Heliyon 10 (2024) e34569

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Diagnostic accuracy of galactomannan and lateral flow assay in invasive aspergillosis: A diagnostic meta-analysis

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ARTICLE INFO

Keywords:
Invasive *aspergillosis*
Lateral flow assay
Galactomannan
Diagnostic meta-analysis

ABSTRACT

Background: Efficient diagnosis of patients at high risk for invasive *aspergillosis* (IA) improves the outcome of the disease. Lateral flow assay (LFA) is a novel technology and assessing its diagnostic accuracy is of great significance in the clinical management of IA.
Methods: A meta-analysis using case-control studies was performed to assess the diagnostic performance of LFA alone or galactomannan (GM) combined with LFA (GM-LFA) as screening tests for IA. The sensitivity, specificity, and summary receiver operating characteristic curves were constructed.
Results: Nineteen studies with 2838 patients were included. The pooled effect sizes for different indicators included: sensitivity (77 % for LFA and 75 % for GM-LFA), specificity (88 % for LFA and 87 % for GM-LFA), positive likelihood ratio (6.65 for LFA and 12.02 for GM-LFA), negative likelihood ratio (0.26 for LFA and 0.27 for GM-LFA), and the diagnostic odds ratio (25.81 for LFA and 44.87 for GM-LFA). The area under the curve was 0.91 for LFA and 0.94 for GM-LFA with a cut-off value $\geq$ 0.5.
Conclusion: The present meta-analysis suggested that LFA or GM-LFA at an optical density index (ODI) cutoff of $\geq$0.5 was a useful diagnostic tool for IA in patients. The results showed no significant differences in the accuracy of LFA alone and GM-LFA in diagnosing IA. In the clinical diagnosis and treatment of IA, LFA can be recommended if timely results are needed.

1. Introduction

Aspergillus fumigatus is a saprotrophic fungus that is widespread in soil and decaying vegetation [1]. Invasive *aspergillosis* (IA) is a difficult infection to diagnose and treat, especially in a subgroup of immunocompromised patients (e.g., hematologic malignancies and chronic obstructive pulmonary disease), who are very susceptible to acquiring infections with this type of fungus, which leads to a higher mortality [2]. For example, in hematologic patients, and despite antifungal therapy, crude mortality rates as high as 75 % have

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https://doi.org/10.1016/j.heliyon.2024.e34569
Received 29 January 2024; Received in revised form 8 July 2024; Accepted 11 July 2024

been described, which were largely related to delayed diagnosis [3].

Therefore, to reduce morbidity and mortality in general or in specific populations, earlier diagnosis of IA infections is crucial as it has been shown that any delay in antifungal treatment may lead to worsening of the condition [4]. Recently, several techniques have been developed to diagnose IA in clinical practice. The Aspergillus galactomannan (GM) test is an enzyme-linked immunosorbent assay (ELISA) for the detection of GM polysaccharides that are mainly present in the cell wall of Aspergillus species [5]. However, the ELISA GM assay has some limitations, including cost and turnaround time, especially in an environment where batch testing is infrequent or where samples need to be submitted to a central laboratory [6,7]. In addition, it was discovered that only 23 % of the Asian laboratories surveyed offered a GM assay, thereby further illustrating the limitations of the application of this technology [8]. Furthermore, molecular tests, such as a polymerase chain reaction (PCR), have been used for the diagnosis of IA, but the lack of standardization of such tests has shown a wide variation in the diagnostic level of the PCR in different studies [9,10]. In particular, a poor diagnostic accuracy was observed when the PCR technique was used on serum samples [11].

Overall, exploring new techniques to improve the diagnostic accuracy and timeliness of IA with the ability to reduce costs can be beneficial for the timely treatment of IA. Currently, lateral flow assay (LFA) is a point-of-care (POC) diagnostic test for IA. This assay is simple to use, does not require sophisticated laboratory equipment, and produces results in less than an hour. Therefore, LFA prevents the need for complex laboratory equipment that is required for PCR, and improves timeliness [12]. The GM antigen assay combined LFA (GM-LFA) is a self-contained sandwich immunochromatographic test for the qualitative and quantitative detection of Aspergillus GM from serum and bronchoalveolar lavage fluid (BALF) samples [13]. Diagnostic meta-analysis is a method of synthesizing data that includes the development of an effective search strategy to identify published articles on the subject, determining criteria for inclusion in the study, evaluating methodological quality, performing data extraction, and analyzing and pooling data [14,15]. However, current meta-analyses usually explore the diagnostic efficacy of common techniques (e.g., GM, PCR) for IA. However, for LFA-related techniques, meta-analyses are still lacking, and the diagnostic efficacy of the techniques remains unclear in terms of evidence-based conclusions. Therefore, in this diagnostic meta-analysis, the objective was to explore the diagnostic level of LFA and GM-LFA for IA compared with existing studies. This meta-analysis innovatively analyzed both LFA and GM-LFA techniques, which fills the gap in current evidence-based research while providing clearer evidence for the clinical diagnosis of IA.

2. Methods

2.1. Search strategy

The purpose of this systematic review was to gather studies examining the diagnostic accuracy of LFA and GM for IA. English databases such as PubMed, Embase, and Web of Science (WOS) were comprehensively searched from database establishment to October 2023. The search terms were as follows: (invasive *aspergillosis* OR IA OR *aspergillosis*) AND (lateral flow assay OR LFA OR galactomannan OR GM).

2.2. Inclusion and exclusion criteria

Studies that met the following selection criteria were included: (1) the study design was typically a case-control study, where information from each group was clearly reported, and the original data of each study was presented in two-by-two tables and (2) participants included IA patients with gold-standard diagnosis criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG), required participants included proven/probable/no IA. Studies were excluded if the following criteria were met: (1) insufficient data, such as meeting summaries, (2) meta-analysis and systematic reviews, and (3) animal studies.

2.3. Literature selection and data extraction

The retrieved literature was imported into literature management software (EndNote v.8x) and studies were independently selected by two investigators. During the evaluation process, if there was a difference between the two investigators, a third investigator was consulted to discuss and resolve the disagreement. First, the study was screened based on the title and abstract, the full text was obtained for the studies that were identified or might meet the criteria. Then, inclusion or exclusion was decided based on the full text. During the data extraction phase, two reviewers independently extracted information from eligible articles. The information extracted from original publications included the first author, study design, year of publication, country or region of the study, characteristics of the study population (mean age, sex, concomitant disease), sample size, sample processing method, sample source, sample detection method, cut-off value and gold standard.

2.4. Assessment of study quality

The quality of studies was assessed using the revised quality assessment of diagnostic accuracy studies (QUADAS-2) tool [16] and the standards for reporting diagnostic accuracy (STARD) tool [17]. Some items could be judged as ‘‘yes’’, ‘‘no’’, or ‘‘unclear’’ (when the study provided insufficient information to make an accurate judgment), while other domains could be classified as low risk, high risk, or unclear risk of bias.

2.5. Statistical analysis

EORTC/MSG is the most accurate and reliable reference standard for diagnosing IA, and its role in assessing the accuracy and reliability of other tests is very important. Patients were classified into the following three groups according to the EORTC/MSG criteria: proven IA, probable IA, and no IA. The two technologies, GM-LFA and individual LFA were used to test for IA (proven or probable IA vs. no IA), and for each study, two-by-two tables were constructed, and patients were divided into four groups according to their IA diagnosis. In addition, for studies that reported multiple cutoffs, the cutoff values that provided the best performance were used. In general, cutoff values of $\geq$0.5 based on the included studies were assessed. Similarly, in the preliminary analysis, there was no limit to the source of samples, BALF was used first, and if not available, serum samples were considered. A binary regression method with a 95 % confidence interval (CI) was used to assess the overall specificity (SPE) and sensitivity (SEN), and a layered summary receiver operating characteristic (SROC) curve was constructed. Moreover, the diagnostic accuracy (area under the curve, AUC) was provided [18,19]. The diagnostic odds ratio (DOR) was calculated, which describes the odds of positive test results in a patient compared to non-IA subject. Furthermore, pooled positive likelihood ratios (pooled PLR) and pooled negative likelihood ratios (pooled NLR) were calculated, in which pooled PLR values of $>$10 and pooled NLR values of $<$0.1 were considered convincing diagnostic evidence, whereas strong diagnostic evidence was based on pooled PLR values of $>$5 and NLR values of $<$0.2 [20,21].

The statistically significant heterogeneity was assessed using I^2 statistics and explored the potential heterogeneity between studies [22]. To better investigate the impact of different factors on the diagnosis, subgroup analysis was performed for different variables, such as cutoff (0.5 vs > 0.5), sample type (BALF vs. serum), and antifungal therapy (Yes or No). Stata 15.1 software was used for all statistical calculations.

3. Results

3.1. Results of the systematic literature search

A total of 842 studies were identified and screened, and after exclusion based on title and abstract review, the remaining 54 studies

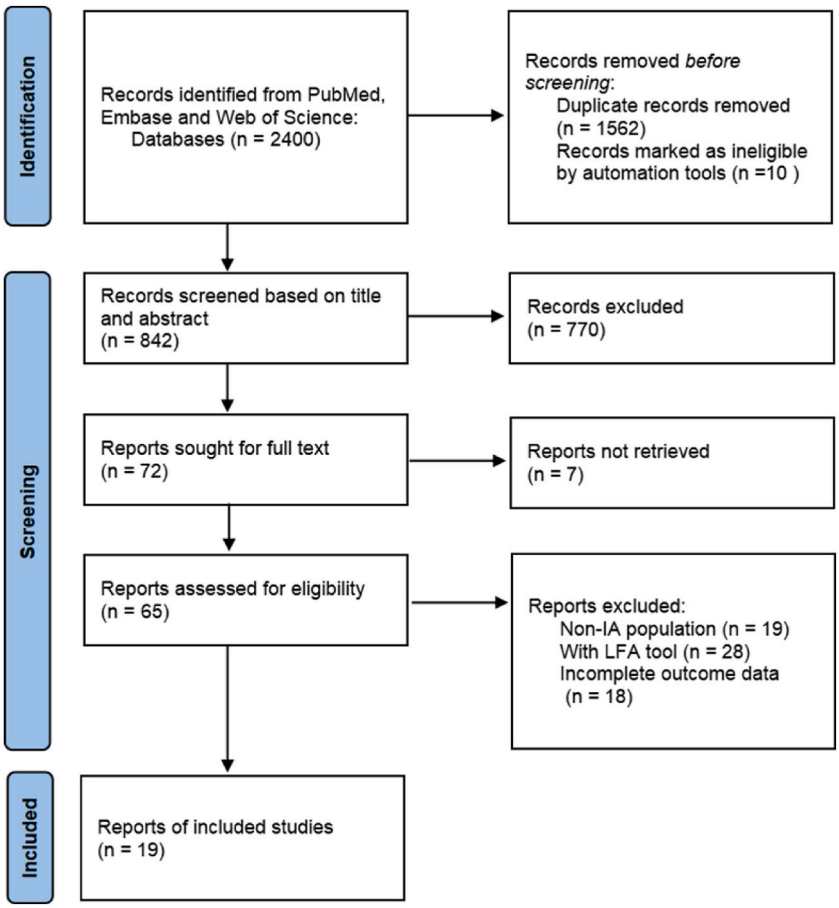

Fig. 1. PRISMA diagram of literature screening process.

Table 1
Characteristics of the included trials.

Study	Country	Setting	Sample processing	Design	Sample method	Gender (F/M)	Total (N)	Proven/ Probable IA	Age	Test	Sample type	Cut off	Reference criteria	Antifungal therapy
Serin 2022	Turkey	CAPA	Prospective	Cohort	Unclear	50/68	118	10	67 ± 16.9	LFA	Serum	0.5 ODI	2020 ECMM/ ISHAM	No
Ghazanfari 2022	Iran	CAPA	Prospective	Cohort	Unclear	47/58	206	43	65.2 (25–95)	GM-LFA	BALF Serum	≥1.0 ODI >0.5 ODI	2020 ECMM/ ISHAM	Yes
Chaturvedi 2022	Lucknow	CAPA HD	Retrospective	Case-control	Unclear	24/17	41	18	38 (21–65) 42 (23–58)	MP-LFA	Serum	–	2020 EORTC/MSG	No
Autier 2022	France	CAPA	Retrospective	Case-control	Random	76/163	90	29	61 (58–64) 61 (58–63)	LFA	Serum BALF TA	0.5 ODI 1.0 ODI	2020 ECMM/ ISHAM	No
Almeida 2022	Brazil	PD	Retrospective	Case-control	Unclear	–	200	100	–	GM-LFA	Serum	0.5 ODI	2020 EORTC/MSG	No
Serin 2021	Turkey	Febrile neutropenia	Prospective	Cohort	Unclear	44/43	87	11	53.30 ± 16.43	GM-LFA	Serum	0.5 ODI 1.0 ODI	2020 EORTC/MSG	No
Roman 2021	Mexico	CAPA	Retrospective	Case-control	Consecutive	31/103	144	14	48.6 ± 11.5	GM-LFA	TA	0.8 ODI 1.0 ODI >1 ODI	2008 EORTC/MSG	Yes
Mercier 2021	Belgium	HD	Prospective	Cohort	Consecutive	89/150	239	41	60 [51.5, 66]	LFA GM-LFA	Serum	≥2.36 ODI	2020 EORTC/MSG	Yes
Jenks 2021	USA	HD SOT ICU/other	Prospective	Cohort	Unclear	104/128	295	88	60 (18–86)	LFA	BALF	0.5 ODI 1.0 ODI >1 ODI	2020 EORTC/MSG	Yes
Jani 2021	USA	Cancer	Retrospective	Case-control	Unclear	298/81	379	12	60 (18–85)	LFA	BALF Serum	3.56 ODI	2020 EORTC/MSG	Yes
Hoenigl 2021	USA	CAPA	Retrospective	Cohort	Unclear	45/77	122	28	60 (54–76)	GM-LFA	Serum	0.5 ODI 1.0 ODI	2020 EORTC/MSG	Yes
Arkell 2021	United Kingdom	HM SOT	Prospective	Cohort	Unclear	37/55	92	15	59 (48–65.5)	LFA	BALF	–	2020 EORTC/MSG	Yes
White 2020	United Kingdom	HM	Retrospective	Case-control	Unclear	–	132	32	58	GM-LFA	Serum	0.5 ODI 0.33 ODI 0.61 ODI	2020 EORTC/MSG	Yes
Mercier 2020	Belgium	HM PD COPD	Retrospective	Case-control	Unclear	78/100	178	55	63 [56, 68] 57 [46, 66]	GM-LFA	BALF	≥0.5 ODI	2008 EORTC/MSG	Yes
Mercier 2020a	Belgium	HD HSCT	Retrospective	Case-control	Unclear	143/92	235	75	64 [52, 71]	GM-LFA	BALF	1.0 ODI	2008 EORTC/MSG	Yes
Linder 2020	USA	SOT HM	Prospective	Cohort	Unclear	16/24	40	20	55.1 ± 17.4 55.1 ± 17.1	GM-LFA	BALF	≥0.5 ODI ≥1.0 ODI	2020 EORTC/MSG	No
Lass 2019	Austria	Respiratory disease	Retrospective	Case-control	Unclear	–	52	48	–	LFA	BALF	–	2008 EORTC/MSG	Yes
Jenks 2019	USA	HM	Prospective	Cohort	Unclear	8/9	17	9	70 (24–78) 56 (32–75)	GM-LFA	BALF	–	2008 EORTC/MSG	Yes
Alhan 2023	Turkey	HM	Prospective	cohort	Consecutive	71/100	171	28	54 (18–91)	GM-LFA	Serum	≥0.5 ODI	2008 EORTC/MSG	Yes

CAPA: COVID-19-associated pulmonary aspergillosis; HM: hematological malignancy. HSCT: hematopoietic stem cell transplant. SOT: solid organ transplantation; PD: pulmonary disease; HD: hematological disease; ICU: Intensive Care Unit; GM-LFA: sōna Aspergillus galactomannan lateral flow assay; LFA: Lateral Flow Assay; MP-LFA: mannoprotein lateral flow assay; EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group; ECMM/ISHAM: European Confederation of Medical Mycology and the International Society for Human and Animal Mycology; BALF: bronchoalveolar lavage fluid; TA: tracheal aspiration.

were subjected to full-text assessment for eligibility. Among these studies, 20 were duplicates or targeted patients, five were non-human studies, and 10 studies did not report data of interest. Ultimately, 19 articles [23–41] were analyzed following eligibility assessment (Fig. 1).

3.2. Basic characteristics of included studies

Most of the 19 included studies were published in recent years. Regarding patient comorbidities, the most common comorbidities were hematologic diseases (n = 9), and the conventional mean age of the population was 60 years. The study design included case-control studies and cohort studies. Most studies reported BALF as the source of the samples, others included serum samples. Among the cut-off values, most studies reported an optical density index (ODI) of 0.05, whereas others ranged the ODI from 1 to 4. The gold standard used in all studies was EORTC/MSG of different years (Table 1). The quality assessment results are represented in a bar chart (Fig. 2), including Risk of Bias (four domains) and Applicability Concerns (three domains). All studies had a low risk of bias in terms of Flow and Timing and a high risk of bias in terms of Patient Selection. The assessment results for specific items (domains) of each study are shown in Supplementary Table 1.

3.3. Results of diagnostic meta-analysis

3.3.1. LFA test for patients with proven/probable IA vs. no IA

The analysis for proven/probable vs. no IA was included in 7 of the 19 studies, and all 7 studies demonstrated a cutoff value of ≥0.5. The pooled SEN and pooled SPE were 0.77 (95 % CI, 0.65–0.86) and 0.88 (95 % CI, 0.81–0.93), respectively (Fig. 3). The PLR and NLR were 6.65 (95 % CI, 3.96–11.17) and 0.26 (95 % CI, 0.16–0.41), respectively (Fig. 4). DOR was 25.81 (95 % CI, 12.27–54.33), and the diagnostic score was 3.25 (95 % CI, 2.51–3.99) (Fig. 5). The SROC curve is displayed in Fig. 6 and represents the relationship between SPE and SEN throughout the study. The area under the SROC curve (AUC) was 0.91 (95 % CI, 0.88–0.93), thereby indicating that the LFA had a high diagnostic capability.

3.3.2. GM-LFA test for patients with proven/probable IA vs. no IA

The analysis for proven/probable vs. no IA was included in 13 of the 19 studies, all 13 studies demonstrated a cutoff value of ≥0.5. The pooled SEN and pooled SPE were 0.75 (95 % CI, 0.54–0.89) and 0.87 (95 % CI, 0.78–0.93), respectively (Fig. 3). The PLR and NLR were 12.02 (95 % CI, 6.42–22.51) and 0.27 (95 % CI, 0.13–0.54), respectively (Fig. 4). DOR was 44.87 (95 % CI, 16.14–124.79), and the diagnostic score was 3.80 (95 % CI, 2.78–4.83) (Fig. 5). The SROC curve is displayed in Fig. 6, the area under the SROC curve (AUC) was 0.94 (95 % CI, 0.92–0.96), thereby indicating that the GM-LFA had a high diagnostic capability.

3.3.3. Heterogeneity analysis of different variables

Heterogeneity analyses with different covariates showed that, for LFA, the method of data collection (retrospective vs. prospective), study design (cohort vs. case-control), sample source (BALF vs. serum), cut-off value (0.5 vs. >0.5), and sample size (<100 vs. >100) could potentially affect the sensitivity of the diagnosis (P = 0.05). Other variables, including patients suffering from neutropenia and consecutive sampling significantly affected the sensitivity of the diagnosis (P = 0). For GM-LFA, consecutive sampling had an impact on diagnostic sensitivity, whereas the other variables did not have a significant impact on sensitivity and specificity. See Table 2 for details.

4. Discussion

From the results of this meta-analysis, the sensitivity and specificity of LFA for the diagnosis of IA were 0.77 (95 % CI, 0.65–0.86) and 0.88 (95 % CI, 0.81–0.93), respectively. In addition, the AUC value showed that the diagnostic accuracy of LFA was 91 %. Regarding GM-LFA, the sensitivity and specificity were slightly lower compared to LFA, but the diagnostic accuracy was higher than LFA (94 %). Overall, no significant differences were observed in the level of diagnosis of IA between the two techniques, and

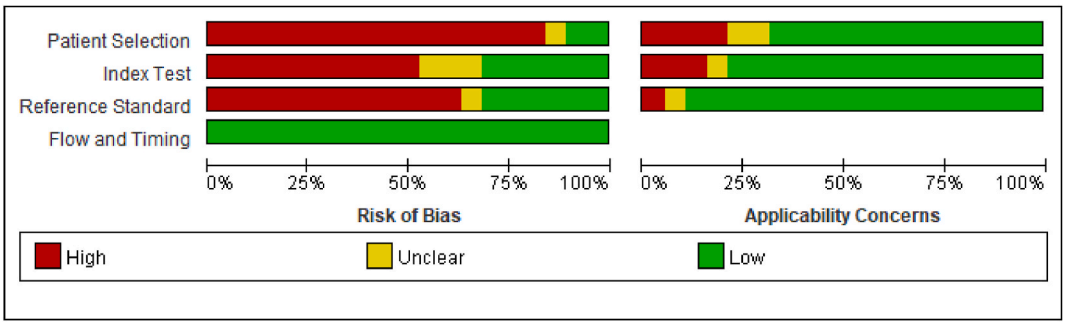

Fig. 2. Overall quality assessment of all 19 included studies.

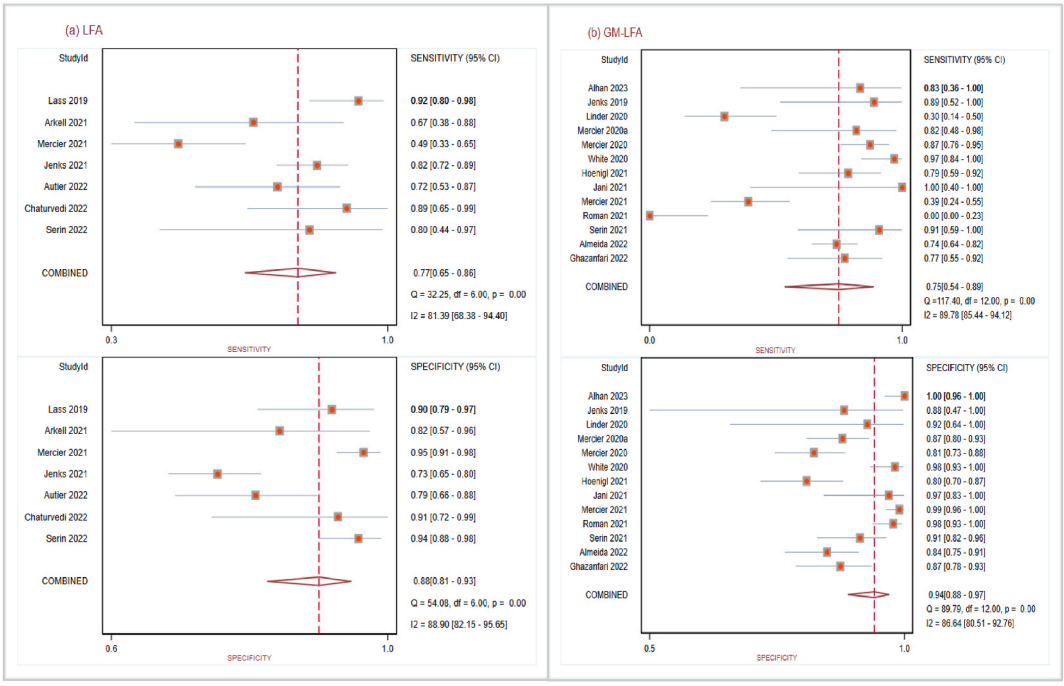

Fig. 3. Forest plot of sensitivities and specificities of LFA or GM-LFA test accuracy in the diagnosis of proven or probable IA.

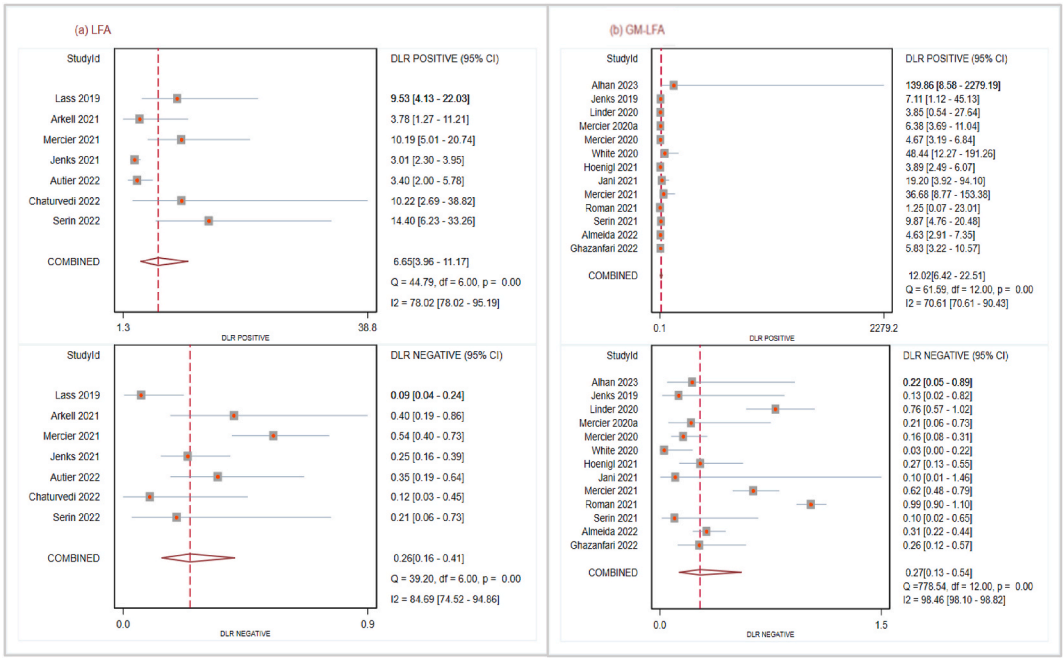

Fig. 4. Forest plot of PLR and NLR of LFA or GM-LFA test accuracy in the diagnosis of proven or probable IA.

subsequent studies are needed to investigate the diagnostic level of the two techniques. Notably, a similar study recently reported on LFA in the diagnosis of invasive pulmonary *aspergillosis* (IPA). The authors indicated that the overall sensitivity and specificity for diagnosing IPA were 0.78 and 0.87, respectively, and the AUC was 0.86 [42]. However, in this study, it was clearly stated that the samples were derived from BALF only, which was different than the source of the samples in our study, therefore, the possible effect of the difference in sample sources could not be ignored.

Clarifying the diagnostic accuracy of other techniques had important implications for our findings. First, for GM antigen testing, in

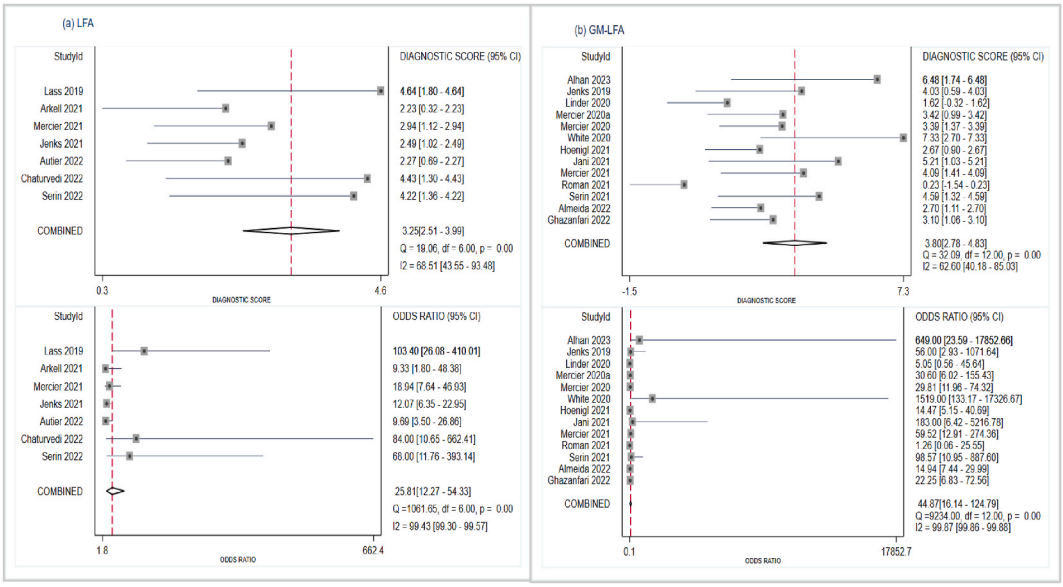

Fig. 5. Forest plot of DOR of LFA or GM-LFA test accuracy in the diagnosis of proven or probable IA.

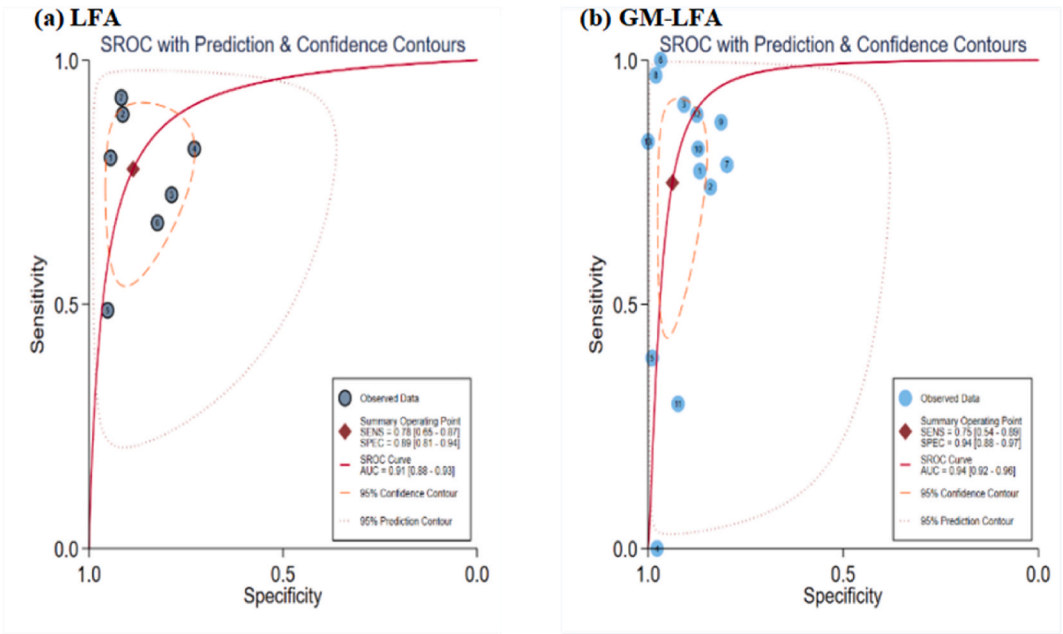

Fig. 6. Summary SROC plots of SEN and SPE.

a recent meta-analysis, Oliveira et al. explored the diagnosis of chronic pulmonary *aspergillosis* by GM antigen testing, the results showed that the sensitivity and specificity were 0.29 and 0.88, respectively, and the AUC value was 0.53 in serum samples with a cutoff value of 0.96 [43]. These findings differed from the results of the LFA in this study. Moreover, in another study, Bukkems et al. reported galactomannan antigen assays (GM) for diagnosing invasive pulmonary *aspergillosis* in hematological patients [44]. The pooled data resulted in an overall serum sensitivity of 0.76, a specificity of 0.92, an overall BALF sensitivity of 0.80, and a specificity of 0.95 [44], which was not significantly different from the results of LFA or GM-LFA in our study. As for the PCR, in 2013, a diagnostic meta-analysis was performed, investigating the value of BALF PCR in the diagnosis of IPA. The summary sensitivity and specificity for proven/probable IPA were 0.75 (95 % CI = 0.67–0.81) and 0.94 (95 % CI = 0.90–0.96), respectively. This study showed that BALF PCR was a useful diagnostic tool for IPA in immunocompromised patients and was effective for diagnosing IPA. In addition, in an earlier systematic review, it was concluded that the diagnostic performance of PCR in BALF (sensitivity with 0.9 and specificity with 0.96) was

Table 2
Heterogeneity analysis of different variables.

Covariates		Sensitivity	Specificity	P value for sensitivity	P value for specificity
Heterogeneity assessment for LFA					
Data collection	prospective	0.70 [0.53–0.86]	0.90 [0.83–0.98]	0.05	0.38
	retrospective	0.82 [0.71–0.93]	0.87 [0.77–0.96]		
Study design	cohort	0.70 [0.53–0.86]	0.90 [0.83–0.98]	0.05	0.38
	case-control	0.82 [0.71–0.93]	0.87 [0.77–0.96]		
Sample type	BALF	0.83 [0.72–0.94]	0.82 [0.71–0.94]	0.05	0.64
	Serum	0.71 [0.56–0.87]	0.92 [0.86–0.97]		
Neutropenia	yes	0.49 [0.30–0.68]	0.95 [0.90–1.00]	0	0.59
	no	0.84 [0.78–0.90]	0.86 [0.79–0.93]		
Antifungal therapy	yes	0.76 [0.62–0.89]	0.88 [0.79–0.96]	0.3	0.15
	no/unclear	0.80 [0.64–0.97]	0.89 [0.80–0.98]		
Cut-off	0.5	0.72 [0.60–0.85]	0.85 [0.77–0.94]	0.05	0.01
	>0.5	0.83 [0.71–0.96]	0.92 [0.86–0.99]		
Sample size	<100	0.70 [0.53–0.86]	0.90 [0.83–0.98]	0.05	0.38
	>100	0.82 [0.71–0.93]	0.87 [0.77–0.96]		
QUADAS	No bias	0.85 [0.78–0.92]	0.88 [0.80–0.97]	0.57	0.24
	bias	0.61 [0.49–0.73]	0.88 [0.79–0.98]		
Sample method	Consecutive	0.60 [0.45–0.75]	0.90 [0.80–0.99]	0	0.41
	non-consecutive/unclear	0.83 [0.76–0.90]	0.88 [0.80–0.96]		
Reference criteria	EORTC/MSG 2008	0.92 [0.82–1.00]	0.91 [0.77–1.00]	0.24	0.95
	2020 EORTC/MSG or ECMM/ISHAM	0.71 [0.61–0.81]	0.88 [0.81–0.94]		
Heterogeneity assessment for GM-LFA					
Data collection	prospective	0.64 [0.33–0.95]	0.96 [0.93–1.00]	0.28	0.75
	retrospective	0.82 [0.64–1.00]	0.90 [0.83–0.97]		
Study design	cohort	0.58 [0.31–0.84]	0.96 [0.93–0.99]	0.04	0.76
	case-control	0.88 [0.75–1.00]	0.90 [0.82–0.97]		
Sample type	BALF	0.82 [0.64–1.00]	0.91 [0.83–0.99]	0.42	0.02
	Serum	0.66 [0.39–0.94]	0.95 [0.92–0.99]		
Neutropenia	yes	0.80 [0.53–1.00]	0.94 [0.87–1.00]	0.33	0.64
	no	0.72 [0.50–0.95]	0.94 [0.89–0.99]		
Antifungal therapy	yes	0.77 [0.58–0.96]	0.95 [0.91–0.98]	0.61	0.96
	no/unclear	0.68 [0.28–1.00]	0.90 [0.78–1.00]		
Cut-off	0.5	0.73 [0.53–0.93]	0.95 [0.91–0.98]	0.83	0.36
	>0.5	0.83 [0.50–1.00]	0.86 [0.65–1.00]		
Sample size	<100	0.75 [0.55–0.95]	0.94 [0.90–0.98]	0.9	1
	>100	0.75 [0.38–1.00]	0.92 [0.81–1.00]		
QUADAS	No bias	0.78 [0.55–1.00]	0.92 [0.86–0.99]	0.76	0.06
	bias	0.71 [0.43–0.99]	0.95 [0.90–1.00]		
Sample method	Consecutive	0.46 [0.08–0.83]	0.98 [0.95–1.00]	0.05	0.79
	non-consecutive/unclear	0.84 [0.70–0.98]	0.90 [0.84–0.96]		
Reference criteria	EORTC/MSG 2008	0.70 [0.37–1.00]	0.94 [0.88–1.00]	0.67	0.34
	2020 EORTC/MSG or ECMM/ISHAM	0.78 [0.57–0.98]	0.93 [0.88–0.99]		

good and comparable to that of GM in BALF [45].

Overall, among the available technologies, the diagnostic accuracy of different technologies for IA reflects their respective advantages. For LFA, its diagnostic level in a specific setting is comparable to GM and PCR. Seeking potential sources of heterogeneity in the analysis could clarify the impact of different factors on the accuracy of diagnostic methods related to LFA. In this meta-analysis, a heterogeneity analysis was conducted to address the effect of different variables on diagnostic levels. The data showed that some variables (e.g., disease characteristics, cutoff values, sample source, etc.) significantly affected diagnostic accuracy, and several studies have supported these findings. For example, for sample sources, Rawlings et al. stated that GM was more sensitive than culture, with a sensitivity and specificity from blood of 82 % and 81 %, respectively [46]. However, Heer et al. stated that GM on BALF had shown better diagnostic performance than on blood, with a sensitivity and specificity of 88 % and 81 %, respectively [47]. Regarding cutoff values, in the study by Bukkems et al., it was demonstrated that in the GM assay for BALF, when the cutoff value was 0.5, there was a pooled sensitivity of 0.75 and a specificity of 0.88. In addition, BALF ODI 1.0 pooling resulted in a sensitivity of 0.75 and a specificity of 0.96 [44]. Moreover, in another meta-analysis, it was shown that the AUCs were 0.92, 0.86, 0.93, 0.89, 0.88, and 0.94 when the cut-off values were 0.5, 0.8, 1.0, 1.5, 2.0, and 3.0, respectively [48]. For the other factors, differences in diagnostic levels of the different variables were explored by regression in the heterogeneity assessment, where neutropenia and consecutive sampling significantly affected the sensitivity of the diagnosis. Notably, patients with different comorbidities or different healthcare settings may affect the accuracy of the LFA technique in diagnosing IA, which may ultimately limit the applicability of LFA. As noted in a recent study [49], these particular patients remain challenging due to overlapping clinical features, poor sensitivity of blood cultures, leading to missed or delayed diagnosis. For this, non-culture-based techniques such as galactomannan assays and PCR-based tests can aid in diagnosis.

Therefore, from the various analyses described above, it is clear that the choice of different techniques in the diagnosis of IA should be based on the actual environment. For example, for the sample source, the current collection routes are mainly from BALF, serum, sputum, tracheal aspirate, etc., and from the current evidence, the preference of BALF is an important factor to improve the diagnostic

accuracy, which greatly facilitates the rapid diagnosis and timely treatment of clinical IA [47]. Furthermore, the selection of cutoff values should take full account of the fact that differences in cutoff values could affect diagnostic accuracy, thereby providing clinical researchers with an optimal reference range of cutoff values as an important way to improve the accuracy of diagnostic IA [50]. It is worth considering that the cost and time of different technologies is an important reference factor, which not only affects the patient's experience, but also has an impact on the values of clinical staff. It has previously been noted that techniques such as LFA could be recommended for the diagnosis of LFA if low cost and rapid results are considered [51]. If necessary, a combined method can better improve diagnosis accuracy, such as the GM antigen assay combined with LFA. For a group of patients for whom the result of a technical diagnosis is uncertain, LFA can be used for emergency diagnosis first, and GM antigen assay can be used for clinical standard method later, which is more conducive to the treatment of patients [52].

The main limitation of this study was that the control of some variables remained inadequate. Firstly, regarding population characteristics, the population included in this analysis had concomitant diseases, such as hematologic neoplasms and respiratory diseases, and limited by the number of studies, the diagnostic effectiveness of the population with specific diseases was not assessed. Furthermore, in terms of cutoff values, there was a single definition of the range, with the only cutoff value of 0.5 comparing the results of cutoff value $>$ 0.5, which might not provide the best ODI cutoff value relative to more detailed categorization in other studies (e.g., 0.5, 1, 1.5, and 2, etc.). Finally, further subgroup analysis was not performed due to the limitation of the number of included studies. Thus, this analysis could be conducted in the future.

In conclusion, the present meta-analysis suggested that the LFA or GM-LFA at an ODI cutoff of $\geq$0.5 was a useful diagnostic tool for IA in patients. The results showed no significant difference in the accuracy of LFA alone and GM-LFA in diagnosing IA. In the clinical diagnosis and treatment of IA, LFA can be recommended if timely results are needed.

Financial support

This research was supported by the National Natural Science Foundation of China (Project Number 72074103).

Ethics approval and consent to participate

Not applicable.

Data availability statement

Data included in article/supplementary material/referenced in article.

CRediT authorship contribution statement

Xiaohong Zhang: Writing – original draft, Software, Formal analysis. **Xue Shang:** Methodology, Formal analysis, Data curation. **Yinghua zhang:** Software, Methodology, Investigation. **Xiuxia Li:** Validation, Supervision, Resources, Methodology. **Kehu Yang:** Visualization, Validation, Supervision, Methodology. **Yan Wang:** Writing – original draft, Methodology, Investigation, Data curation. **Kangle Guo:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34569.

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