Assessing PET/CT's diagnostic accuracy in idiopathic inflammatory myopathies

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Abstract

Objective: Recent studies have utilized fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) specifically to diagnose cases of idiopathic inflammatory myopathies (IIM), excluding inclusion body myositis (IBM). Conversely, carbon-11 (^{11}C) labeled Pittsburgh compound B (PIB)-PET imaging is exclusively used for the detection of IBM. This research is designed to evaluate the diagnostic accuracy of PET/CT in identifying IIM by employing rigorous diagnostic accuracy testing methodologies. **Materials and Methods:** A systematic review and meta-analysis were conducted across multiple databases including Pubmed, Embase, and Chinese database. We focused on the diagnostic utility of PET/CT in IIM, assessing sensitivities, specificities, and deriving likelihood ratios (LR+ and LR-). The study was registered with PROSPERO (CRD42022343222). **Results:** This systematic review identified 635 citations, of which 10 eligible trials were included, with a total of 419 participants. The results indicated a sensitivity of 0.86 (0.81-0.90), and a specificity of 0.93 (0.88-0.96). The synthesis of LR revealed the LR+ of 10.35 (6.31-16.98), and LR-of 0.15 (0.07-0.32). The summary receiver operating characteristic curve (SROC) showed an area under the curve (AUC) of 0.9658. Regarding IBM, the sensitivity was 0.84 (0.60-0.97), and the specificity was 1 (0.69-1). The synthesis of LR showed the LR+ of 9.61 (1.46-63.15) and an LR- of 0.21 (0.09-0.51). For disease activity, the sensitivity was 0.96 (0.92-0.99), and the specificity was 0.91 (0.084-0.96). The synthesis of LR showed an LR+ of 9.43 (5.39-16.51) and an LR- of 0.05 (0.02-0.11). **Conclusion:** Positron emission tomography/CT has great potential for accurately diagnosing and monitoring patients with IIM, and may have implications for their clinical management.

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Introduction

Idiopathic inflammatory myopathies (IIM) encompass a diverse group of disorders, with polymyositis (PM) and dermatomyositis (DM) being the principal subtypes. The diagnostic approach for PM and DM is comprehensive, involving multiple facets. This includes clinical evaluations, muscle biopsies, electromyography, detection of specific autoantibodies, and additional investigative studies [1]. In contrast, inclusion body myositis (IBM) is a less common variant of myositis. Its diagnosis is more challenging due to its atypical pathological features, which differ from those typically seen in other forms of myositis.

The invasiveness of diagnostic procedures like skin and muscle biopsies often leads to reluctance among a significant number of patients to undergo these tests [2]. Consequently, there has been a shift in recent scientific research towards exploring the diagnostic efficacy of muscle magnetic resonance imaging (MRI) in myositis cases [3]. Despite its promise, the use of MRI is limited by several factors. These include its incompatibility with patients who have pacemakers, the challenges faced by individuals with claustrophobia, and the restricted availability of whole-body muscle MRI [4]. Given these limitations, there is an increasing need for the development and exploration of more precise, non-invasive methods for assessing systemic muscle inflammation in patients with myositis.

Positron emission tomography/computed tomography (PET/CT), traditionally used in cancer detection, has recently shown potential as a diagnostic tool for myositis, supported by a growing body of empirical evidence [5, 6]. In the last two decades, research interest in the use of PET/CT for myositis, particularly for identifying specific manifestations of IBM, has increased significantly. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT has been specifically utilized to diagnose cases of IIM, with the exception of IBM [7]. In contrast, carbon-11 (^{11}C) labeled Pittsburgh compound B (PIB)-PET imaging is employed exclusively for the detection of IBM [7]. To evaluate the diagnostic accuracy and specificity of PET/CT in myositis, we conducted a systematic review and meta-analysis. This research, registered with PROSPERO (CRD42022343222), strictly follows the guidelines of

the preferred reporting items for systematic reviews and meta-analyses (PRISMA), including the updated PRISMA-2020 standards [8]. Our approach ensures a thorough and detailed examination of the literature on this topic.

Materials and Methods

Data sources and search strategy

To ensure the comprehensive identification of relevant literature for our systematic review and meta-analysis, we conducted an extensive search across both English and Chinese databases. This search included PubMed, Embase, Cochrane, CNKI, CBM, and Cqvip, and spanned the period from the inception of each database to 22 May 2022. The detailed search strategy, outlined in our supplementary material, involved a combination of specific keywords and phrases tailored to each database. For instance, our search strategy utilized Medical Subject Headings (MeSH) in PubMed, the Emtree Thesaurus in Embase, and a combination of title, subject, and abstract searches in CNKI. This tailored approach ensured that we gathered a comprehensive collection of relevant literature (Figure 1).

Study selection

Study selection for this systematic review and meta-analysis was conducted through a meticulous screening process by two independent researchers, Liang Feng and Li Guanxi. They applied pre-established inclusion criteria to identify eligible studies. These criteria stipulated that the studies must:

I Employ PET/CT for the diagnosis of IIM.

ii) Provide sufficient data to ascertain the sensitivity and specificity of PET/CT in diagnosing IIM.

iii) Be published in either English or Chinese.

Studies were excluded if they were abstracts, duplicates, reviews, case reports, conference submissions, or letters without original research content. Any disagreements between the two reviewers were resolved through arbitration by Xuli Chang.

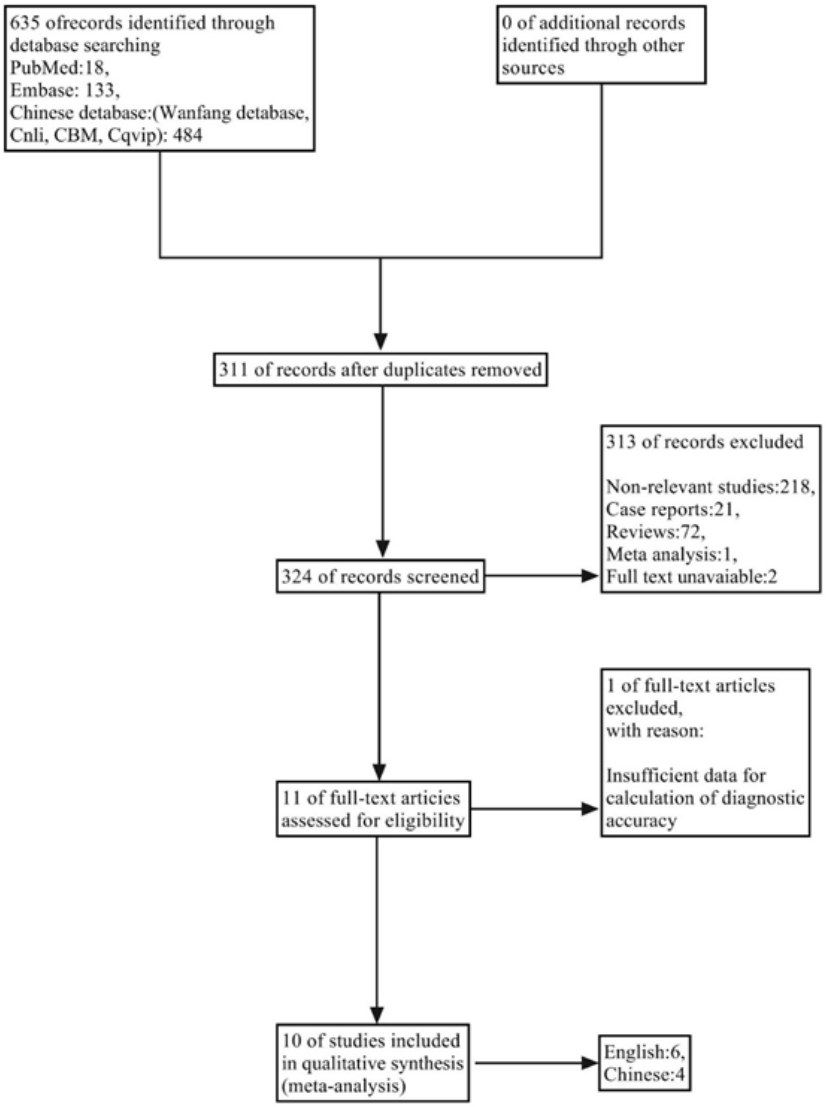

Figure 1. Flow chart of the search for eligible studies on the diagnostic performance of PET/CT for diagnosing IIM.

Data extraction and quality assessment

Data extraction for this systematic review and meta-analysis was conducted independently by the authors using a standardized form to ensure consistency and accuracy. The extracted data included variables such as study design, authorship, publication year, patient demographics, technical details, and other relevant information (Table 1). To evaluate the quality of these studies, we employed the modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [9] (Figure 2). Any discrepancies encountered during data extraction were resolved through consensus discussions.

Data analysis

For the purpose of our meta-analysis, diagnostic data from the selected studies were extracted and analyzed using Metadisc 1.4, a leading software specifically designed for evaluating diagnostic test accuracy in meta-analyses. This software facilitated a quantitative synthesis of the data from various studies, thereby providing a clear picture of the diagnostic accuracy of PET/CT in the assessment of myositis.

Heterogeneity test

To assess the heterogeneity in sensitivity and specificity across the included studies, we employed χ^2 tests and Spearman correlation analysis. Additionally, the Cochrane-Q test was utilized to evaluate heterogeneity in diagnostic odds

Table 1. *Characteristics of the included studies.*

Authors	Year	Patient	Disease
Shigeru Tanaka [2]	2013	31	PM
Lei Pei [10]	2016	58	DM
Lu Sun [11]	2017	22	PM,DM
Julien Matuszak [12]	2018	34	IIM
Wang Dongyan [13]	2018	17	DM
Nihal Martis [14]	2019	24	DM
James B Lilleker [15]	2019	10	IBM
Yu-Ichi Noto [16]	2020	9	IBM
Zhou Hang [17]	2020	13	PM,DM
Jiang Chong [18]	2020	23	PM,DM

DM: dermatomyositis; PM: polymyositis; IBM: inclusion body myositis

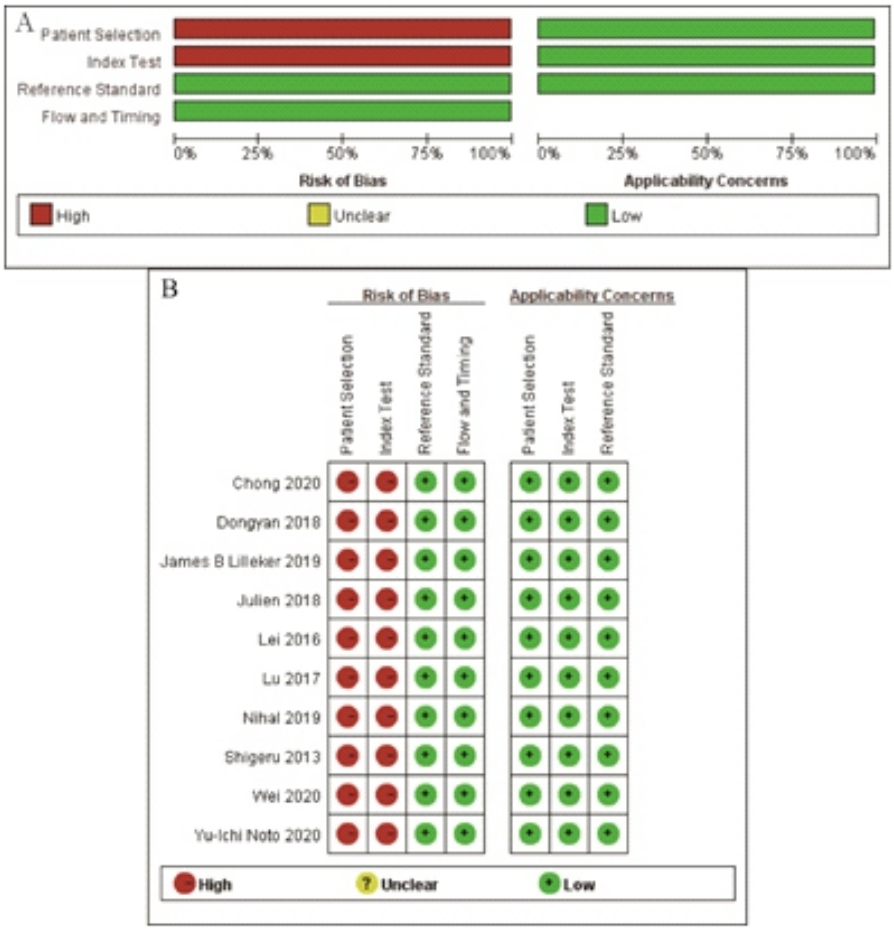

Figure 1. Flowchart of the search for eligible studies on ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in patients of gastric cancer. Five articles were finally selected for this meta-analysis.

ratios and likelihood ratios (LR) [19]. We classified the levels of heterogeneity based on I^2 statistics as low (I^2<25%), moderate (25%≤I^2≤70%), or high (I^2>70%), as referenced in our methodology [19].

Evaluation index

Using Metadisc 1.4 software, we computed the summary receiver operating characteristic curve (SORC) and determined both the area under the curve (AUC) and Q* index. To further validate our findings, sensitivity analysis and the Deeks publication bias test were performed using STATA 14.0. These statistical tools were instrumental in rigorously evaluating the authenticity of our results and in identifying any potential biases, as described in our methodology [20, 21].

Results

Threshold effect

In the analysis conducted with Metadisc software, the Spearman correlation coefficient between the logarithm of sensitivity and the logarithm of (1-specificity) was calculated to be -0.091 (P=0.803). This finding suggests the absence of a threshold effect in our study. Further supporting this conclusion is the symmetric shape of the SROC, which does not exhibit a 'shoulder-arm' pattern (Figure 3E). These results collectively indicate the lack of a threshold effect in the analysis.

Heterogeneity of non-threshold effects

In our study, the Cochran-Q test for the diagnostic odds ratio (DOR) yielded a value of 20.11 (P=0.017), indicating the presence of heterogeneity attributable to non-threshold effects (Figure 3B). However, when amyopathic DM patients were ex cluded from the analysis, the Cochran-Q value significantly decreased to 5.15 (P=0.82), suggesting the elimination of

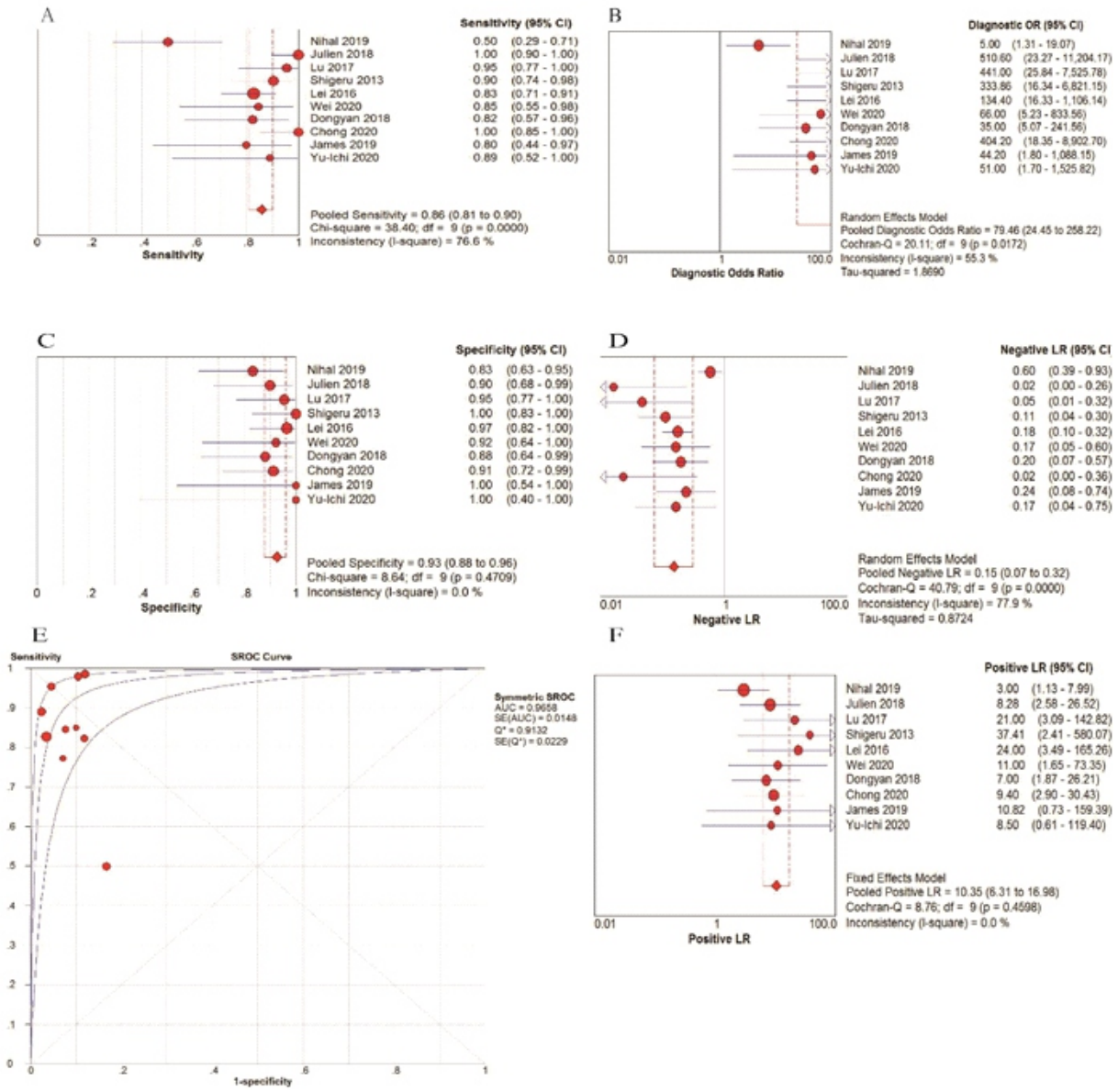

Figure 3. Diagnostic test evaluation indicators of PET/CT for diagnosing IIM.

heterogeneity (Figure 4B). In the context of disease activity, the Cochran-Q test displayed a value of 17.05 (P=0.0019) (Figure 5B), while for IBM, the Cochran-Q was 0.00 (P=0.9520), indicating no heterogeneity (Figure 6E). Moreover, in this study, if the I^2 statistic for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and DOR exceeds 50%, a random-effects model will be applied for pooling these effect sizes. If it is below 50%, a fixed-effects model will be utilized.

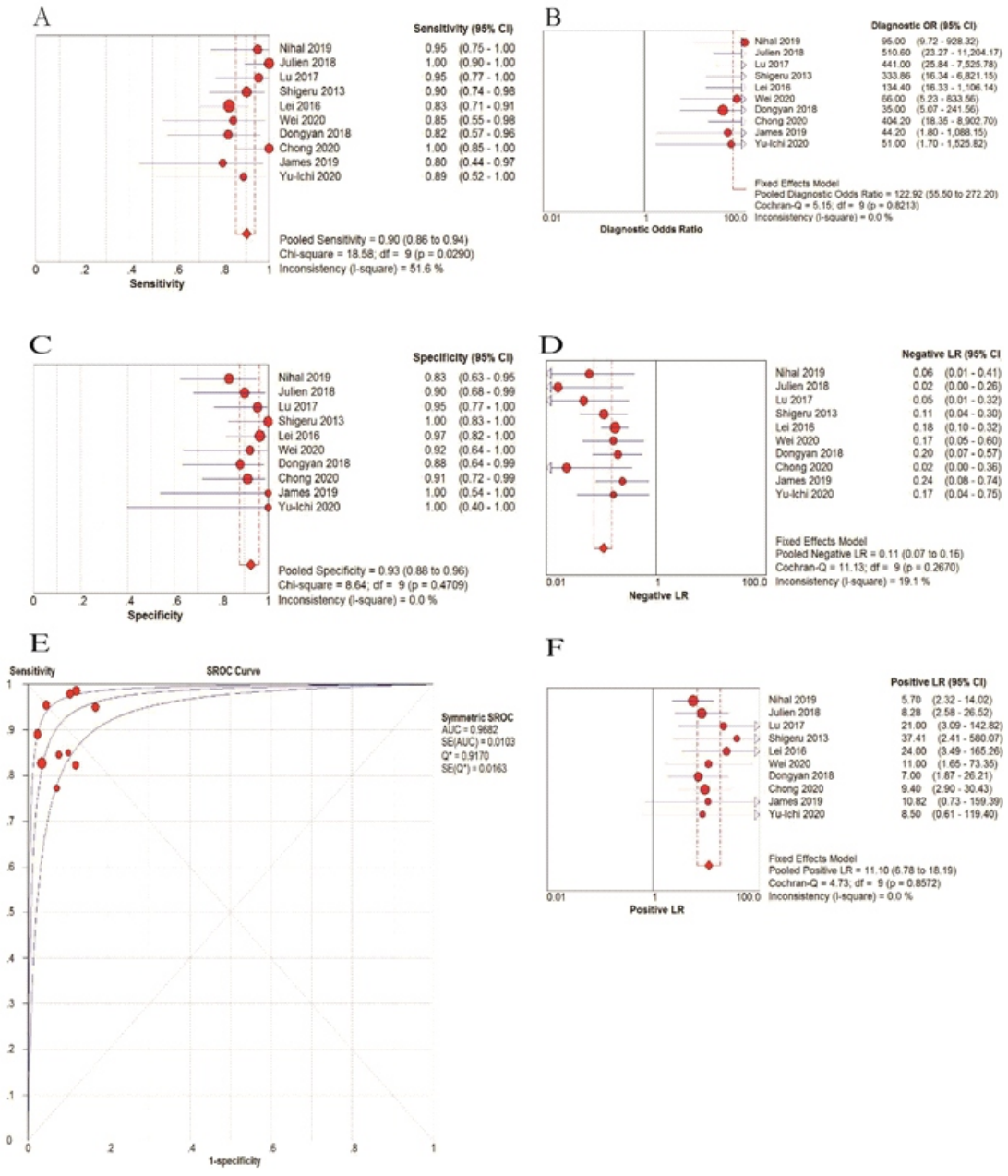

Figure 4. Diagnostic test evaluation indicators of PET/CT for diagnosing IIM (without amyopathic DM patients).

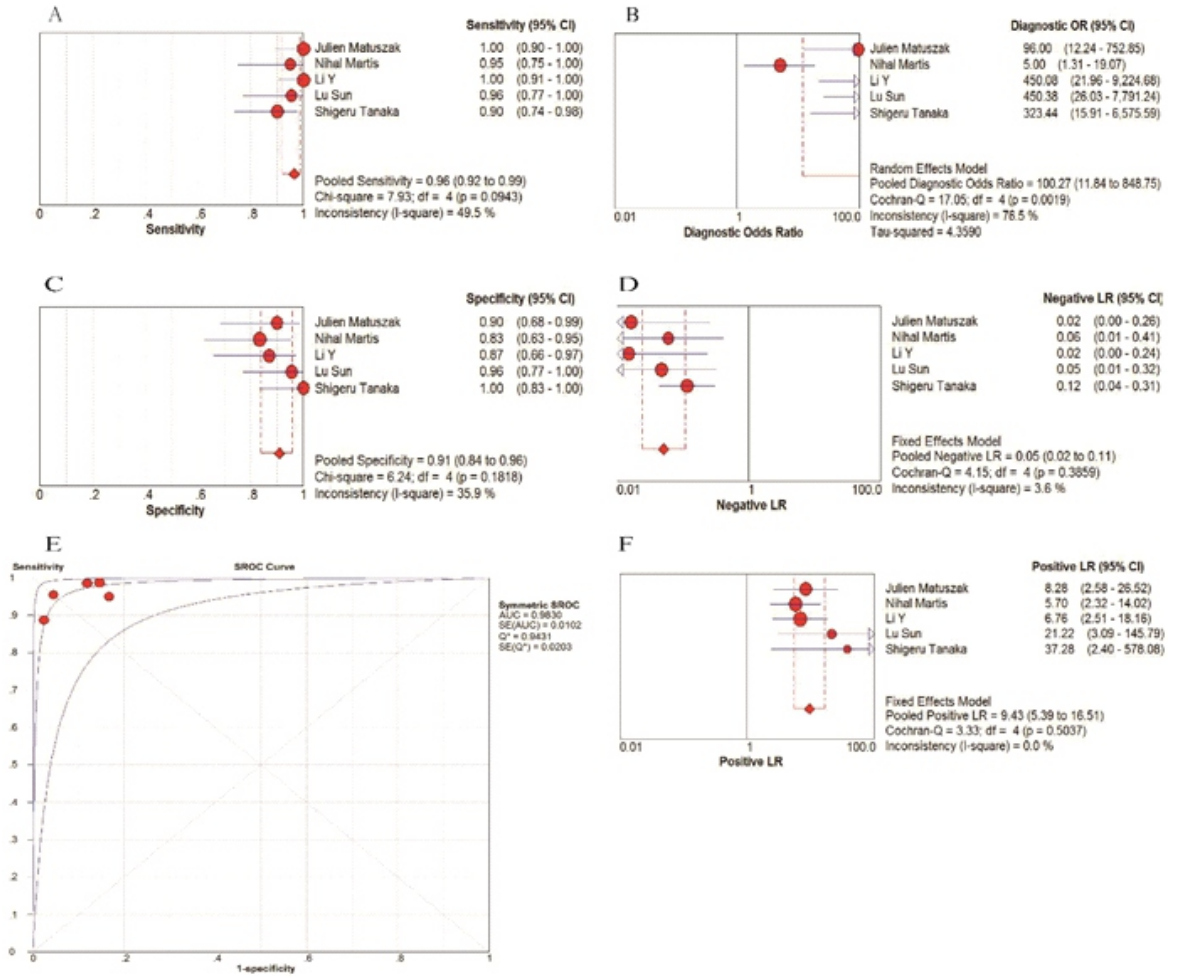

Figure 5. Diagnostic test evaluation indicators of PET/CT for the determination of the disease activity of IIM.

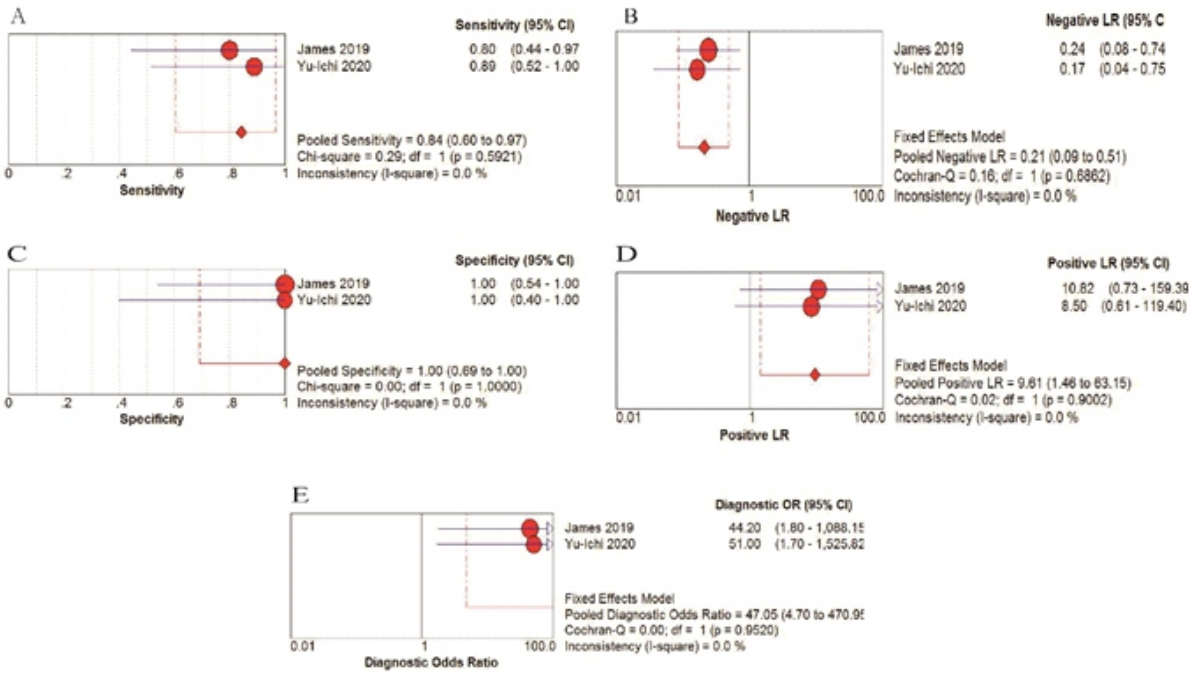

Figure 6. Diagnostic test evaluation indicators of PET/CT for diagnosing IBM.

Diagnostic test evaluation indicators

In our meta-analysis, the aggregated results indicated a pooled sensitivity of 0.86 (95% CI: 0.81-0.90) and a pooled specificity of 0.93 (95% CI: 0.88-0.96). The combined positive likelihood ratio (LR+) was 10.35 (95% CI: 6.31-16.98), and the negative likelihood ratio (LR-) was 0.15 (95% CI: 0.07-0.32). Additionally, the pooled AUC for the SROC was 0.9658, with a Q index of 0.9132 (Figure 3A). The odds ratio (OR) for combined diagnosis was 79.46 (95% CI: 24.45-258.22) (Figure 3C).

Upon excluding amyopathic DM patients from the analysis, the pooled sensitivity increased to 0.90 (95% CI: 0.86-0.94) with moderate heterogeneity (I^2=51.6%, P=0.0290), while the pooled specificity remained stable at 0.93 (95% CI: 0.88-0.96) with no heterogeneity (I^2=0.0%, P=0.4709) (Figures 4A, C). The synthesized LR+ and LR- were 11.10 (95% CI: 6.78-18.19) and 0.11 (95% CI: 0.07-0.16), respectively (Figures 4D, F). The combined DOR was 122.92 (95% CI: 55.50-272.20) (Figure 4B), and the hierarchical SROC curve depicted an AUC of 0.9682 (Figure 4E).

Regarding disease activity (Figure 5), the pooled sensitivity and specificity were 0.96 (95% CI: 0.92-0.99) and 0.91 (95% CI: 0.84-0.96) respectively, both without significant heterogeneity (I^2=49.5%, P=0.0943 for sensitivity and I^2= 35.9%, P=0.1818 for specificity). The overall LR+ and LR- were 9.43 (95% CI: 5.39-16.51) and 0.05 (95% CI: 0.02-0.11). The pooled DOR was 100.27 (95% CI: 11.84-848.75).

For IBM (Figure 6), the pooled sensitivity was 0.84 (95% CI: 0.60-0.97) and the pooled specificity was 1.00 (95% CI: 0.69-1.00), both without heterogeneity (I^2=0.0% for both, P= 0.5921 for sensitivity and P=1.0000 for specificity). The synthesized LR+ was 9.61 (95% CI: 1.46-63.15), and LR- was 0.21 (95% CI: 0.09-0.51). The pooled DOR stood at 47.05 (95% CI: 4.70-470.95).

Sensitivity analysis

In this study, STATA 14.0 was employed for conducting sensitivity analysis on the data. As illustrated in Figure 7A, it was observed that the inclusion of the first study influenced the sensitivity of the calculation results. However, when amyopathic DM patients were excluded from the analysis, none of the studies significantly affected the sensitivity of the results, as shown in Figure 7B. This indicates that the overall findings of our analysis are relatively stable.

Deeks publication bias test 3

For this study, STATA 14.0 was utilized to perform a publication bias test on our dataset. The results indicated that with a P-value greater than 0.05, the funnel plot was symmetrical, suggesting the absence of publication bias in our study (Figures 7C and 7D). This assessment contributes to the robustness of our meta-analysis concerning the combined effect size.

Discussion

The rapid and accurate diagnosis of IIM is crucial, as it enables

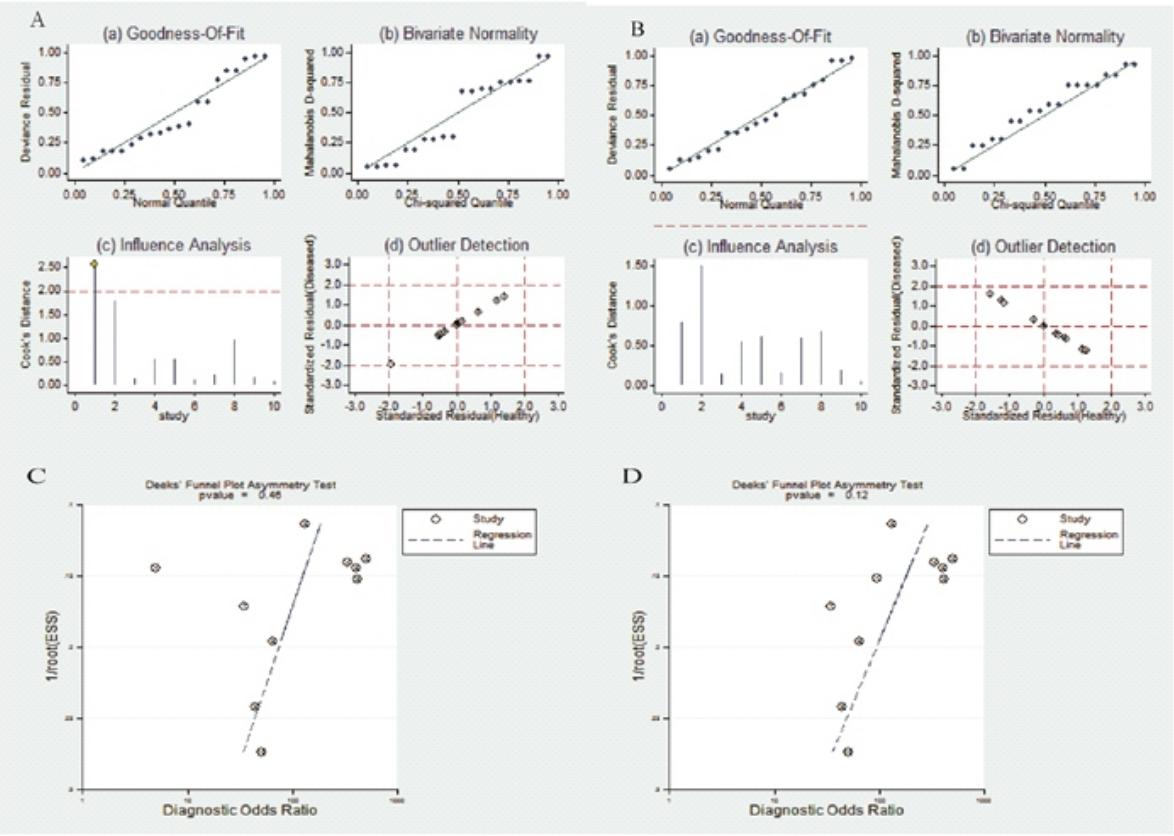

Figure 7. Results of Deeks`s funnel plot of asymmetry test for publication bias (B, D without amyopathic DM patients).

timely and effective treatment, reducing the risk of muscle damage due to inflammation and preventing the occurrence of adverse events. In certain clinical scenarios, muscle biopsies may be contraindicated or not feasible, which can delay diagnosis and exacerbate muscle weakness. In these situations, PET/CT serves as a valuable alternative diagnostic tool. Our analysis demonstrates the high efficacy of PET/CT in diagnosing IIM, evidenced by its impressive sensitivity and specificity, both exceeding 90%. Its diagnostic accuracy also stands out, surpassing 95%. A notable advantage of PET/CT is its ability to simultaneously provide images of the entire body, allowing for a comprehensive assessment of disease extent [22].

Positron emission tomography/CT offers insights into regions that are not typically examined in standard pathological biopsies and helps in assessing the severity of muscle lesions. While muscle biopsy remains the gold standard for identifying muscle pathologies, it faces limitations, particularly concerning the representativeness of the biopsy sample. The chosen sampling site may not accurately reflect the presence of acute lesions [22]. Although PET/CT is not set to replace muscle biopsies entirely, it can effectively guide the selection of more appropriate biopsy sites. Compared to MRI, PET/CT offers greater precision in identifying sites for muscle biopsy, thereby enhancing its role in the diagnostic approach for IIM.

In their 2021 meta-analysis, Kim et al. (2021) [8] scrutinized four studies to evaluate the efficacy of PET/CT in detecting ac-tive states of myositis. This thorough investigation revealed that PET/CT demonstrated high sensitivity (94%) and specificity (90%) in identifying active phases of myositis. Furthermore, additional studies, including those using creatine kinase levels as a reference for assessing myositis activity via PET/CT, reported even higher aggregated sensitivity and specificity than those found by Kim et al. (2021) [8]. Recent reviews in the field, exploring the relationship between PET/CT and IIM activity, consistently affirm that PET/CT is a highly effective imaging technique for diagnosing active IIM [7, 23]. These findings unequivocally establish PET/CT as a critical diagnostic tool, particularly in identifying active phases of IIM, thereby reinforcing its importance in the management of IIM patients.

The tendency to mistakenly diagnose IBM as PM can result in inappropriate treatments, including unnecessary immunosuppressant therapy [24]. In this context, PET/CT becomes crucial, helping to improve diagnostic accuracy in IBM. Our study demonstrated that PET/CT had an exceptional specificity (100%) and a high sensitivity (84%) for IBM diagnosis. Notably, ^{11}C Pittsburgh compound B (PIB)-PET showed increased sensitivity compared to ^{18}F-FDG PET/CT in diagnosing IBM, although both maintained a specificity of 100%. This difference in effectiveness could be attributed to the distinct imaging capabilities of PIB-PET, a tool typically used in Alzheimer's disease (AD) diagnosis [25].

There has been growing interest in using PIB-PET to identify β-amyloid (Aβ) deposits in IBM, in parallel with explorations into the diagnostic potential of tau-PET for this condition. For instance, research by Li et al. (2020) has detailed tau-PET imaging characteristics in patients with IBM [26]. Considering the typical presence of rimmed vacuoles filled with neurodegenerative proteins like Aβ in muscle biopsies of IBM patients, our findings indicate that PET/CT can significantly enhance diagnostic precision for IBM.

Our meta-analysis, which investigates the diagnostic utility of PET/CT in myositis, comes with certain limitations. A key constraint is the geographical bias in the study selection, as a substantial proportion of the analyzed papers are from China. This geographic skew may limit the global applicability of our findings, indicating the necessity for a more geographically diversified research approach. Additionally, there is a potential risk of bias in the studies selected, particularly in terms of case selection, which might affect the overall trustworthiness of our conclusions. The difficulties of ensuring blinding in retrospective studies are also apparent, underlining the need for more prospective studies designed to minimize such biases.

Moreover, the inclusion of case-control studies in our analysis, despite their propensity to introduce confounding factors, could weaken the validity of our results. While our meta-analysis does account for the effect of excluding amyopathic DM patients on heterogeneity, a more detailed exploration or subgroup analysis based on different types of myositis might have yielded more precise insights. The lack of such stratification leaves an area of research unexplored, which could have further refined our understanding of the effectiveness of PET/CT across various myositis subtypes.

Dermatomyositis and PM are both characterized by symmetrical proximal limb and band muscle involvement [27]. Notably, ^{18}F-FDG is a radiopharmaceutical used in PET/CT imaging that is avidly taken up by metabolically active cells, such as macrophages and fibroblasts, which are abundant in inflammatory tissues [28]. This uptake is facilitated by the over-expression of glucose transporters, specifically glucose transporter-1 and glucose transporter-3 (GLUT-1 and GLUT-3), on the surface of these cells [28]. Consequently, PET/CT imaging of patients with DM and PM often reveals abnormally increased ^{18}F-FDG uptake in the proximal muscles of the extremities [2, 29, 30]. In patients identified with IBM, there was a significant increase in the uptake of ^{11}C PIB observed in the quadriceps, forearm, and calf muscles, as demonstrated through PET imaging [16, 31, 32].

In conclusion, this meta-analysis, anchored by a robust methodology, substantiates the effectiveness of PET/CT in diagnosing myositis. The findings are indeed promising, but they also highlight the need for further research. We advocate for more geographically diverse and prospective studies to solidify PET/CT's role in myositis diagnostics. As the field of medicine evolves towards precision-based approaches, innovative and evidence-backed tools like PET/CT have the potential to significantly enhance patient-centered care. This study contributes to the growing body of evidence in this realm, emphasizing the importance of continued research and validation.

The authors declare that they have no conflicts of interest.

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