^{18}F-FDG PET/CT for assessing of disease activity of idiopathic inflammatory myopathies. A systematic review and meta-analysis

Keunyoung Kim[1] **MD, PhD,**
Seong-Jang Kim[2, 3, 4] **MD, PhD**

1. Department of Nuclear Medicine, Pusan National University Hospital, Busan, Korea
2. Department of Nuclear Medicine, College of Medicine, Pusan National University, Yangsan, 50612, Korea
3. BioMedical Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, 50612, Korea
4. Department of Nuclear Medicine, Pusan National University Yangsan Hospital, Yangsan, 50612, Korea

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Corresponding author:
Seong-Jang Kim MD, PhD
Department of Nuclear Medicine, Pusan National University Yangsan Hospital, Yangsan, 50612, Korea
BioMedical Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, 50612, Korea
Department of Nuclear Medicine, College of Medicine, Pusan National University, Yangsan, 50612, Korea
Tel; 82-55-360-1900, Fax; 82-55-360-1915
growthkim@daum.net & growthkim@pusan.ac.kr

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Abstract

Objective: The purpose of current investigation was to evaluate the diagnostic accuracy of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for the determination of disease activity of idiopathic inflammatory myopathies (IM) using diagnostic accuracy test. **Subjects and Methods:** The PubMed and EMBASE database, from the earliest available date of indexing through August 31, 2020, were searched for results investigating the diagnostic accuracy of ^{18}F-FDG PET/CT for the determination of disease activity of IM. We calculated the pooled sensitivities and specificities of included studies, calculated positive and negative likelihood ratios (LR+ and LR-) and obtained summary receiver operating characteristic (SROC) curves. **Results:** Across 4 studies with 5 results (90 patients), the pooled sensitivity was 0.94 (95% CI; 0.87-0.97) without heterogeneity (I2=0.0, P=0.8) and a pooled specificity was 0.90 (95% CI; 0.72-0.97) with heterogeneity (I^2=65.1, P=0.02). Likelihood ratio (LR) syntheses showed an overall positive likelihood ratio (LR+) of 9.2 (95% CI; 3.1-28.0) and negative likelihood ratio (LR-) of 0.07 (95% CI; 0.03-0.16). The pooled DOR was 131 (95% CI; 26-664). The hierarchical SROC curve shows the areas under the curve of 0.96 (95% CI; 0.94-0.98). **Conclusions:** Fluorine-18-FDG PET/CT has a good performance for the detection of active disease status in patients with IM. Although there are no guidelines for adopting imaging techniques, more objective and updated criteria for the assessment of disease activity incorporated with ^{18}F-FDG PET/CT should be introduced and validated. Further studies are necessary to determine if ^{18}F-FDG PET/CT-based treatment of IM can improve outcomes.

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Introduction

Idiopathic inflammatory myopathies (IM) is a heterogeneous clinical condition characterized by symmetrical muscle weakness, decreased muscle endurance, and elevated serum levels of skeletal muscle-derived enzymes, such as creatine kinase (CK) and aldolase [1, 2]. Dermatomyositis (DM) and polymyositis (PM) are major disease subgroups of idiopathic IM, which have common and distinct clinical and histological characteristics. The pathological change of the diseases is non-suppurative inflammation of striated muscle [3]. The diagnosis of diseases is based on the standards set by Bohan and Peter (1975) [4].

The measurement of serum muscle-derived enzyme, muscle biopsy, electromyography, and magnetic resonance imaging (MRI) are known to be useful for detection of IM. Generally, MRI is considered to be useful to detect the inflammatory site for biopsy and the assessment of disease activity of the diseases [5]. However, whole body MRI availability is low and correlation with disease activity might depend on the IM subgroups [6].

Cellular uptake of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is determined by the expression of glucose transporter proteins, which is increased in activated inflammatory cells and tumor cells. Thus, ^{18}F-FDG positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) have been proposed to be useful imaging modalities in the diagnosis and management of patients with suspected infectious diseases [7-9]. The common histopathologic findings of PM/DM include infiltration of inflammatory cells, and degeneration and regeneration of muscle fibers, with the major muscles involved being the limb girdles, neck and pharynx, although the dominant inflammatory cell types and the typical site of infiltration within the muscle are different between PM and DM [10, 11].

Although, ^{18}F-FDG PET/CT could detect inflammatory lesions in DM and PM patients, the elevated muscular ^{18}F-FDG uptake does not correlate with MRI findings and serum le-

vels of skeletal muscle-derived enzymes [12].

The purpose of this study is to carry out meta-analysis of the published data on the performance of ^{18}F-FDG PET/CT in the assessment of disease activity of IM, in order to provide more evidence-based data for formulating the guidelines on appropriate use of ^{18}F-FDG PET/CT imaging in IM.

Subjectives and Methods

Data sources and search strategy

We used PubMed, Cochrane, and EMBASE database from the earliest available date of indexing through August 31, 2020. We used a search algorithm based on a combination of terms: (1) "PET" OR "positron emission tomography" OR "positron emission tomography/computed tomography" OR "PET/CT""positron emission tomography-computed tomography" OR "PET-CT"; OR "FDG" and (2) "Myositis" OR "Dermatomyositis" OR "Polymyositis". For PubMed, the search strategy comprised both free text search and usage of Medical SubHeadings (MeSH). For Embase, free text search and the Emtree Thesaurus were used in the current study.

Study selection

Two researchers evaluated retrieved studies. The inclusion criteria for relevant studies were ^{18}F-FDG PET/CT used to assess the disease activity; studies limited to IM including DM and/or PM; sufficient data for sensitivity and specificity of ^{18}F-FDG PET/CT to assess the disease activity of IM or the absolute numbers of true-positive (TP), false negative (FN), false positive (FP), and true negative (TN) test results were available, which allowed us to construct 2 by 2 table. Abstracts were excluded from this analysis because of insufficient data to evaluate the methodological quality and to allow the calculation of diagnostic accuracy. The duplicated publications were excluded. The review articles, case reports, conference papers, and letters, which do not contain the original data were also excluded for the current study. Disagreements were resolved in consensus.

Data extraction and quality assessment

The authors independently extracted relevant data (authors, year of publication, design, patients' characteristics, technical aspects) using a data collection form. The number of TP, TN, FP, and FN were calculated from each study based on ^{18}F-FDG PET/CT scan as the index test. The methodological quality of the included studies was assessed using 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) [13]. Discrepancies between the researchers were resolved by discussion.

Data synthesis and analysis

We calculated pooled sensitivity and pooled specificity of ^{18}F-FDG PET/CT. The positive (LR+) and negative likelihood ratios (LR-), and diagnostic odds ratios (DOR) were calculated with 95% confidence intervals (CI). A DOR represents the ratio of the odds of positivity in a disease state relative to the odds of positivity in the non-disease state [14]. The heterogeneity was assessed using the chi-square and I-square tests [15, 16]. A random-effects model was used for analysis [17, 18]. The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. We also calculated summary receiver operating characteristics curves (SROC) and the area under the curve [19]. When statistical heterogeneity was identified, meta-regression was performed to find any potential source of bias [20]. Two-sided $P<0.05$ was considered statistically significant. Statistical analyses were performed with commercial software programs (STATA, version 13.1; StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA).

Results

Literature search and Selection of studies

We found 576 studies, of which 67 of duplicated studies were excluded. The non-relevant 261 studies, 13 case reports, 81 conference abstracts, 36 letters, 6 editorials, 19 notes, and 86 review articles were excluded. Remaining 7 full text articles were evaluated for eligibility and 3 articles were excluded because of inadequate data for estimation of sensitivity and specificity of ^{18}F-FDG PET/CT for the determination of disease activity of IM. Finally, 4 studies (5 results) were selected and included for this study [21-24]. The characteristics of the included studies are presented in Table 1. The detailed procedure of study selection in the current meta-analysis is shown in Figure 1.

Study description, quality and publication bias

We conducted per-patient data analysis. There were a total of 90 patients in the included studies, and the age ranged from 30 to 79 years. All 4 studies performed retrospective investigations. Three studies [21, 23, 24] used SUVmax for interpretation of ^{18}F-FDG PET/CT and 1 study [22] used visual interpretation method. The diagnosis of DM/PM was established by Bohan & Peter criteria [4]. The principal characteristics of the 4 studies included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks's funnel plot asymmetry tests were designed. The non-significant slope indicates that no significant bias was found. The P value was 0.20 (Figure 2).

Methodological quality assessment

Summary of the risk of bias and applicability concerns based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies are presented in Figure 3 and the overall quality of the included studies is deemed satisfactory.

Diagnostic accuracy of ^{18}F-FDG PET/CT for the determination of disease activity of IM

The diagnostic performance results of ^{18}F-FDG PET/CT for the assessment of disease activity of IM in the 5 included

Table 1. *Characteristics of the included studies.*

Authors	Year	Country	Patient number	M/F	Age (range)	Patient group	PET indication	Other imaging	SUVmax	Muscle sites for SUVmax	GS	Study design
Matuszak J	2019	France	26	7/19	59.3	DM, PM, NAM, OM	34 IM patients for cancer screening and 20 normal controls for evaluation of pulmonary nodules	None	Mean muscular SUVmax Active IM; 0.9 Inactive IM; 0.58, NC; 0.41	Deltoideus, Biceps brachii, Triceps brachii, Pectoralis major, Psoas major, Gluteus group, Adductor group, Quadriceps	B & P criteria	R
Motegi S	2019	Japan	22	9/13	50.9	DM	For evaluation of interstitial lung disease just before receiving initial treatment	MRI detected 16 patients in 22 DM (76%)	Total SUVmax Active IM; 15.4 Inactive IM; 8.0 NC; NR	SUVmax of muscles of whole body	B & P criteria	R
Sun L	2018	China	22	6/16	52.8	PM, DM	Before initial corticosteroid treatment for evaluation of IM	None	DM/PM; 2.58 Non-myopathy; 1.74	Cervical, Thoracic, Lumbar, Upper arm, Shoulder, Pelvic and Thigh regions Muscle	B & P criteria	R
Tanaka S	2013	Japan	20	4/16	55.5 (30~79)	PM, DM	Determine whether F-18 FDG PET/CT discriminates PM/DM from non-muscular diseases and also whether FDG uptake in proximal muscles reflects the activity and severity of muscular inflammation in PM/DM.	MRI	DM/PM; 1.05 Non-myopathy; 0.69	Trapezius, Deltoid, Biceps, Iliopsoas, Gluteus medius, Gluteus maximus, Quadriceps	B & P criteria	R

Analysis: PB, Patient based; B & P criteria: Bohan & Peter criteria; DM; Dermatomyositis; GS: Gold standard, NAM; Necrotizing autoimmune myositis; NC: Normal controls; NR; Not reported; OM: Overlap myositis; PM; Polymyositis; Study design; R, Retrospective; SUVmax: Maximal standardized uptake value.

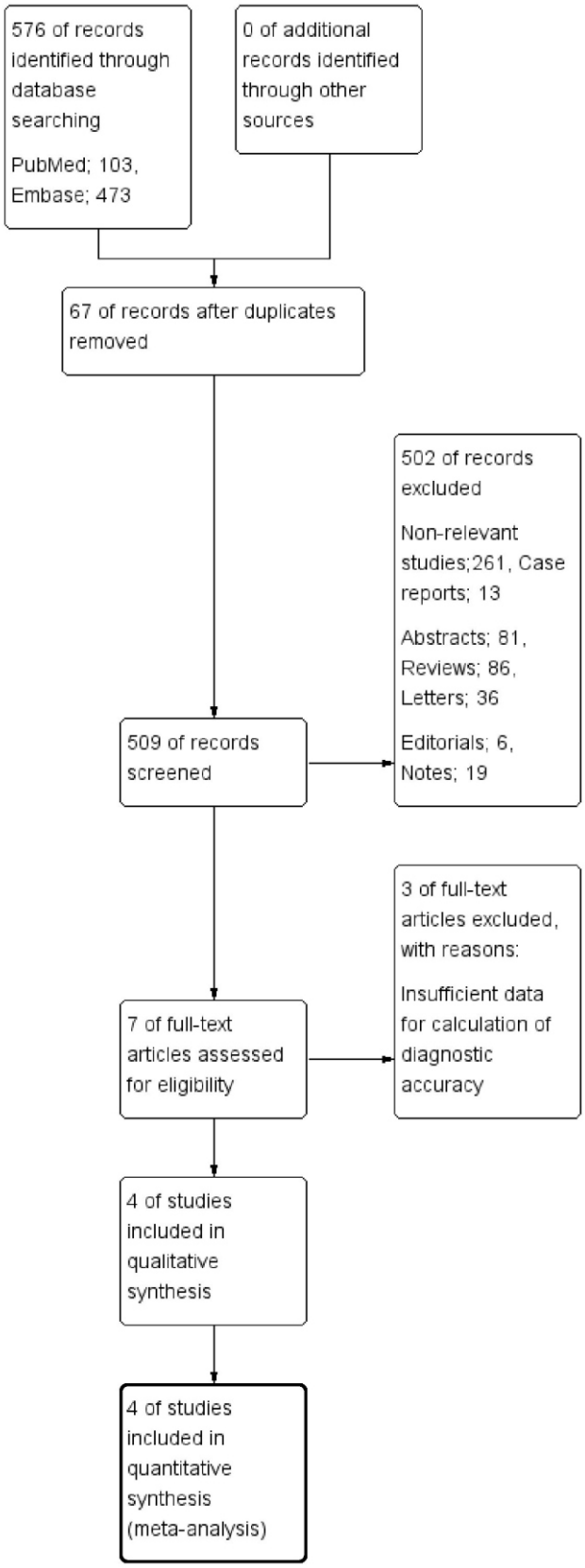

Figure 1. Flow chart of the search for eligible studies on the diagnostic performance of ^{18}F-FDG PET/CT for the determination of the disease activity of IM.

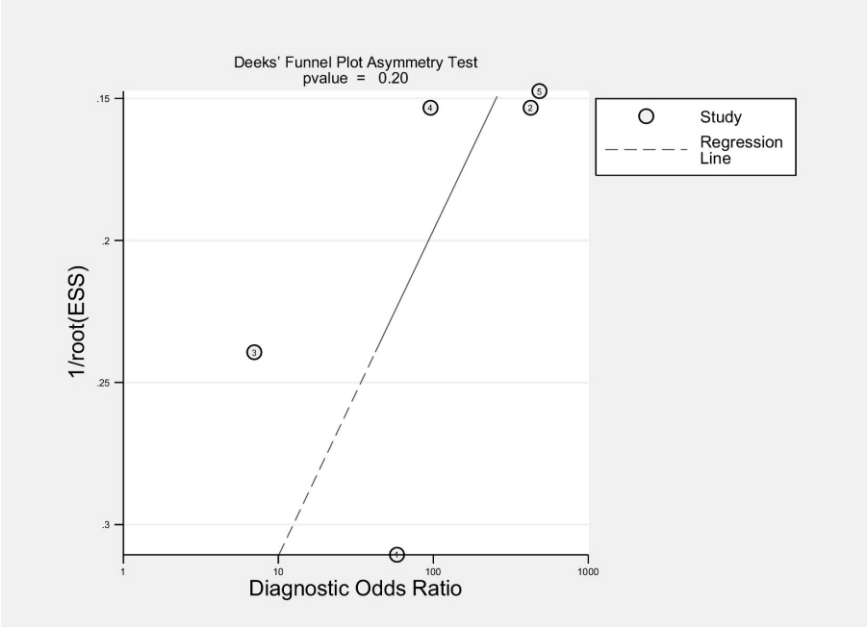

Figure 2. Results of Deeks`s funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. ESS; Effective sample size.

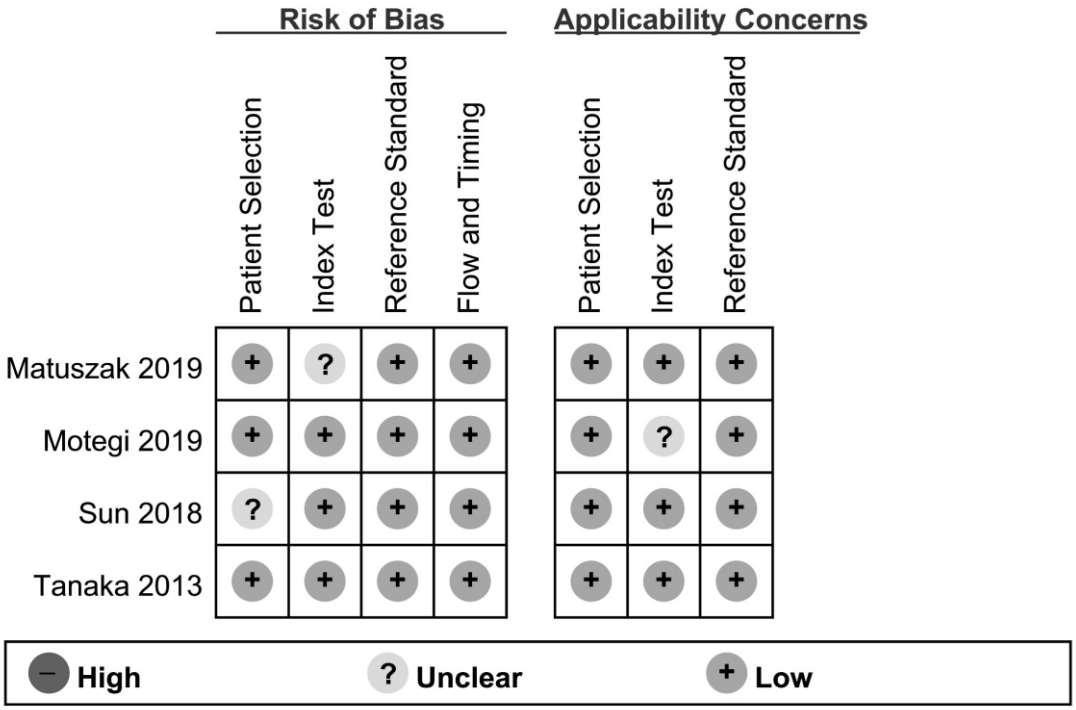

Figure 3. Risk of bias and applicability concerns summary.

studies are shown in Figure 4. The pooled sensitivity for ^{18}F-FDG PET/CT was 0.94 (95% CI; 0.87-0.97) without heterogeneity (I2=0.00, P=0.8) and a pooled specificity was 0.90 (95% CI; 0.72-0.97) with heterogeneity (I^2=65.1, P=0.02). The positive likelihood ratio (LR+) was 9.2 (95% CI; 3.1-28.0) and negative likelihood ratio (LR-) was 0.07 (95% CI; 0.03-0.16). The pooled DOR was 131 (95% CI; 26-664). Forest plots of the sensitivity and specificity ^{18}F-FDG PET/CT for the assessment of disease activity of IM are shown in Figure 4. Figure 5 shows HSROC curve and indicates that the areas under the curve was 0.96 (95% CI; 0.94-0.98).

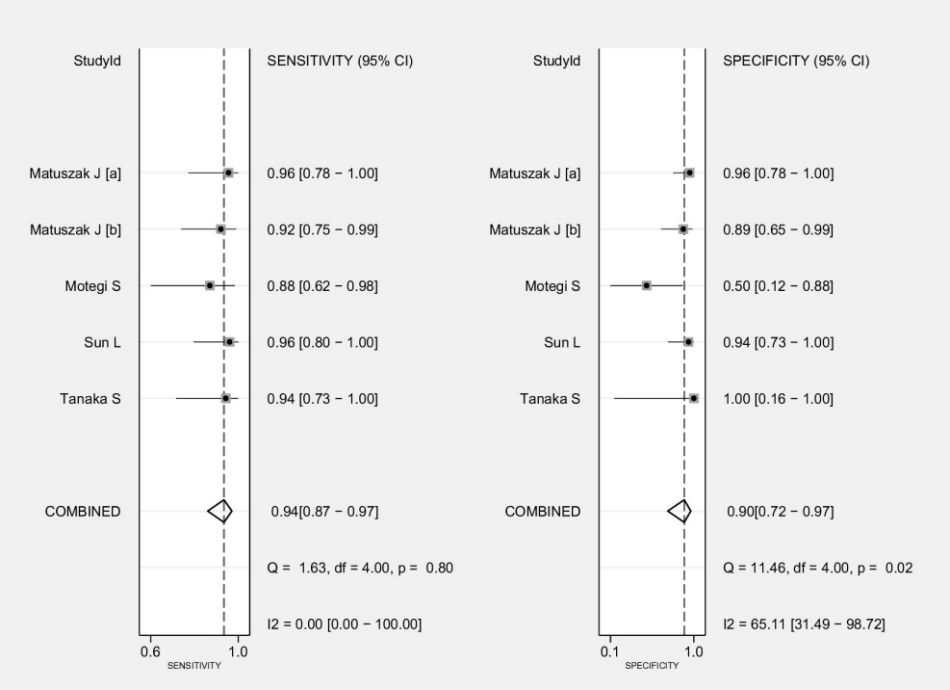

Figure 4. Forest plot of pooled sensitivity and specificity of ^{18}F-FDG PET/CT for the determination of the disease activity of IM.

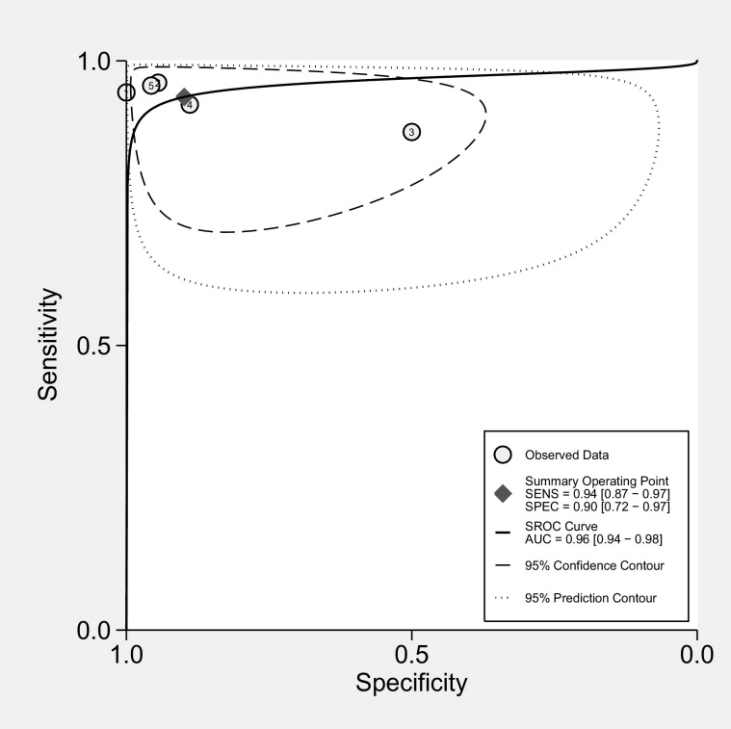

Figure 5. Hierarchical summary receiver operating characteristic (HSROC) curves of ^{18}F-FDG PET/CT for the determination of the disease activity of IM.

Heterogeneity evaluation and meta-regression analysis

Between-study heterogeneity was present for specificity among studies of ^{18}F-FDG PET/CT imaging for the assessment of disease activity of IM. A meta-regression analysis was performed to explore other sources of heterogeneity in the current studies. Meta-regression showed that no definite variable was the source of heterogeneity in the current meta-analysis (Table 2).

Table 2. *Effects of moderators.*

Variables	Coefficient*	SE	DOR	95 % CI of DOR		P**
Ethnicity (Caucasian vs Asian)	-1.393	1.7297	0.25	0.00	265.7	0.7080
CK Level (>1876U/L vs ≤1876 U/L)	-0.153	1.8709	0.86	0.00	2690.1	0.9425
Interpretation criteria (Quantitative vs Qualitative)	-2.367	4.7935	0.09	0.00	13.68	0.5684

Regression coefficient.P-value of random effect meta-regression using maximum likelihood estimation (ML) between study variances and the weighted least squares of study size for regression model estimation. Ethnicity (1, Caucasian vs 0, Asian); CK Level (1, >1876U/L vs 0, ≤1876 U/L); Interpretation criteria (1, Quantitative vs 0, Qualitative). DOR; Diagnostic odds ratio, SE; Standard error, CI; Confidence interval*

Discussion

The DM and PM are thought to be immune-mediated disorders that could be treated if properly managed. The immunomodulatory drugs are effective in active inflammatory muscle injury but have no effect on muscle damage. Therefore, accurate surveillance of active disease status of IM is essential to provide successful treatment. However, due to lack of appropriate biochemical or imaging biomarkers, the assessment of disease activity of IM has been a challenging issue during or after immunomodulatory therapy. Serum creatine kinase levels are generally known to be higher in patients with active IM, but it can be misleading [25]. Also, the quantification of antibodies whose levels have been reported to correlate with disease activity of IM is not routinely available [26].

Some previous studies have demonstrated that ^{18}F-FDG PET/CT could detect the inflammatory muscle lesions. Pipitone et al. (2012) demonstrated that the proximal muscle SUVmax was higher in patients with DM and PM than in normal controls [12]. Matuszak et al. (2019) analyzed total of 44 ^{18}F-FDG PET/CT examinations in 34 IM patients and 20 normal controls [21]. They showed that the SUVmax was increased in IM patients compared with controls and the SUVmax allowed the identification of patients with high vs low muscle disease activity [21]. Also, they showed, the subsequent examinations showed good accuracy to detect changes in muscle disease activity [21]. Motegi et al. (2019) found that ^{18}F-FDG PET/CT might be useful evaluation of the location and activity of myositis in DM patients [22]. Sun et al. (2018) compared the SUVmax between 22 cases with definite or probable PM/DM (PM/DM group) that underwent ^{18}F-FDG PET/CT examination and the same number of patients with no myopathy [23]. They showed that the SUVmax was markedly different between the PM/DM group and the non-myopathy group. Furthermore, they demonstrated that ^{18}F-FDG PET/CT has a diagnostic value for PM/DM, may be used for examination to assess the severity of myositis, and it may provide detection sites for muscle biopsy in patients with myositis [23]. Tanaka et al. (2013) measured the mean SUV using ^{18}F-FDG PET/CT in 14 proximal muscle groups of 20 patients with PM/DM and demonstrated that an increased SUV in proximal muscles of myositis patients as well as the mean proximal muscle SUV were correlated with serum creatine kinase (CK) and muscle strength [24]. They also found that local ^{18}F-FDG uptake in a proximal muscle reflects the activity of inflammation in the same muscle and provides useful information in determining the region for muscle biopsy [24].

Interpretation criteria of ^{18}F-FDG PET or PET/CT is also major concern for the determination of the disease activity of IM. The use of different quantitative indices of ^{18}F-FDG PET/CT between studies is also major concern for the determination of the disease activity of IM. The current meta-analysis showed a considerable heterogeneity of specificity between studies. The included studies were statistically heterogeneous in their estimates of specificity. This heterogeneity is likely to arise through diversity in methodological aspects between different studies and the basic differences among the patients in the included studies may have contributed to the observed heterogeneity of the results too. However, in meta-regression analysis of the current review, the interpretation criteria in this study did not possess some sources of heterogeneity. To minimize bias in the selection of studies and in the data extraction, reviewers who were blinded to the journal, author, institution, and date of publication independently selected articles based on the inclusion criteria, and scores were assigned to study design characteristics and examination results by using a standardized form that was based on the QUADAS2 tool. Also, publication bias is a major concern in all meta-analyses as studies reporting significant findings are more likely to be published than those reporting non-significant results. We assessed the publication bias in our analysis by using funnel plots which showed no definite asymmetry.

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

The authors have no conflict of interests to declare.

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