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Detecting serum galactomannan to diagnose acute invasive *Aspergillus* sinusitis: a meta-analysis

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Abstract

Purpose The serum galactomannan test has been used for diagnosing acute invasive fungal sinusitis (AIFS), especially invasive *Aspergillus*. We aimed to assess the accuracy of the test to diagnose acute invasive *Aspergillus* sinusitis (AIAS).

Methods We searched all relevant articles published in PubMed, Embase, the Cochrane Library, and Web of Science databases up until September 14, 2020. The available data for serum galactomannan test to diagnose AIAS from selected studies were assessed. The diagnostic odds ratio (DOR), summary receiver operating characteristics (SROC), sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were estimated. Additionally, we analysed four studies with a cut-off value of 0.5.

Results Five eligible articles were selected in this study. The total number of enrolled patients was 118, and 62 patients had confirmed AIAS. Among these 62 patients, the summary estimates of the serum galactomannan assay were as follows: DOR, 3.37 (95% confidence interval [CI]: 1.47–6.66); sensitivity, 0.63 (95% CI 0.50–0.74); specificity, 0.65 (95% CI 0.51–0.76); PLR, 1.83 (95% CI 1.21–2.74); NLR, 0.58 (95% CI 0.39–0.83). The SROC was 0.68.

Conclusion In this current meta-analysis, the serum galactomannan test was classified as less accurate for purposes of diagnosing confirmed AIAS. These results suggest that the initial diagnosis of AIAS should not solely be dependent upon serum galactomannan test results. More studies of the test are needed in patients with AIAS to more accurately assess its diagnostic value.

Keywords Acute invasive fungal sinusitis · Galactomannan · Meta-analysis · *Aspergillus*

Introduction

Acute invasive fungal sinusitis (AIFS) is a rare but high mortality infectious disease in patients with uncontrolled diabetes mellitus or immunocompromised patients undergoing chemotherapy. If AIFS is not properly treated, complications can include orbital, intracranial extension with cavernous sinus thrombosis, meningitis, and osteomyelitis. In particular, if the disease is not diagnosed early, mortality is as high as 50–80% [12]. Early diagnosis can reduce morbidity or mortality, but early detection is difficult because symptoms of AIFS are non-specific and often overlap with other diseases [9].

The most common cause of AIFS is *Aspergillus*. It is found in soil, dust, and damp wall [11]. The serum galactomannan test is used as a non-invasive diagnostic method for *Aspergillus*. Polysaccharide cell-wall component of galactomannan is secreted into the blood in cases of *Aspergillus* growth. Enzyme-linked immunosorbent assays that measure galactomannan have been widely studied in invasive pulmonary aspergillosis, and they have recently been used in AIFS [5, 20].

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To date, several studies have focused on whether the serum galactomannan test can be used to diagnose AIFS. However, the diagnostic usefulness of this test remains disputed, and no meta-analysis has been conducted to estimate the general accuracy of the test. Therefore, the goal of the current meta-analysis was to evaluate the diagnostic value of the serum galactomannan test in patients with AIFS, especially in those with acute invasive *Aspergillus* sinusitis (AIAS).

Materials and methods

Search strategy

To identify eligible articles for this study, two investigators (SWC and NWK) searched the English databases of PubMed, Embase, the Cochrane Library, and Web of Science for articles published up until September 14, 2020. The search was conducted using the following keywords and MeSH terms: 'galactomannan', '*Aspergillus* galactomannan', 'acute invasive fungal sinusitis", 'invasive fungal sinusitis', 'IFS', '*Aspergillus* sinusitis', 'invasive aspergillosis', 'sinusitis', '*Aspergillus*', and 'aspergillosis'. We describe the full strategy in Supplementary Table 1.

Study selection criteria

The population, intervention, comparator, outcome, and study design (PICOS) criteria were applied to determine study eligibility, as follows: (1) P, patients with AIFS; (2) I, serum galactomannan test for AIFS; (3) C, sensitivity and specificity of the serum galactomannan test; (4) O, diagnostic value of the serum galactomannan test; (5) S, observational studies, including cohort and case–control studies.

The meta-analysis included all relevant articles focusing on the diagnostic value of the serum galactomannan test in patients with AIFS. Studies that met the following inclusion criteria were included: (1) fully published primary study; (2) number of included patients with AIFS reported; (3) inclusion of infections based on the standard diagnostic criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [8] as a reference standard.

The following exclusion criteria were applied: (1) failure to differentiate between AIAS and other fungal infections; (2) duplicate publications; (3) insufficient data for analysis.

Assessment of study quality

The revised quality assessment of diagnostic accuracy studies (QUADAS-2 [25]) and the Standards for Reporting Diagnostic Accuracy (STARD [3]) were used to assess the quality of articles. We scored each item as 'yes', 'no', or 'unclear' (when the information was insufficient to judge accuracy).

Data extraction

Two independent reviewers (SWC, JSN) extracted all data from eligible articles. The extracted data as follows: title, first author, year of publication, study design, country of study, diagnosis criteria, characteristics of the study population (sex, mean age, and number of patients), and cut-off values of the serum galactomannan test. Additionally, we extracted information from the full-text review that included the number of positive pathological samples.

Statistical analysis

The true-positive, true-negative, false-positive, and false-negative rates were extracted from each study. Based on these results, we calculated sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR), along with their 95% confidence intervals (CIs). Additionally, we constructed the summary receiver operating characteristics (SROC) curve to visualise the data and calculated the diagnostic odds ratio (DOR). Heterogeneity across the enrolled studies was evaluated using the chi-square test. We also used funnel plots for assessing publication bias. We also assessed the serum galactomannan tests in the included five studies, regardless of the cut-off value. However, in one study, a different cut-off value (0.48) was used, so we conducted analysis excluding that one study to evaluate different cut-off values. All the analyses of enrolled articles were performed using RevMan 5.4 and R 4.0.1 version statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

Results of the literature search

We identified and screened 4233 studies using the aforementioned keywords and search strategies. One additional article was identified through other sources. Among them, 1713 articles were excluded because of duplication. After screening based on title and abstract, we read the full text of seven articles. Two articles were excluded because they lacked sufficient data. Ultimately, five articles were included in this meta-analysis [2, 5–7, 17] (Fig. 1).

The basic characteristics of these five articles are summarised in Tables 1 and 2. The studies were published between 2011 and 2019, and the sample size of each study ranged from 18 to 29. The total number of enrolled patients in the present analysis was 118, of whom 62 had confirmed

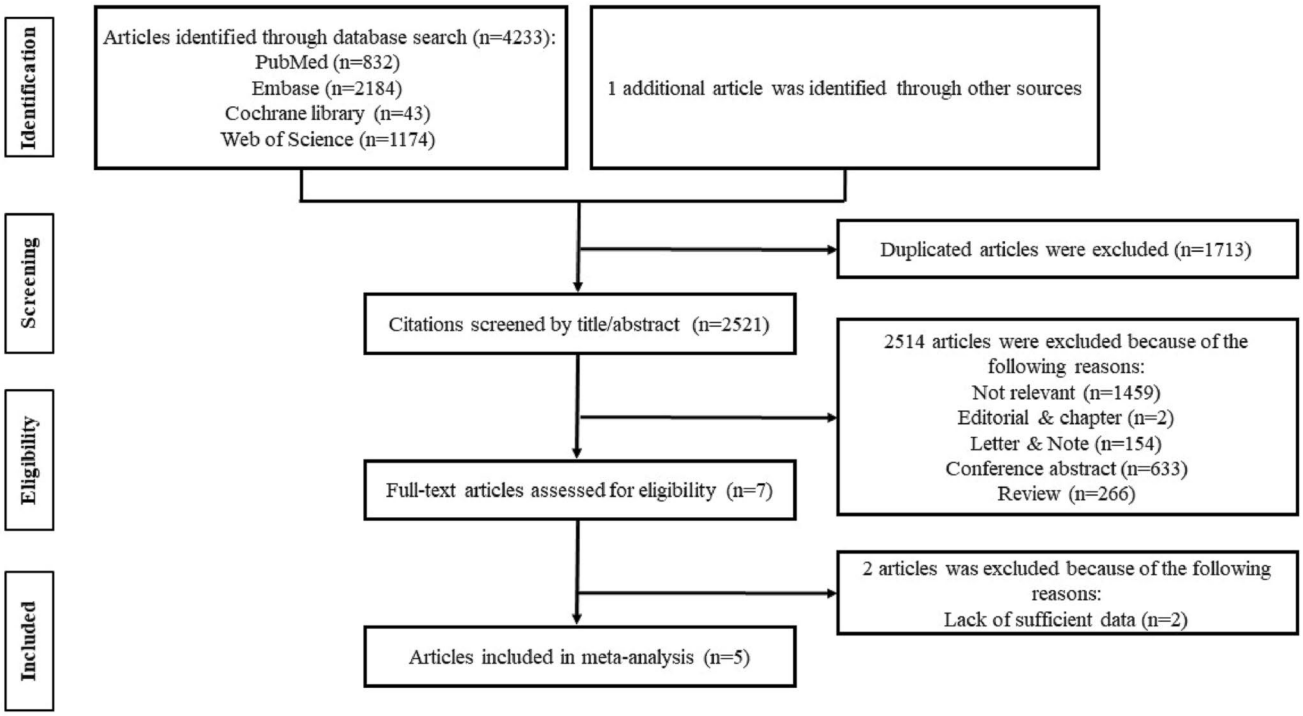

Fig. 1 Flowchart of study search and selection

Table 1 Characteristics of the eligible studies

Study	Year	Data collection	Region/period	Diagnostic standard	Patient demographics			
					Male	Female	Mean age (year MD)	Number
Badiee et al. [2]	2016	Prospective	Iran/2011–2012	EORC/MSG2008	10 (55%)	8 (45%)	35.6 (11–75 years)	18
Chen et al. [5]	2011	Retrospective	Taiwan/2005–2009	EORC/MSG2008	NA	NA	NA	16
Cho et al. [6]	2016	Retrospective	Korea/2007–2014	EORC/MSG2008	15 (54%)	13 (46%)	60.6 (10–80 years)	28
Davoudi et al. [7]	2015	Retrospective	USA/2004–2014	EORC/MSG2008	NA	NA	NA	27
Melancon et al. [17]	2019	Retrospective	USA/2006–2017	EORC/MSG2008	NA	NA	NA	29

NA not applicable

invasive *Aspergillus*. The index cut-off of the serum galactomannan test results was either 0.5 or 0.48, with the most common cut-off being 0.5. We assessed the quality of each article and described in a bar graph using the QUADAS-2 tool (Fig. 2).

Serum galactomannan test in patients with confirmed AIAS

All included articles offered the diagnostic value of serum galactomannan for AIFS patients and used a cut-off value of 0.5 or 0.48. No heterogeneity in sensitivity or specificity was observed among the studies ($p = 0.55$, chi-squared = 3.07; $p = 0.34$, chi-squared = 4.54, respectively). The sensitivity of the serum galactomannan test was 0.63 (95% CI 0.50–0.74), and the specificity was 0.65 (95% CI 0.51–0.76; Fig. 3). The mean DOR was 3.37 (95% CI 1.47–6.66) (Fig. 4). Figure 5 showed the SROC of the included articles. The area under the curve (AUC) was 0.68. The PLR was 1.83 (95% CI 1.21–2.74) and NLR was 0.58 (95% CI 0.39–0.83). Following discretionary guidelines [21], researchers classified accuracy into non-informative ($AUC = 0.5$), low accuracy ($0.5 < AUC \leq 0.7$), moderate accuracy ($0.7 < AUC \leq 0.9$), high accuracy ($0.9 < AUC < 1$), and perfect accuracy ($AUC = 1$). According thereto, the current study showed the serum galactomannan test is a less accurate method to diagnose confirmed AIAS. However, the diagnostic evidence of the test varied across the studies—from low to convincing (Table 2).

Table 2 Results of included studies for diagnosing confirmed AIAS using serum galactomannan test

Study	Year	Results					Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	Cut-off
		TP	FP	FN	TN	Total					
Badiee et al. [2]	2016	6	0	3	9	18	0.65 (0.35–0.86)	0.95 (0.66–01.99)	13.00 (0.84–201.26)	0.37 (0.16–0.87)	0.5
Chen et al. [5]	2011	7	2	4	3	16	0.62 (0.35–0.84)	0.58 (0.24–0.86)	1.50 (0.53–4.26)	0.64 (0.24–1.74)	0.5
Cho et al. [6]	2016	15	2	6	5	28	0.70 (0.50–0.85)	0.69 (0.36–0.90)	2.26 (0.78–6.53)	0.43 (0.19–0.95)	0.48
Davoudi et al. [7]	2015	5	7	1	14	27	0.79 (0.42–0.95)	0.66 (0.45–0.82)	2.30 (1.15–4.63)	0.32 (0.08–1.39)	0.5
Melancon et al. [17]	2019	7	6	8	8	29	0.47 (0.26–0.69)	0.57 (0.33–0.78)	1.08 (0.50–2.36)	0.94 (0.50–1.78)	0.5

AIAS acute invasive *Aspergillus* sinusitis, *TP* true positive, *FP* false positive, *TN* true negative, *CI* confidence interval, *FN* false negative, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio

Of the articles included in the present analysis, one [6] used a different serum galactomannan cut-off (0.48) value, so we conducted an analysis in the four studies [2, 5, 7, 17] that used a galactomannan cut-off value of 0.5. There was no heterogeneity in sensitivity or specificity among the studies ($p = 0.51$, chi-squared = 2.29; $p = 0.21$, chi-squared = 4.53, respectively). The sensitivity was 0.59 (95% CI 0.44–0.73), and the specificity was 0.64 (95% CI 0.49–0.77; Supplementary Fig. 1). The mean DOR was 2.87 (95% CI 1.10–6.16; Supplementary Fig. 2). The SROC of the four studies showed that the AUC was 0.65 (Supplementary Fig. 3). The PLR and NLR were 1.70 (95% CI 1.05–2.66) and 0.65 (95% CI 0.41–0.96), respectively. The results of the four studies did not significantly differ from those of the five studies and showed that the serum galactomannan test is a less accurate method to diagnose confirmed AIAS.

Publication bias

The Funnel plot test of the five studies revealed may have publication bias, as indicated by the Egger's test p value of 0.04. After applying the trim and fill method, Egger's test p value was 0.97, indicating no publication bias. However, the power of this test may have been decreased because the number of studies was small.

Discussion

AIFS is gradually increasing in immunocompromised patients due to haematological malignancy, diabetes mellitus, organ transplantation, and systemic steroid use. AIFS remains the leading cause of morbidity and mortality in immunocompromised patients [18, 23]. Early diagnosis with surgical resection and administration of antifungal agents can improve clinical outcomes. However, early diagnosis is difficult because the symptoms of AIFS are usually non-specific, including nasal discharge, stuffiness, epistaxis, periorbital swelling, and headache [15]. The gold standard for diagnosing the invasive fungal disease is pathological confirmation, but this can be delayed and sometimes leads to false-negative results [13].

Aspergillus and *Mucor* are the two fungal genera that account for more than 90% of AIFS. Depending on the cause species of AIFS, different antifungal agents are effective. The galactomannan test was approved by the United States Food and Drug Administration in 2003 and is used to diagnose AIFS. Recently, the test has been used for early diagnosis of AIFS, [2, 4–6, 16, 17]. However, no meta-analysis has been conducted to evaluate the overall diagnostic value of the test in AIFS. Therefore, we conducted the current meta-analysis to evaluate the diagnostic value of the serum galactomannan test for AIFS, especially AIAS.

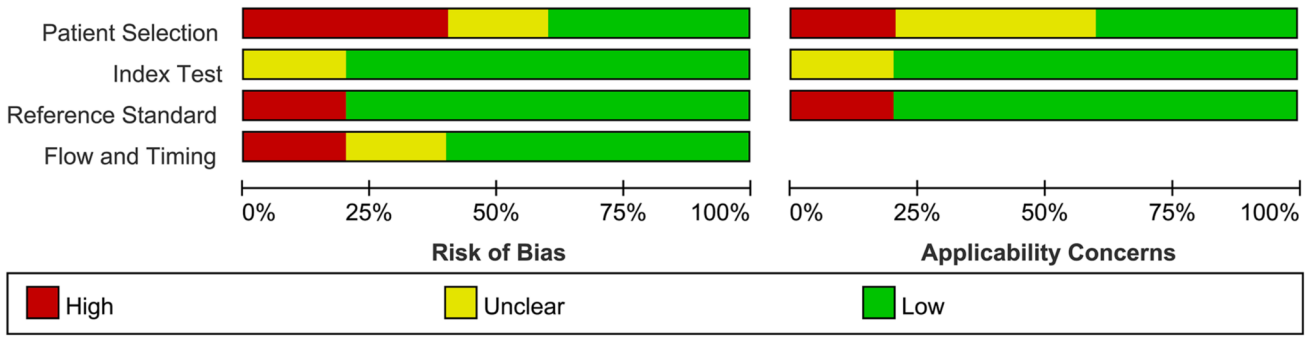

Fig. 2 Overall quality assessment of included studies (QUADAS-2 tool)

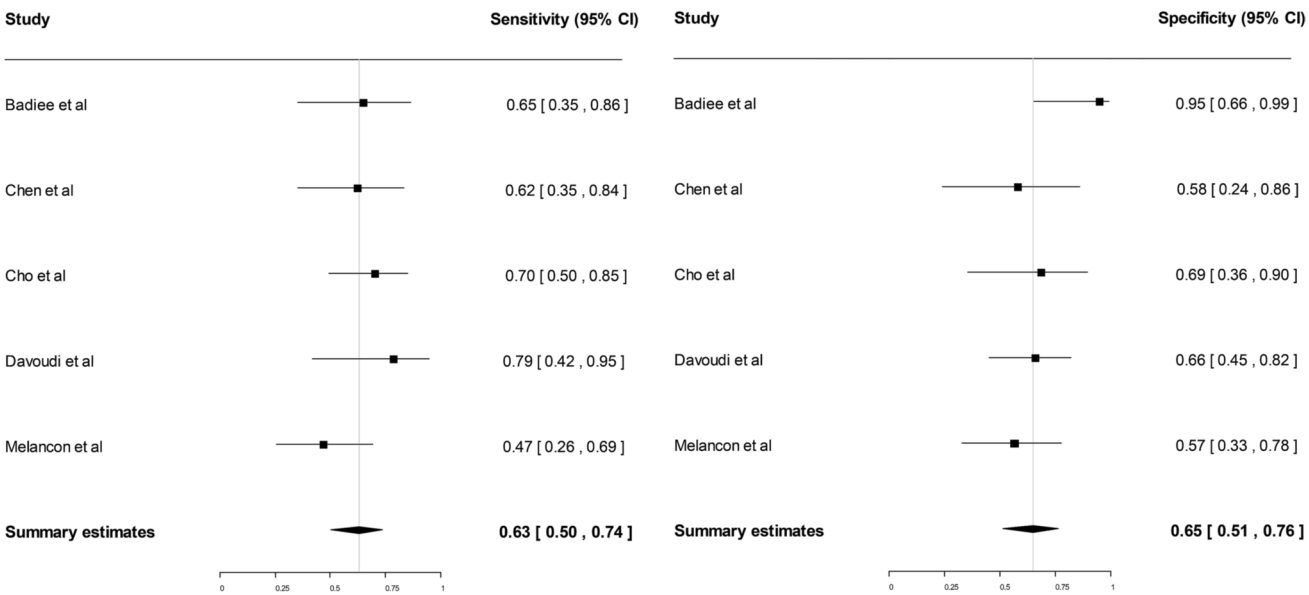

Fig. 3 Forest plot of sensitivities and specificities in the analysis of serum galactomannan test accuracy to diagnose confirmed acute invasive *Aspergillus* sinusitis

We selected five studies to evaluate the diagnostic value of the serum galactomannan test based on the EORTC/MSG definitions. Our results suggested that the test is a less accurate method to diagnose confirmed AIAS (DOR = 3.37, AUC = 0.68, sensitivity = 0.63, specificity = 0.65). We also calculated likelihood ratios to incorporate both sensitivity and specificity. Jackson et al. suggested that a PLR > 10 and an NLR < 0.1 represent convincing diagnostic evidence, and that a PLR of > 5 and an NLR of < 0.2 represent strong diagnostic evidence [14]. However, our meta-analysis showed PLR and NLR values of 1.83 and 0.58, respectively, for the test in cases of confirmed AIAS. Additionally, we conducted an analysis in the four studies that used a galactomannan cut-off value of 0.5. The results of that analysis also suggested that the test is a less accurate method to diagnose confirmed AIAS (DOR = 2.87, AUC = 0.65, sensitivity = 0.59, specificity = 0.64, PLR = 1.70, NLR = 0.65).

We tried to enrol patients with probable or passible AIFS; however, the data of the included studies were insufficient. AIFS is a rare disease, and serum galactomannan tests are not usually performed to diagnose it. Therefore, we could not compare the accuracy of the serum galactomannan test between confirmed or probable AIAS and possible AIAS. Our meta-analysis only included cases in which fungus had been confirmed using pathology or culture of AIAS, so probable cases of AIAS may have been excluded, even if they were clinically suspected. Therefore, the serum galactomannan test may have shown low accuracy in the present study because only confirmed cases of AIAS were assessed.

Several studies have reported that the cause fungus is not always identified pathologically in AIFS [1, 10, 24]. This may have influenced the accuracy of the serum galactomannan test in the present study. Specifically, the accuracy of the test to diagnose AIAS would increase if probable cases of

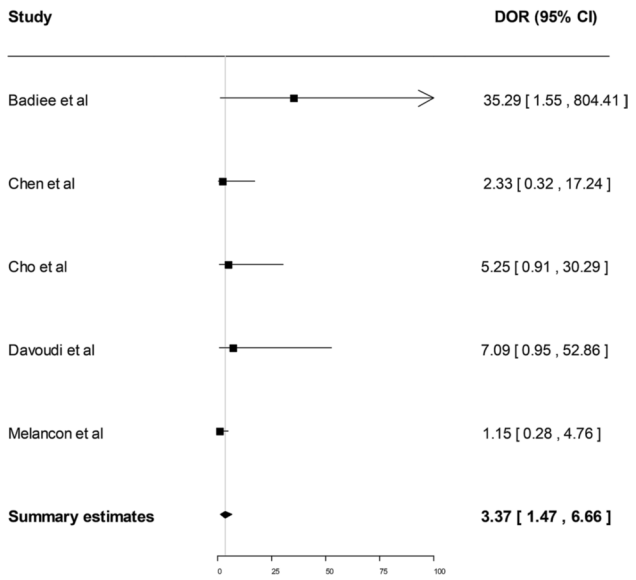

Fig. 4 Forest plot of diagnostic odds ratios in the analysis of serum galactomannan test accuracy to diagnose confirmed acute invasive *Aspergillus* sinusitis

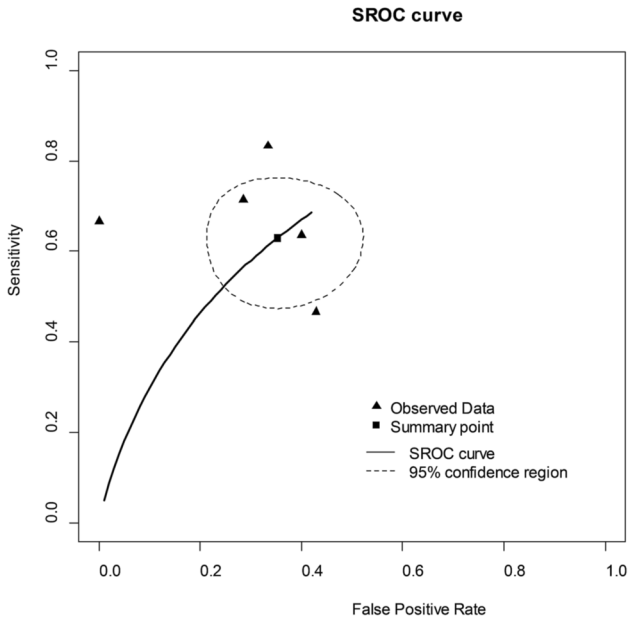

Fig. 5 SROC curve of the serum galactomannan test's accuracy to diagnose confirmed acute invasive *Aspergillus* sinusitis in each individual study

AIAS had been included in the current study. In one meta-analysis of galactomannan tests in pulmonary invasive aspergillosis, which is well studied, the test had moderate-to-high accuracy [20, 22, 26]. Recently, the serum galactomannan test for AIAS has been gradually studied in the field of otorhinolaryngology [4, 17, 19]. Therefore, future studies involving more data may find a higher accuracy of the serum galactomannan test to diagnose AIAS.

This current meta-analysis had several limitations. First, each included article only involved a small number of patients with AIAS, and the varying distribution of patient age made it difficult to analyse specific age groups. Second, we eventually assessed a small number of selected studies; therefore, publication bias may have occurred (Egger's test p value of 0.04). Third, the serum galactomannan test may have been less accurate for diagnosing AIAS because we did not enrol probable or possible cases of AIAS due to insufficient data.

Despite the limitations and the results of the current meta-analysis, recent studies have shown that the importance of serum galactomannan tests is increasing [4, 17]. The test can play an important role in determining the initial diagnosis of AIAS and the early use of antifungal agents. It shows relatively high sensitivity and specificity, in company with high positive and negative predictive values [6]. More importantly, high serum galactomannan levels are significantly related to low survival in patients with AIFS [6]. However, the serum galactomannan test in the current meta-analysis was less accurate for diagnosing confirmed AIAS. Therefore, the initial diagnosis of AIAS should not be dependent solely on serum galactomannan test results. In the initial diagnosis of AIAS, a patient's clinical symptoms and imaging tests should be used along with a serum galactomannan test.

Conclusion

In conclusion, even though the serum galactomannan test has been used in the initial diagnosis of AIFS, the accuracy thereof in the current meta-analysis exhibited low accuracy for diagnosing confirmed AIAS. Further investigations of the serum galactomannan test must be conducted in patients with AIAS to more accurately assess its diagnostic value.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00405-021-06857-8.

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Author contributions Conceptualization: SWC, HJC. Data curation: SWC, NWK, JGH. Formal analysis: SWC, JSN, JGH. Funding acquisition: CHK, JHY, HJC. Methodology: WFA, CHK. Project administration: SWC, WFA. Visualization: SWC, JGH, JSN. Writing—original draft: SWC. Writing—review and editing: CHK, JHY, HJC.

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Availability of data and materials The data used in this study is available in the assessed articles.

Declarations

Conflict of interest No potential conflict of interest relevant to this article was reported.

Ethics approval This study does not require Ethics Committee approval.

Consent to participate Not applicable.

Consent for publication Not applicable.

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