
18F-FDG-PET in assessing disease activity in Takayasu arteritis: a meta-analysis

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Received on August 6, 2012; accepted in revised form on October 22, 2012.

Clin Exp Rheumatol 2013; 31 (Suppl. 75): S22-S27.

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Key words: Takayasu arteritis, PET, 18F-FDG, meta-analysis

ABSTRACT

Objective. To assess the diagnosis value of 18F-FDG-PET in estimating disease activity in Takayasu arteritis.

Methods. A complete search of PubMed, EMBASE and The Cochrane Library was finished to July 25, 2012. Sensitivity and specificity as well as pooled estimates of positive and negative likelihood ratios (PLR and NLR) were calculated by Meta-Disc. We also calculated the area under the sROC curve (AUC) and the Q^* index.

Results. The meta-analysis was finished with 6 study retrieved from the database search. The pooled sensitivity, and specificity with 95% confidence interval were 70.1% (95% CI, 58.6–80.0) and 77.2% (95% CI, 64.2–87.3). The PLR and NLR were 2.313 (95% CI 1.108–4.829) and 0.341 (95% CI 0.142–0.824). The AUC was 0.805(± 0.084) and Q^* index was 0.7402 (± 0.0739).

Conclusion. 18F-FDG-PET had moderate diagnosis value in assessing TA activity. It may add additional value to the current diagnosis methods.

Introduction

Takayasu arteritis (TA) is a rare non-specific inflammatory disease with unknown cause, predominantly affecting the aorta and its main branches, coronary arteries, and pulmonary arteries (1). TA diagnosis is usually delayed because of the insidious onset and non-specific clinical symptoms. Further progression leads to stenoses and occlusions as well as to aneurysmatic dilatation (1), therefore, monitoring disease activity is essential for the prognosis.

The current “gold standard” for the diagnosis and follow-up of patients with TA is x-ray angiography. However, it is invasive and can only provide morphological changes rather than information on vessel wall. C-reactive protein and erythrocyte sedimentation rate are usually used as markers for estimating

TA activity. However, they both did not correlate well with the histological evidence of active disease (2, 3). 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) scanning is a non-invasive metabolic imaging modality based on the regional distribution of 18F-FDG. Increased 18F-FDG uptake can be detected in inflammatory cells (4, 5), which usually have high metabolic rates. 18F-FDG-PET can reflect metabolic changes in the vessel wall. 18F-FDG-PET has now been widely used to diagnose vasculitis. Its diagnosis value has been documented in aortitis in the setting of TA (6) and giant cell arteritis (GCA) (7) as well as in vascular lesions in regions affected by polymyalgia rheumatica (8) as well as in cases secondary to sarcoidosis or ulcerative colitis (9, 10). Furthermore, several researches have been made to estimate the utility of 18F-FDG-PET in TA activity estimating. However, the sample sizes are all small, we did this meta-analysis to increase statistical power and to explore this effect.

Methods

Literature search strategy

Systematic literature search without language restriction was done by searching electronic databases including PubMed, EMBASE and The Cochrane Library. The search strategy was completed by searching words (‘Takayasu arteritis’) AND (‘positron emission tomography/computed tomography’ OR ‘PET/CT’ OR ‘positron emission tomography-computed tomography’ OR ‘PET-CT’ OR “fluorodeoxyglucose” OR “FDG”). Additional studies were identified in the references lists of publications. The last literature search was done in July 2012, without language limits.

Study selection criteria

The inclusion criteria still included: (a) 18F-FDG-PET was used to assess the

Funding: This research was supported by the National Natural Science Foundation of China (grant no. 30770859).

Competing interests: none declared

activity of TA; (b) data on true positives (TP), false-positives (FP), true-negatives (TN) and false-negatives (FN) can be calculated from the original study; (c) all patients included should fulfil American College of Rheumatology (ACR) criteria for TA; (d) NIH diagnosis was used as the reference standard. When data was presented in more than one article, the article with smaller participants was excluded. All the studies were reviewed by two reviewers (CY. and LN.) independently. And the data were extracted by the two reviewers. Any disagreement was settled by the third reviewer DA.

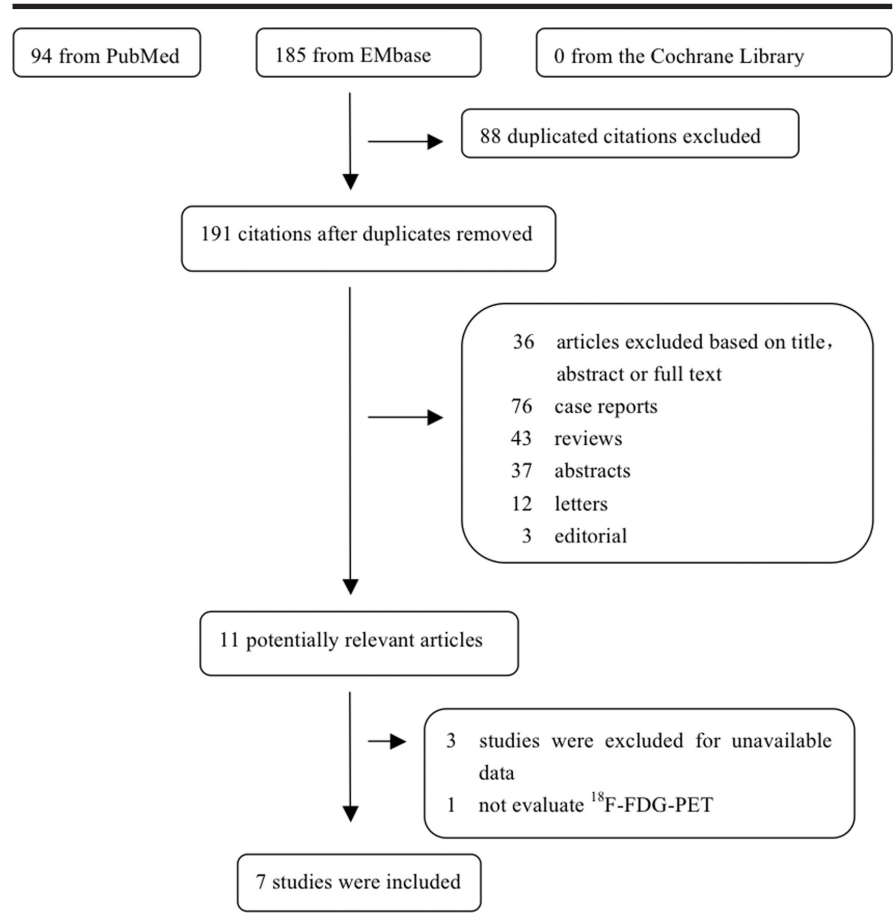
Date extraction and quality assessment

Two investigators (CY. and LN.) independently did the search data extraction. Any disagreement was settled by the third reviewer DA. For each report, we extracted the following items: (1) the name of the first author; (2) the year of publication; (3) study type; (4) study method; (5) PET interpretation method; (6) age distribution of study population; (7) the sample size; (8) blood glucose levels; (9) female/male; (10) Length of fasting before PET; (11) duration from intravenous administration to the time of inspection; (12) number of patients taking immunosuppressive medication; (13) TP, FP, FN, TN. Two reviewers evaluated the selected studies, using the quality assessment for studies of diagnostic accuracy QUADAS standard (maximum score 14) independently (11). QUADAS includes 14 items, each of which was assessed as “yes”, “no”, or “unclear”. If the answer is “yes” then score “1”, and if the answer is “no” or “unclear” then score “0”.

Statistical analysis

We calculated pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio and diagnostic odds ratio (DOR) with the corresponding 95% confidence intervals (CI). We added 0.5 to each cell that contained one or more zero values (12). I-squared (I^2) statistic was calculated to measure the heterogeneity between studies. A study with $I^2 > 50\%$ was considered

Fig. I. Detailed procedure of study selection in the meta-analysis.



to have substantial heterogeneity and random-effects model was applied. The receiver-operating-characteristics (sROC) curve and the area under the sROC curve (AUC) and specificity (Q^* index) were estimated. Publication bias was examined by constructing a funnel plot using the Egger regression model. Analyses were performed with Meta-Disc 1.4 (XI Cochrane Colloquium; Barcelona, Spain) (13) and STATA (version 9.0; Stata Corporation, College Station, Tex, USA). All p -values were two tailed and $p < 0.05$ was considered statistically significant.

Results

Search results and study characteristics

Totally 279 articles were retrieved from PubMed, EMBASE and the the Cochrane Library, of which 11 studies potentially related to our issue were identified. Figure I describes the flow of candidate and eligible papers selecting. Three were excluded for unavail-

able data (14-16). Seven studies finally were included in our study. The characteristics of those studies were shown in Table I. Blinding was used in 3 studies (17-19), but the remaining 4 studies were either not blinded or not clarified.

Study quality assessment and publication bias

Three studies scored 14 using QUADAS standard (17-19). Two of the remaining 4 scored 12 (20, 21). The other two scored 11 (6, 22). To assess publication bias, funnel plots were designed using the log diagnostic odd ratios (DORs) of individual studies against standardised effect. The plots showed symmetrical distribution, demonstrating no publication bias (Egger's test: $p = 0.280$) (Fig. 2).

Summary estimates of sensitivity, specificity, PLR, NLR, DOR and AUC
In the study by Andrew *et al.*, there was no inactive TA patients assessed

Table I. Characteristics of studies included in the meta-analysis.

Author	Year	Study type	Method	PET interpretation method	Number	Mean Year \pm SD (range)	Female/Male	Length of fasting before PET	Time	Number (taking immuno-suppressive medication)	TP	FP	FN	TN	Score
Andrew	2004	Retrospective	FDG-PET	Semi-quantitative	6	29.5 \pm 5.6	5/1	4h	90min	6/6	5	0	1	0	11
Arnaud	2009	Retrospective	FDG-PET/CT	Semi-quantitative	28	36 (15-67)	21/7	>12h	60min	28 of the 40 scans (70%) were obtained from patients receiving immuno-suppressive treatments	5	4	13	6	14
Kobayashi	2005	Prospective	FDG-PET/CT	Quantitative	14	28 (14-50)	13/1	>12h 96.8 mg/dl (80-138)	45min	11/14	10	0	1	3	12
Lee	2012	Prospective	FDG-PET	Semi-quantitative	38	43.0 \pm 11.8	34/4	>6h 92.9 mg/dl (74-122)	40-60 min	14/38	18	5	6	9	14
Lee	2009	Retrospective	FDG-PET/CT	Semi-quantitative	32	45.4 (21-66)	26/6	>6h((97 \pm 16mg/dL)	60min	10/32	7	3	2	20	14
Webb	2004	Retrospective	FDG-PET	Semi-quantitative	16	39.3 (23-64)	15/1	4h	90min	9/16	12	1	0	3	12
Vista	2010	Retrospective	FDG-PET	ND	4	35.3 (23-48)	4/0	ND	ND	2/4	2	1	0	1	11

Time: from intravenous administration to inspection. ND indicates that the data was not documented.

by NIH criteria (6), so it was not evaluated in the analysis. In the study by Webb *et al.*, two patients were excluded for not fulfilling the ACR criteria for TA (21).

The sensitivity and specificity of FDG-PET in estimating TA activity ranged from 28% to 100% and from 50% to 100% respectively. The overall pooled estimates of sensitivity and specificity

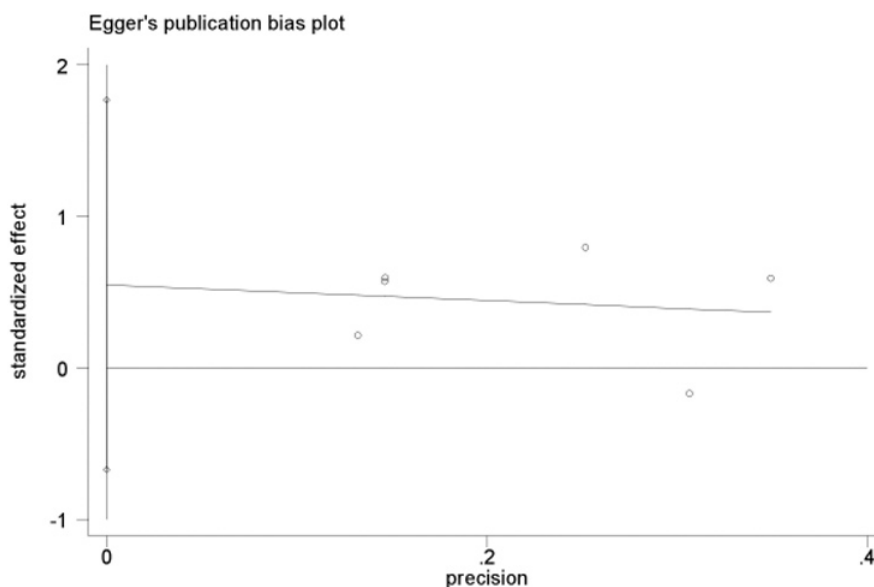
were 70.1% (95% CI, 58.6–80.0) and 77.2% (95% CI, 64.2–87.3), respectively (Fig. 3-4). The PLR and NLR was 2.313 (95% CI 1.108–4.829) and 0.341 (95% CI 0.142–0.824), respectively (Fig. 5-6). The pooled DOR was 7.498 (95% CI 1.650–34.071) (Fig. 7). The AUC was 0.805 (\pm 0.084) and Q* index was 0.7402 (\pm 0.0739) (Fig. 8). The heterogeneity among studies was

as follow: for sensitivity, $I^2=77.6\%$, $p=0.000$; for specificity, $I^2=36.4\%$, $p=0.164$; for PLR, $I^2=48.7\%$, $p=0.083$; for NLR, $I^2=71.0\%$, $p=0.004$; for DOR, $I^2=60.8\%$, $p=0.026$).

Discussion

To the best of our knowledge, this is the first meta-analysis study in evaluating the diagnosis value of 18F-FDG-PET in estimating TA activity. In our study, the pooled estimates of sensitivity and specificity were 70.1% and 77.2%. The diagnosis values were moderate. Although 18F-FDG-PET was not evaluated high enough to monitor TA activity in our study, it may add additional value to the current diagnosis methods.

18F-FDG-PET seemed to be more sensitive than other image modality (6, 23), moreover, the diagnosis value of 18F-FDG-PET in TA and GCA has been reported. TA and GCA are the most common form of large-vessel vasculitides, characterised by granulomatous inflammation with large- and medium-sized arteries involved. GCA predominantly affects the cranial arteries, whereas TA primarily involves the aorta, its main branches and the coronary and pulmonary arteries. However,

Fig. 2. Publication bias evaluated by funnel plot.


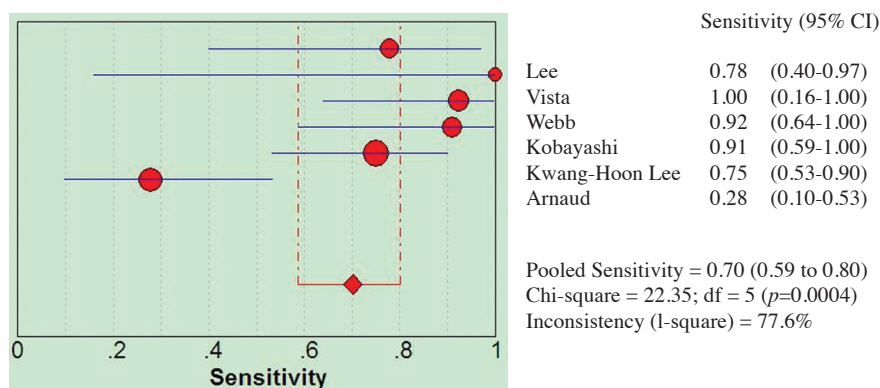


Fig. 3. Forest plot of pooled sensitivity for 18FDG-PET in assessing TA activity.

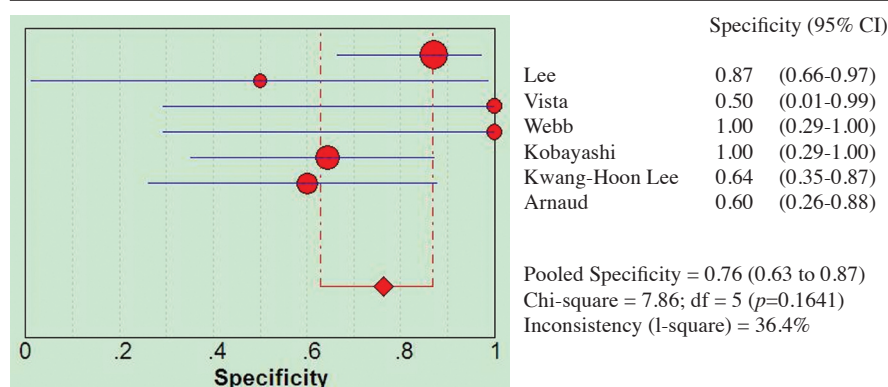


Fig. 4. Forest plot of pooled specificity for 18FDG-PET in assessing TA activity.

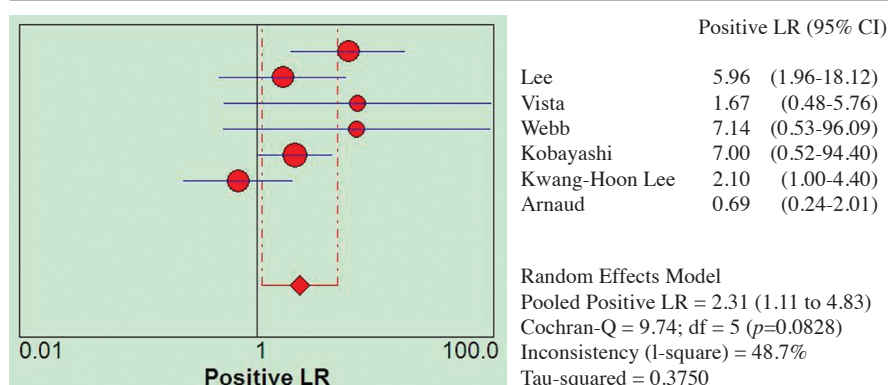


Fig. 5. Forest plot of pooled PLR for 18FDG-PET in assessing TA activity.

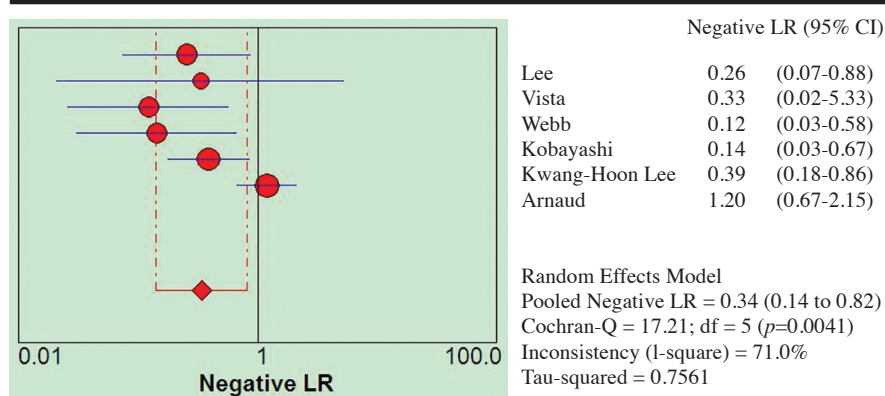


Fig. 6. Forest plot of pooled NLR for 18FDG-PET in assessing TA activity.

overlapping clinical, radiological and pathological features usually makes it difficult to differentiate GCA from TA. A meta-analysis of assessing the usefulness of 18F-FDG-PET in GCA diagnosis revealed a pooled sensitivity of 80% and a specificity of 89% (24). In the study by Kobayashi *et al.*, the sensitivity and specificity of 18F-FDG-PET in detecting TA is 90.9% and 88.8%, respectively (20). Given all that 18F-FDG-PET might be a potential image modality to differentiate TA from GCA.

TA activity assessment is of extreme importance. Histopathology is gold standard in determining the activity of TA. However, it is impossible unless the surgery was carried out (25). Activity reference criteria adopted in these studies was NIH criteria rather than histological evidence. Although the ACR criteria were reported to have a sensitivity of 90.5% and a specificity of 97.8% (26), in the study by Kerr *et al.*, 4 out of 9 specimens (44%) that were obtained from patients who were clinically inactive had histological evidence of active disease (2). The disease activity may be underestimated by NIH criteria, for it could not figure out disease status preceding the pulseless phase. So validated activity criteria estimating method remains to be discovered. Twenty-nine (83%) out of 35 biopsy proved GCA patients had vascular 18F-FDG uptake in at least 1 vascular territory (27). So the 18F-FDG-PET might be better to monitoring disease activity, if it is not so much uncertainty.

As for using 18F-FDG-PET in diagnosing TA activity, the following points should be noted. PET/CT is a very sensitive imaging modality which can localise areas of high metabolic activity. False-positive results might be present. Increased 18F-FDG accumulated not only in inflammatory blood vessels in TA but also in vasculitic conditions such as atherosclerosis (28). Moreover, 18F-FDG-PET inadequately assesses disease activity of large-vessel GCA in patients with immunosuppressive medication (29, 30). Immunosuppressive drugs could exert impressive influence on immune response. In the

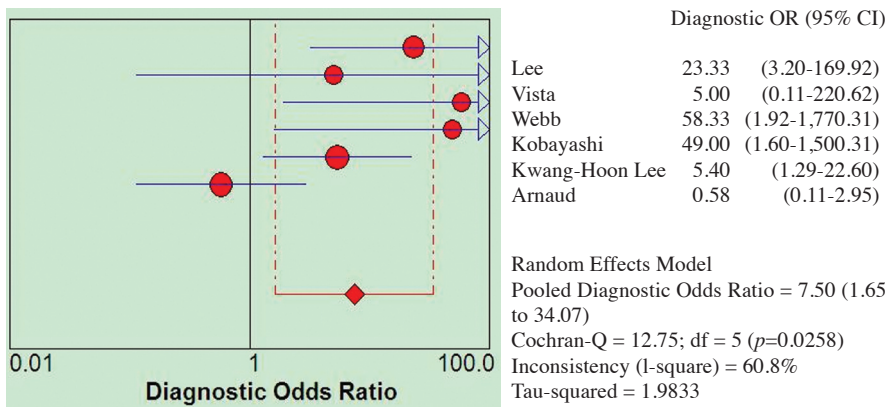


Fig. 7. Forest plot of pooled DOR for 18F-FDG-PET in assessing TA activity.

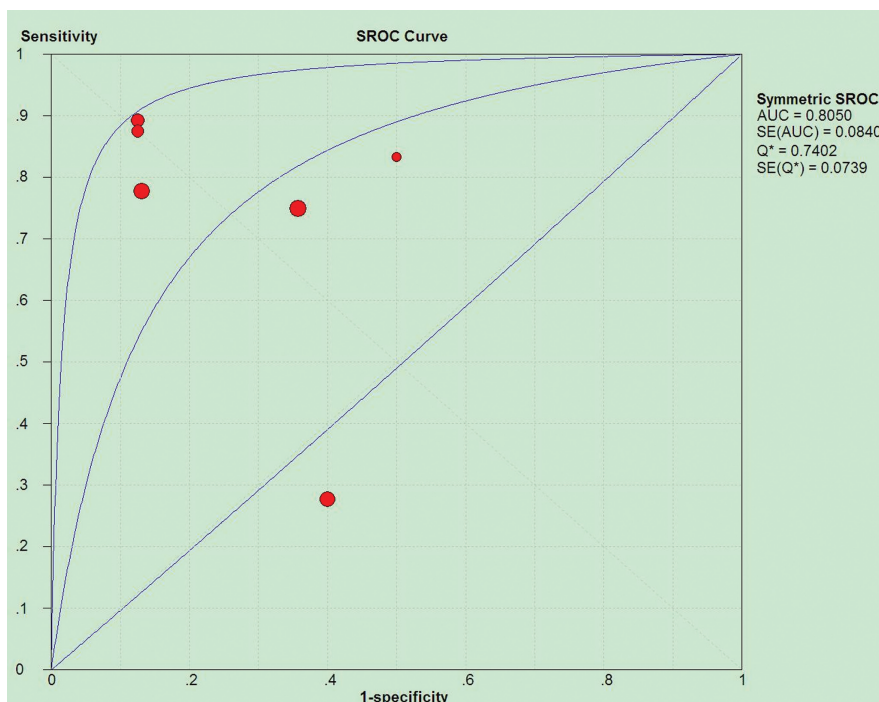


Fig. 8. The sROC curve and the Q* index of 18F-FDG-PET in assessing TA activity.

studies included in our meta-analysis, the percentages of patients taking immunosuppressive drugs varied from 25% to 79%.

There are some limitations in our study. Diagnosis methods applied were different. It is reported that visual estimation had a good reproducibility (31, 32). Three studies included employed semi-quantitative method by visually comparing the arterial wall 18F-FDG uptake with hepatic uptake (17-19) or normal background activity (21). One was performed based on quantitative interpretation (20). The additional diagnosis value of CT has not yet been fully evaluated. The heterogeneity

among studies might be a limitation factor for assessing the diagnosis value of PET in TA activity estimation. The sample sizes in the studies are small, varying from 4 to 38, and the number of the studies was too small to do subgroup analysis. Larger sample size and more studies are needed to increase the statistic power.

In conclusion, the sensitivity and specificity of 18F-FDG-PET for detecting active disease of TA were moderate. It may add additional value to the current diagnosis methods, for the lack of sensitivity of NIH criteria in detecting active disease, further studies are needed.

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