclear Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea

^c BioMedical Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, South Korea

^d Department of Nuclear Medicine, Busan Seongso Hospital, Pusan, South Korea

Received May 10, 2018; accepted Aug 3, 2018

doi:10.1007/s12350-018-1406-5

Background. The aim of this study is to investigate the performance of F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) or positron emission tomography/computed tomography (PET/CT) for the assessment of disease activity in patients with large vessel vasculitis (LVV) through a meta-analysis.

Methods. The MEDLINE via PubMed and EMBASE were searched for the studies evaluating the performance of F-18 FDG PET or PET/CT in the assessment of disease activity in patients with LVV. Pooled sensitivity, specificity, diagnostic odds ratios (DORs), and summary receiver-operating characteristic (sROC) curve were estimated across the included studies. Possible publication bias was assessed by Deek's funnel plot asymmetry tests.

Results. A total of 439 PET images from 298 patients pooled from nine studies showed that the pooled sensitivity was 0.88 [95% confidence interval (CI) 0.79-0.93] without heterogeneity ($\chi^2 = 14.42$, $P = .07$) and the pooled specificity was 0.81 (95% CI 0.64-0.91) with heterogeneity ($\chi^2 = 63.72$, $P = .00$) for the detection of active LVV. The pooled DOR was 30 (95% CI 8-107). Hierarchical sROC curve indicates that the area under the curve was 0.91 (95% CI 0.89-0.94). There was no significant publication bias ($P = .42$), and meta-regression analysis revealed that none of the variables was the source of the study heterogeneity.

Conclusions. F-18 FDG PET has a good performance for the detection of active disease status in patients with LVV. Revised criteria for the assessment of disease activity incorporated with F-18 FDG PET or PET/CT should be introduced and validated. Further studies are warranted to determine if PET-based treatment of LVV can improve outcomes. (J Nucl Cardiol 2019;26:59–67.)

Key Words: F-18 fluorodeoxyglucose • PET • large vessel vasculitis • disease activity • meta-analysis

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12350-018-1406-5>) 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.

Funding This work was supported by a Grant of the Korea Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (Grant Number HI16C1501).

Reprint requests: Seong-Jang Kim, MD, PhD, Department of Nuclear Medicine, Pusan National University Yangsan Hospital, Yangsan, 50612, Korea; growthkim@daum.net
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Abbreviations

DORs	Diagnostic odds ratios
ESR	Erythrocyte sedimentation rates
FDG	Fluorodeoxyglucose
GCA	Giant cell arteritis
LVV	Large vessel vasculitis
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
SUV _{max}	Maximum standardized uptake value
TA	Takayasu's arteritis

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INTRODUCTION

Large vessel vasculitis (LVV) including Takayasu's arteritis (TA) and giant cell arteritis (GCA) is characterized by chronic granulomatous inflammation involving the aorta and its major branches. The American College of Rheumatology classification has been widely used for the diagnostic criteria of TA and GCA since 1990,^{1,2} although the need for updated criteria has been raised.^{3,4} The assessment of disease activity is also important factor during and after glucocorticoid treatment, but is still challenging as well. Although the National Institutes of Health (NIH) criteria have been applied for the disease activity of TA, the clinical features are variable, and acute phase reactants are not a consistently reliable surrogate marker of disease activity.⁵ Even temporal artery biopsy can demonstrate active vasculitis features during clinical remission state or can give false-negative (FN) result due to skip lesion.⁶

As in the case of glucose, the degree of cellular uptake of F-18 fluorodeoxyglucose (FDG) is influenced by the expression of glucose transporter proteins, which is enhanced in activated inflammatory cells as well as tumor cells. Thus, positron emission tomography (PET) using F-18 FDG has been successfully used in diagnosis and treatment evaluation of various inflammatory diseases.⁷ In patients with LVV, F-18 FDG PET showed promising results as an effective modality in the assessment of the disease activity and the extent of involved vessels using a visual grading scale.⁸ However, Arnaud et al reported lack of correlation between FDG uptake intensity and clinical, biologic, or MRI assessment of disease activity in patients with TA.⁹ These discordant findings in the assessment of disease activity may be attributed to the selection bias related to small number of patients in each study and no definite criteria of the presence of vascular inflammation on F-18 FDG PET.

The purpose of this study is to carry out meta-analysis of the published data on the performance of F-18 FDG PET or positron emission tomography/computed tomography (PET/CT) in the assessment of disease activity of LVV, in order to provide more evidence-based data for formulating the guidelines on appropriate use of F-18 FDG PET imaging in LVV.

METHODS

Data Sources and Search Strategy

This systematic review and meta-analysis was carried out using the PRISMA 2009 guidelines¹⁰ and we performed electronic literature searches of MEDLINE via PubMed and EMBASE for English publications from the earliest available date of indexing through November 30, 2017. We also hand-searched the reference lists of identified publications for additional studies. We used a search algorithm using a combination of the following terms: (1) "positron emission tomography" OR "PET" OR "positron emission tomography/computed tomography" OR "PET/CT," and (2) "large vessel vasculitis" OR "giant cell arteritis" OR "Takayasu arteritis."

Study Selection

The inclusion criteria for relevant studies were F-18 FDG PET or PET/CT used to assess the disease activity; studies limited to LVV including TA and/or GCA; sufficient data for sensitivity and specificity of F-18 FDG PET or PET/CT to assess the disease activity of LVV or the absolute numbers of true-positive (TP), true-negative (TN), false-positive (FP), and FN data presented.

Studies were excluded if F-18 FDG PET or PET/CT had been used only for diagnosis of LVV. Review articles, case reports, conference abstracts, and editorial materials were excluded due to insufficient data for sensitivity and specificity of F-18 FDG PET or PET/CT, and duplicate studies were also excluded. Two authors (Lee SW and Kim SJ) conducted the searches and reviewed all the retrieved publications applying the above-mentioned selection criteria independently, and discrepancies were resolved by discussion.

Data Extraction and Quality Assessment

Basic study information (first author, year of publication, country of study conducted), study design (prospective or retrospective), patients' characteristics (number of patients, number of PET scan, mean age, gender), technical aspects (dedicated PET or PET/CT), F-18 FDG PET criteria [visual grading or cutoff of maximum standardized uptake value (SUV_{max})] and reference standard (NIH criteria, clinical disease features, or immunosuppressive drug requirement) for the assessment of the disease activity were extracted.

Each study was analyzed to calculate the number of TP, TN, FP and FN findings of F-18 FDG PET for the assessment of the disease activity in patients with LVV, according to the

Table 1. Characteristics of the enrolled studies

Authors	Years	Designs	Vasculitis types	Number of patients	Age	Female	Number of PET scans	Imaging devices	Criteria of PET	Criteria of disease activity
Arnaud	2009	R	TA	28	36	21	40	PET/CT	Visual grading, quantitative index (vascular SUV _{max} /liver SUV _{mean})	NIH criteria
Grayson	2017	P	TA, GCA	56	51	39	170 (including 59 controls)	PET/CT	Visual grading, PETVAS (PET vascular activity score)	Clinical disease features
Karapolat	2013	P	TA	22	40.5	20	22	PET/CT	Visual grading	NIH criteria
Kobayashi	2005	P	TA	14	28	13	20 (including 6 controls)	PET/CT	SUV _{max} cutoff 1.3	Prednisolone requirement
Lee	2012	R	TA	38	43	34	38	PET	Visual grading	NIH criteria
Lee	2009	R	TA	32	45.4	26	32	PET/CT	Visual grading	NIH criteria
Santhosh	2014	R	TA	51	30	38	60	PET/CT	Visual grading	NIH criteria and/or PET results
Tezuka	2012	R	TA	39	30	35	39	PET/CT	SUV _{max} cutoff 2.1	NIH criteria
Webb	2004	R	TA	18	40.5	17	18	PET	Visual grading	NIH criteria

R, retrospective; P, prospective; TA, Takayasu's arteritis; GCA, giant cell arteritis; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value

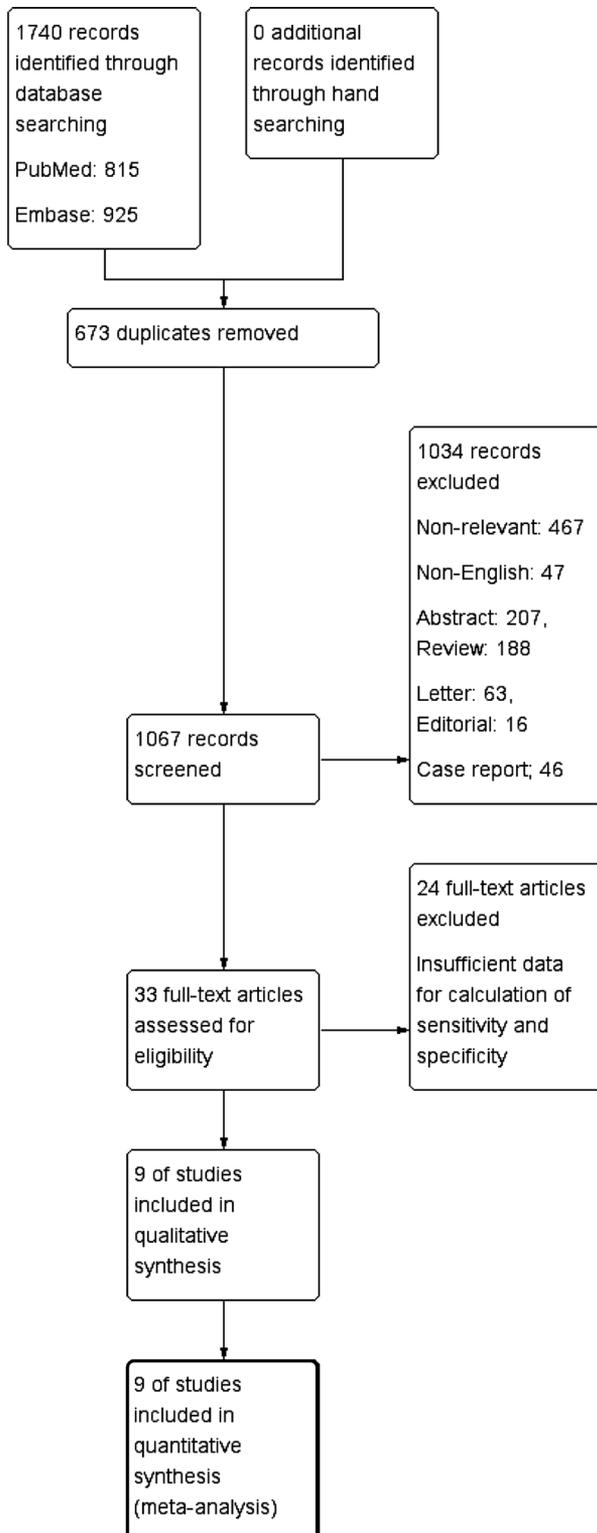


Figure 1. Flow chart of the search for eligible studies on the performance of F-18 FDG PET or PET/CT for the assessment of disease activity of large vessel vasculitis. Nine articles were finally selected for this meta-analysis.

reference standard. Only studies providing such complete information were finally included in the meta-analysis.

The overall quality of the included studies in this meta-analysis was critically appraised using Review Manager (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration) based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies.¹¹

Data Synthesis and Analysis

Continuous numeric variables are presented as mean (standard deviation) values unless stated otherwise, and categorical variables are presented as frequencies or percentages. The pooled sensitivity and specificity, and diagnostic odds ratios (DORs) are reported as estimates with 95% confidence intervals (CIs). Heterogeneity between studies was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis.¹² Meta-regression was also performed to identify potential sources of bias with Meta-DiSc (version 1.4; Hospital Universitario Ramon y Cajal, Madrid, Spain).¹³ Publication bias was evaluated using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks et al.¹⁴ Bivariate random-effects model was used for the analysis and the pooling of the performance measures across studies.^{15,16} This model estimates pairs of logit-transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. Hierarchical summary receiver-operating characteristic (sROC) curve was assessed, and the area under the curve was estimated.¹⁷ Statistical analyses were performed with commercial software programs, Stata (version 15.1; StataCorp LLC, College Station, TX), and P values of less than .05 were considered statistically significant.

RESULTS

Literature Search and Selection of Studies

We identified 815 articles from PubMed and 925 articles from EMBASE through the comprehensive electronic literature searches and cross-checking of references lists, of which 673 duplicated records were excluded. Among 1,067 records, 1,034 records (47 non-English articles, 207 conference abstracts, 63 letters, 16 editorials, 188 review articles, 46 case reports, 467 records found irrelevant to this meta-analysis) were excluded by reviewing the title and abstract. Remaining 33 full-text articles were evaluated for their eligibility and presentation of sufficient data for sensitivity and specificity of F-18 FDG PET or PET/CT to assess the disease activity of LVV. Nine articles were finally selected for this meta-analysis, and their characteristics are presented in Table 1.^{9,18–25}

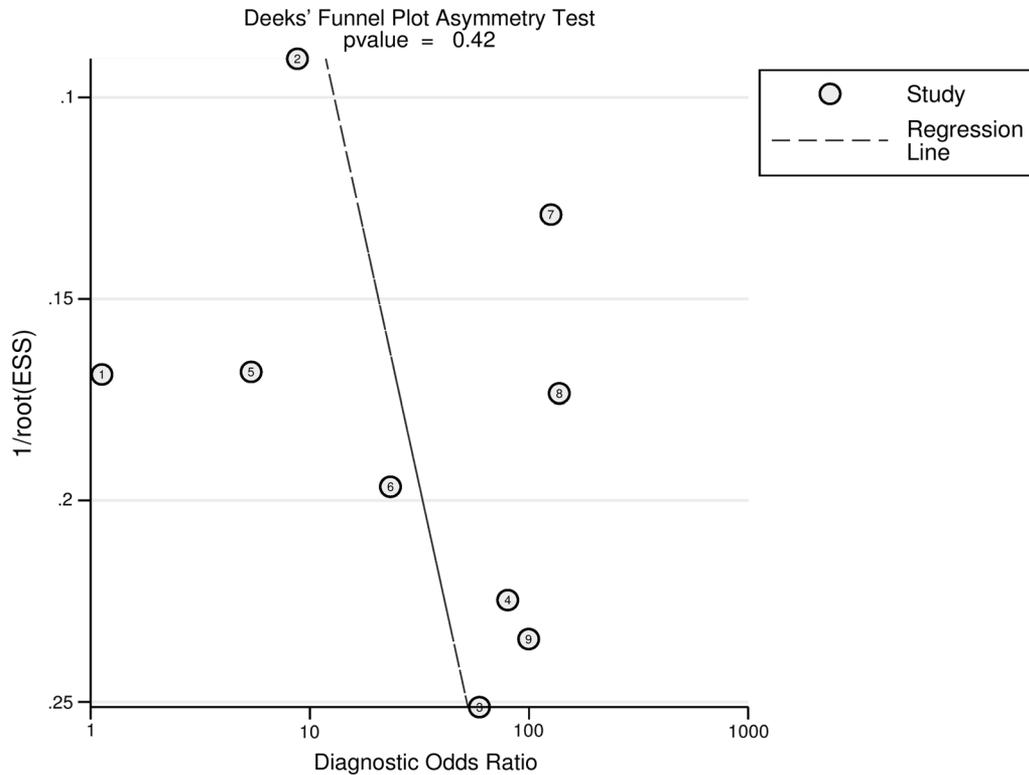


Figure 2. Results of Deek's funnel plot of asymmetry test for possible publication bias. No significant publication bias was found ($P = .42$).

The flow of study selection is demonstrated in Figure 1.

Study Description, Quality, Publication Bias

A total of 439 F-18 FDG PET or PET/CT images from 298 patients of nine studies^{9,18–25} and 65 control subjects of two studies^{18,20} were included for the assessment of disease activity of LVV. Mean age was 38.3 years, and 81.5% (243/298) of patients were female. Of the nine studies, six studies^{9,21–25} were performed in a retrospective manner; all the nine studies enrolled the patients with TA, whereas one study¹⁸ also enrolled the patients with GCA; seven studies^{9,18–20,22–24} acquired images with PET/CT scanner, whereas two studies^{21,25} used dedicated PET scanner. The principal characteristics of the nine studies are summarized in Table 1. Publication bias was evaluated using Deek's funnel plot asymmetry tests (Figure 2), and no significant bias was found ($P = .42$).

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Arnaud 2009	+	+	?	+	+	+	?
Grayson 2017	+	+	+	+	+	+	+
Karapolat 2013	?	+	+	+	?	+	+
Kobayashi 2005	?	+	?	+	?	+	?
Lee 2009	+	+	+	+	+	+	+
Lee 2012	+	+	+	+	+	+	+
Santhosh 2014	?	+	+	?	?	+	+
Tezuka 2012	+	+	+	+	+	+	+
Webb 2004	?	?	?	+	?	?	?

Legend: ● High, ? Unclear, ● Low

Figure 3. Risk of bias and applicability concerns summary based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies. Overall quality of the included studies was deemed satisfactory.

Methodological Quality Assessment

Summary of the risk of bias and applicability concerns based on 15-item modified Quality Assessment

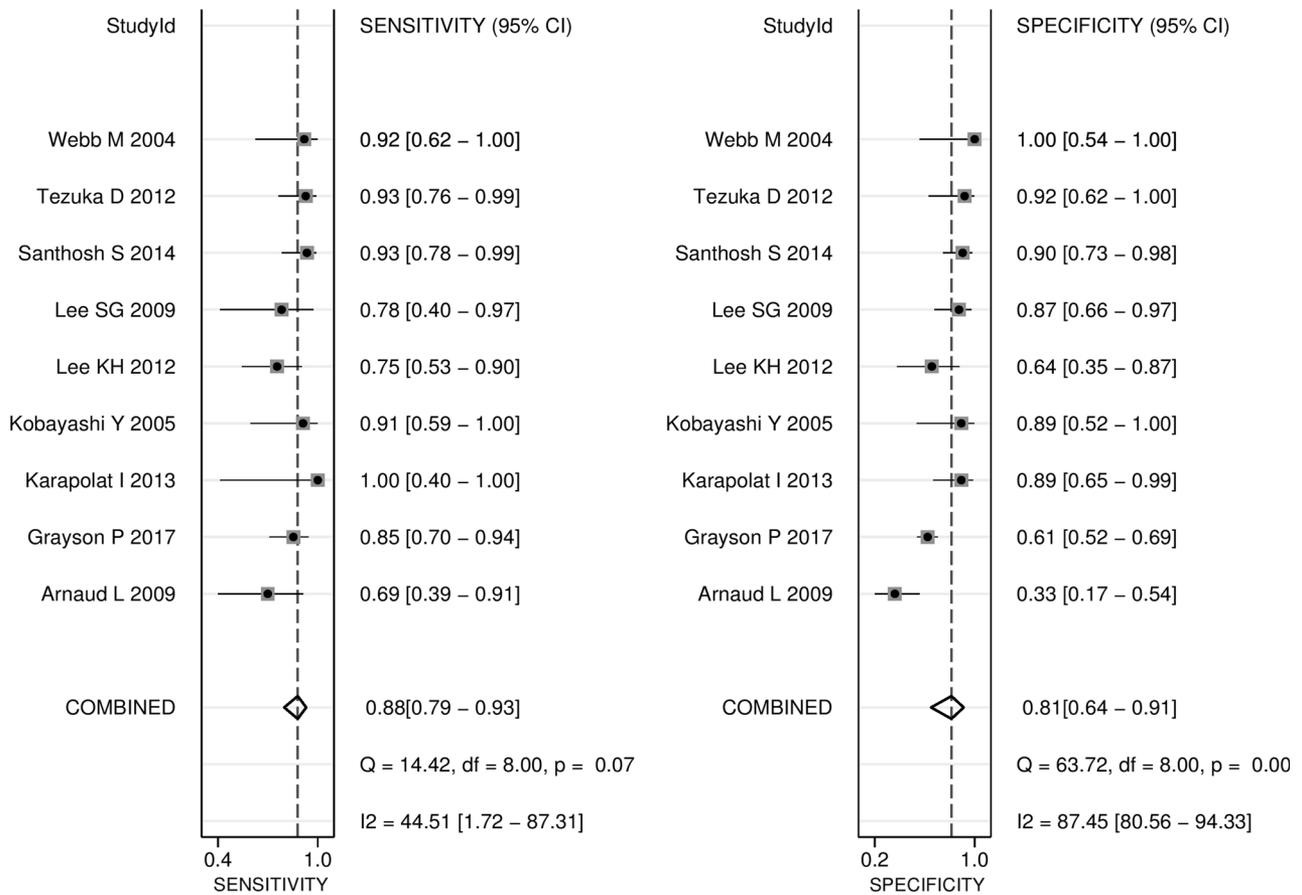


Figure 4. Forest plots of pooled sensitivity and specificity of F-18 FDG PET or PET/CT for the assessment of disease activity of large vessel vasculitis. Summary of sensitivity and specificity was 0.88 (95% CI 0.79-0.93) and 0.81 (95% CI 0.64-0.91), respectively.

of Diagnostic Accuracy Studies are presented in Figure 3, and the overall quality of the included studies is deemed satisfactory.

Diagnostic Accuracy of F-18 FDG PET or PET/CT

Forest plots of the sensitivity and specificity of F-18 FDG PET or PET/CT for the assessment of disease activity of LVV in the nine included studies are shown in Figure 4. The pooled sensitivity of F-18 FDG PET or PET/CT for the detection of active LVV was 0.88 (95% CI 0.79-0.93) without heterogeneity ($\chi^2 = 14.42$, $P = .07$), and the pooled specificity was 0.81 (95% CI 0.64-0.91) with heterogeneity ($\chi^2 = 63.72$, $P = .00$). The overall positive likelihood ratio was 4.5 (95% CI 2.2-9.5), and the negative likelihood ratio was 0.15 (95% CI 0.08-0.29). The pooled DOR was 30 (95% CI 8-107).

Figure 5 shows hierarchical sROC curve and indicates that the area under the curve was 0.91 (95% CI 0.89-0.94), indicating good performance for the assessment of disease activity.

Heterogeneity Evaluation and Meta-regression Analysis

Heterogeneity between studies was found in the specificity of F-18 FDG PET or PET/CT for the assessment of disease activity of LVV. A meta-regression analysis was performed to explore the potential sources of heterogeneity, which demonstrated that study design (prospective vs retrospective), number of analyzed PET scan, positive PET criteria (visual grading vs cutoff value of SUV_{max}), and reference standard of disease activity (NIH criteria vs others) were not the sources of heterogeneity in the meta-analysis (Table 2).

DISCUSSION

Due to lack of appropriate biochemical or imaging biomarkers, the assessment of disease activity of LVV has been a challenging issue during or after immunosuppressive therapy. Erythrocyte sedimentation rates (ESRs) were normal in more than a half of patients with remission, and vasculitis on arterial biopsy specimens was present in 44% patients with clinically inactive TA.⁵ Likewise in GCA, clinical evaluation is often imprecise in determining disease activity and acute phase reactants sometimes do not accurately indicate remission or relapse.^{26,27} Thus, better biomarkers including imaging modalities for the detection of ongoing active vascular inflammation and monitoring of therapy response are needed. The current meta-analysis provides evidence

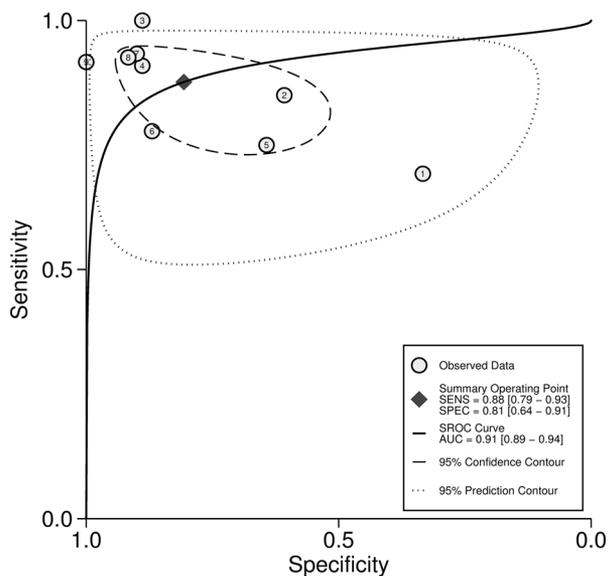


Figure 5. Hierarchical summary receiver-operating characteristic curve of F-18 FDG PET or PET/CT for the assessment of disease activity of large vessel vasculitis. The area under the curve was 0.91 (95% CI 0.89-0.94), indicating good performance for the assessment of disease activity.

that F-18 FDG PET or PET/CT has a good performance for the detection of active disease status in patients with LVV (pooled sensitivity of 88%, pooled specificity of 81%, and the area under the curve of 0.91). It can serve as a surrogate biomarker for assessment of disease activity of LVV during or after immunosuppressive therapy.

In contrast to relatively higher pooled specificity (89%-93%) for the initial diagnostic performance of F-18 FDG PET or PET/CT,^{28,29} the current meta-analysis for the assessment of disease activity of LVV showed relatively lower specificity. The majority of the included studies used the NIH criteria as a reference standard for the disease activity,^{9,19,21–25} in which active disease is defined when new onset or worsening of two or more following features appeared: systemic features, elevated ESR, features of vascular ischemia or inflammation, and typical angiographic features.⁵ However, these criteria are thought to be imperfect because clinical features are variable and acute phase reactant is not a consistently reliable marker, and the use of conventional angiography is limited by its invasiveness. Arnaud et al criticized the results of previous studies performed by utilizing NIH criteria due to lack of validated activity criteria.⁹ Moreover, they pointed out that the undervalued disease activity or a selection bias might exist in previous studies.^{20,25} Lee et al, however, indicated that Arnaud et al might have underestimated the disease activity in clinically inactive patients.²¹ A relatively lower specificity of the current meta-analysis for the assessment of disease activity might be attributed to innate insufficiency of the current criteria as a reference standard. Recently, a new index was developed and evaluated for the assessment of disease activity in TA, Disease Extent Index-Takayasu (DEI.Tak), consisting of only clinical features without any imaging data.³⁰ However, the authors concluded that acute phase reactant levels and imaging data should be incorporated for better assessment of disease activity. Although there are no guidelines for adopting imaging techniques, better criteria for assessment of disease activity incorporated with

Table 2. Meta-regression analysis for identifying potential sources of heterogeneity

Variables	Coefficients	SE	RDOR (95% CI)	P values
Design	0.06	1.20	1.06 (0.02–48.23)	.96
Number of PET scan	0.60	1.43	1.83 (0.02–174.83)	.70
Criteria of PET	1.36	1.08	3.91 (0.13–121.69)	.30
Criteria of disease activity	1.82	1.01	6.15 (0.25–154.15)	.17

SE, standard error; RDOR, relative diagnostic odds ratio; CI, confidence interval

imaging modalities including F-18 FDG PET or PET/CT should be introduced and validated.

Besides a good performance for assessment of disease activity, F-18 FDG PET or PET/CT has several advantages over other proposed imaging techniques such as Doppler ultrasonography, magnetic resonance angiography, or even conventional angiography. The course of imaging acquisition of F-18 FDG PET or PET/CT is noninvasive unlike conventional angiography. It can also provide whole-body information at a single acquisition, which allows assessing the extent of inflammation of the vascular branches and identifying more active regions among the affected vessels.³¹ By performing serial PET imaging, the effects of the treatment on disease activity can be monitored.²⁵ While other imaging modalities show the anatomical changes of involved vessels, F-18 FDG PET or PET/CT can give sensitive information on early inflammatory changes prior to the structural alterations.³² Grayson et al reported that the majority of patients in clinical remission showed positive PET results.¹⁸ Although it is unclear whether such residual vascular FDG uptake represents subclinical vasculitis, vascular remodeling, hypoxia, atherosclerosis, or a combination, the authors suggest that subclinical vascular inflammation would be a major contributor to the vascular FDG uptake based on future clinical relapse during follow-up period in patients with high burden of arterial FDG uptake. Future studies are needed to elucidate the prognostic value of F-18 FDG PET or PET/CT, especially when the PET images show discordant findings with the clinical disease features in LVV patients.

The current meta-analysis has several limitations. First, the majority of patients from the included studies were TA, whereas only one study¹⁸ enrolled the patients with GCA. Several previous studies on the value of F-18 FDG PET for assessment of disease activity in patients with GCA through the follow-up imaging were performed, but failed to meet our inclusion criteria since there were insufficient data for calculation of sensitivity and specificity of F-18 FDG PET to assess the disease activity of LVV.^{8,33–35} Second, the criteria of PET positivity were not standardized among the included studies. Two studies used cutoff value of SUV_{max} as positive PET criteria, while other studies employed visual grading systems for assessment of disease activity. Third, the included studies showed statistically significant heterogeneity in their estimated of specificity. Possible source of this heterogeneity might be a reference standard for clinically active disease or positive PET criteria. However, meta-regression analysis revealed that none of the variables (study design, number of analyzed PET scan, positive PET criteria,

and reference standard of disease activity) was the source of the study heterogeneity.

NEW KNOWLEDGE GAINED

F-18 FDG PET or PET/CT has a good diagnostic performance for the detection of active disease status in patients with LVV. It can serve as a surrogate biomarker for assessment of disease activity of LVV during or after immunosuppressive therapy.

CONCLUSIONS

F-18 FDG PET or PET/CT has a good performance for the detection of active disease status in patients with LVV. Although there are no guidelines for adopting imaging techniques, more objective and updated criteria for the assessment of disease activity incorporated with F-18 FDG PET or PET/CT should be introduced and validated. Further studies are warranted to determine if PET-based treatment of LVV can improve outcomes.

Disclosure

The authors of this manuscript declare no relationships with any companies products or services of which may be related to the subject matter of the article.

Informed Consent

Written informed consent was not required for this study because it is a meta-analysis based on the studies that have been published.

Ethical Approval

Institutional Review Board approval was not required because only the published studies were used in this meta-analysis. The manuscript has not been published before and is not under consideration for publication anywhere else.

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