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REVIEW

Utility of serum galactomannan in diagnosing invasive aspergillosis among hematology patients: a meta-analysis

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ABSTRACT

Objective: In immunocompromised patients, invasive aspergillosis (IA) is a leading cause of morbidity and mortality. The serum galactomannan (GM) assay is a non-invasive test that may assist in IA diagnosis. The purpose of this meta-analysis is to determine the diagnostic accuracy of the serum GM in patients with hematological malignancies.

Materials and Methods: A search was conducted in the MEDLINE database through PubMed. After selection process and data extraction, 2x2 tables were constructed for patients with proven/probable IA and no IA, as well as for patients with proven IA and no IA. The pooled sensitivity and specificity were established using meta-analysis for the cut-off values of 0.5,1.0 and 1.5 ODI. Inter-study heterogeneity was assessed utilizing the inconsistency test (I^2). The receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated. The data analysis was conducted using the Meta-DiSc 1.4 software.

Results: A total of 26 articles, 4502 patients and controls, together with 4761 IA episodes, were included in the meta-analysis. The total number of patients with proven and probable IA was 633 (13.3%). In the group with proven/probable IA versus no-IA, the overall pooled sensitivity and specificity were 80% and 78% (AUC: 0.892) for 0.5 ODI, 74% and 96% (AUC: 0.959) for 1.0 ODI, and 70% and 96% (AUC: 0.964) for 1.5 ODI, respectively. In the group with proven versus no-IA, the overall pooled sensitivity and specificity were 94% and 76% (AUC: 0.922) for 0.5 ODI, 86% and 96% (AUC: 0.979) for 1.0 ODI and 70% and 96% (AUC: 0.974) for 1.5 ODI, respectively.

Conclusion: Our findings indicate that the most appropriate cut-off value for Serum GM in diagnosing IA is 1.0 ODI.

Keywords: Invasive aspergillosis, Galactomannan, Diagnostic accuracy

INTRODUCTION

In immunocompromised individuals, invasive fungal diseases (IFD), particularly Aspergillus infections, are a significant cause of morbidity and mortality [1,2]. Consequently, prompt diagnosis and intervention are crucial, with culture positivity and the identification of hyphae infiltrating tissue in biopsy specimens being the most dependable methods for diagnosing invasive aspergillosis (IA); however, these techniques lack sufficient sensitivity. Furthermore, a biopsy might not be necessary because most patients have neutropenia, thrombocytopenia, bleeding risk, and other potential consequences [3]. As a result, non-invasive strategies for early detection are required. The presence of the galactomannan (GM) antigen, a wall component found in Aspergillus species, may indicate an early diagnosis [4]. GM antigen can be identified using an enzyme-linked immunosorbent

test (ELISA), with results expressed as an optical density index (ODI) [5].

The European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) released consensus definitions in 2002 to standardize the diagnosis of IFDs. [6]. According to this report, IFDs can be classified into three categories: proven, probable, and possible. EORTC/MSG criteria were revised and updated in 2008 and 2020, resulting in a modification in the definition of the probable category, which was expanded while the scope of the possible category diminished [7,8]. One of these modifications pertains to the cut-off value of galactomannan (GM) in serum and bronchoalveolar lavage (BAL). The optimal cut-off for galactomannan antigen ODI remains debatable. The literature presents variable findings for the sensitivity and specificity of this index. We conducted a systematic-review and meta-analysis to assess the diagnostic performance of serum GM and to establish an optimal cut-off value.

METHODS

Literature Search and Article Selection Process

A search was conducted in the MEDLINE database through PubMed for the articles published in English language up to October 2014. The keywords employed for screening articles that assessed the sensitivity and specificity of the serum galactomannan antigen test were '(aspergillus pcr OR galactomannan) AND (sensitivity OR specificity)'.

Among the articles identified through the database search, publications that included adult patients with hematological cancer and/or those who underwent stem cell transplantation were selected. If a publication's population included other host factors along with hematological cancer patients, only those publications where the number of hematological cancer patients was predominant were included in the meta-analysis. Only studies employing the serum GM Platelia ELISA methodology were incorporated.

Case reports, case series, reviews, and systematic reviews were not included. In cases where multiple publications pertain to the same patient population, the publication featuring the larger sample size has been incorporated. Studies with fewer than five patients in the proven and probable IA group, as well as those without adequate data for sensitivity and specificity calculations, were excluded from the analysis.

Data Extraction

Publications that fulfilled the criteria were reviewed meticulously, and the subsequent data were extracted for each study:

1. Mean age
2. Gender distribution percentages
3. Study design (cohort, case-control, randomized controlled trial)
4. Data collection methodology (prospective, retrospective)
5. Sampling method (consecutive, random)
6. The IA diagnostic criteria employed
7. Whether the test was administered to the patient population that represented the entire risk group
8. Whether the reference standard was applied to each and every patient
9. Whether an independent, blinded process was used to evaluate the test results
10. Whether there is any bias that could alter the test outcomes, particularly incorporation bias
11. The total number of patients
12. Number of IA episodes
13. Number of proven, probable, and possible cases
14. The patients' status regarding antifungal treatment or prophylaxis during the test period
15. The minimum number of positive samples required for the test to be considered positive
16. Mean number of samples per patient
17. Prevalence of IA
18. Sensitivity and specificity for the proven or proven and probable patient group
19. The cutoff value of the galactomannan assay

Methodological Quality Assessment

The methodological quality of all publications included in the meta-analysis was assessed using the QUADAS-2 tool [9]. The articles were independently evaluated by two reviewers (A.D. and S.A.) and following individual assessment, the conflicts were analyzed and addressed through discussion. The QUADAS-2 tool comprises four domains, with the risk of bias assessed as unclear, low, or high for each domain.

The reference standard for diagnosing IA, which involves demonstrating Aspergillus hyphae in tissue biopsy, is practically challenging to apply and has not been utilized in all patients in any study. Therefore, the diagnostic criteria employed as the reference standard have been further specified. Each study employed an appropriate reference standard. (2008 EORTC/MSG, 2002 EORTC/MSG, and EORTC similar diagnostic criteria).

Statistical Analyses

The study participants were categorized into four groups as proven IA, probable IA, possible IA and no IA. The possible IA group was excluded from the analysis due to the difficulty to definitively rule out IA and the possibility of its presence. 2x2 tables were constructed for patients with proven/probable IA and no IA, as well as for patients with proven IA and no IA, to ascertain the number of true positives, false positives, false negatives, and true negatives. The pooled sensitivity and specificity were established using meta-analysis. Inter-study heterogeneity was assessed utilizing the inconsistency test (I^2). The receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated. Subgroup analyses were performed due to significant heterogeneity. Because of the variability of cut-off values for GM, separate analyses were performed for 0.5, 1.0, and 1.5 ODI. Due to the variability in the number of samples necessary for a positive GM result between studies, separate analyses were performed for a single positive GM and for at least two consecutive positive GM. Different calculations of the same study with different cut-off values and the minimum number of samples required for the test to be considered positive were recorded as separate data. The data analysis was conducted using the Meta-DiSc 1.4 software.

RESULTS

The full selection process can be reviewed in Figure 1. A total of 26 articles were included in the meta-analysis [10-35]. A total of 4502 patients and controls, together with 4761 IA episodes, were included. The total number of patients with proven and probable IA was 633 (13.3%). Studies involving both adult and pediatric patients were not omitted from the meta-analysis; however, in a study where independent data calculation existed, only the adult patient group data were used [34]. In one study, the sensitivity and specificity of the test were additionally established for individuals from the patient group who underwent autopsy [35].

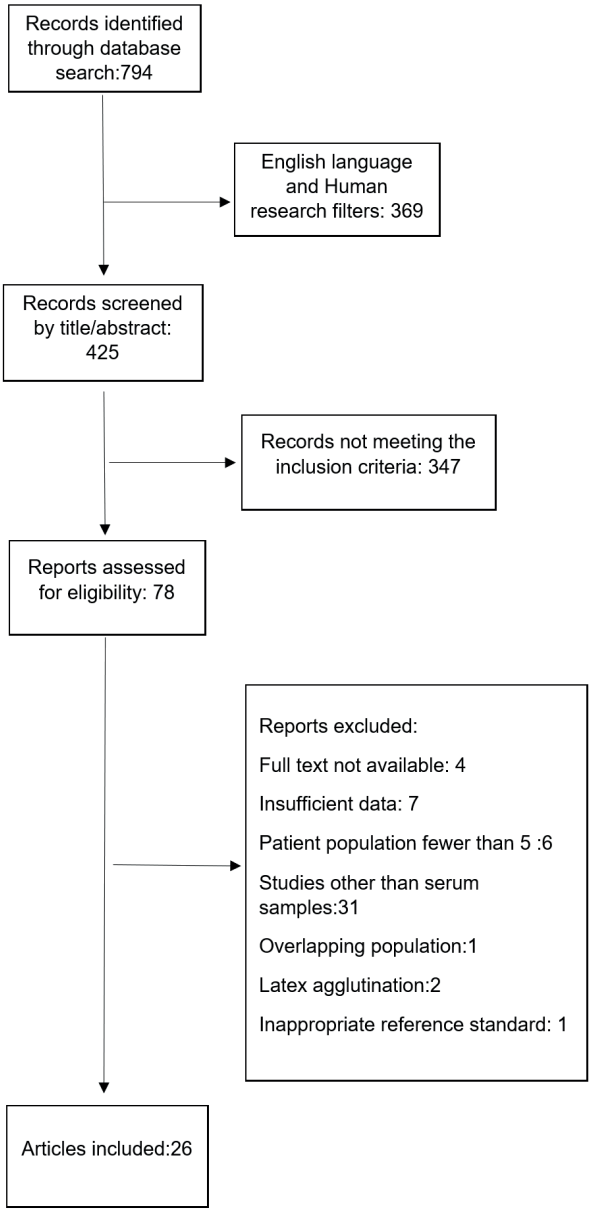


Figure 1. Article Selection Process

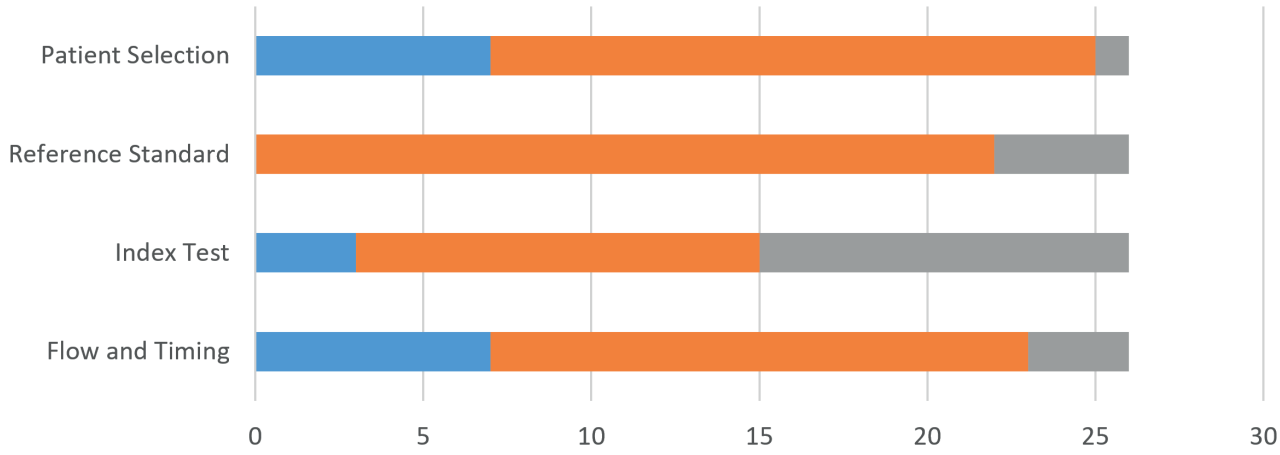
Table 1. General characteristics of the publications

Article	Year	Country	Patient Population	Mean Age	Women (%)	Study Design	Data Collecting Method	Sampling Method
Held et al. [10]	2013	Germany	Adult and Children AHSCT	?	?	Cohort	Prospective	Consecutive
Rogers et al. [11]	2013	Ireland	Adult HM	?	?	Cohort	Prospective	Consecutive
Khanna et al. [12]	2013	India	Adult/child patients with various host factors	32.2	29.6	Cohort	Prospective	Uncertain
White et al. [13]	2013	England	Adult HM	53.3	29.1	Case-contol	Retrospective	Consecutive
Hadrich et al. [14]	2012	Tunusia	Adult and Children HM	37.6	28.6	Cohort	Prospective	Consecutive
Ji et al. [15]	2011	China	Adult and Children AHSCT	30.6	37	Cohort	Retrospective	Consecutive
Tanriover et al. [16]	2010	Türkiye	Adult HM	44	32.8	Cohort	Prospective	Consecutive
Hachem et al. [17]	2009	USA	Adult and Children HM	60	27	Case-control	Prospective	Uncertain
Suarez et al. [18]	2008	France	Adult HM	?	?	Cohort	Prospective	Consecutive
Lai et al. [19]	2007	Taiwan	Adult patients with various host factors	54	50	Cohort	Prospective	Uncertain
Maertens et al. [20]	2007	Belgium	Adult HM	?	40.8	Case-control	Retrospective	Consecutive
Foy et al. [21]	2007	USA	Adult and Children AHSCT	29.5	43	Cohort	Retrospective	Consecutive
Florent et al. [22]	2006	France	Adult HM	?	?	Cohort	Prospective	Consecutive
Weisser et al. [23]	2005	Switzerland	Adult HM	48	38	Cohort	Prospective	Consecutive
Marr et al. [24]	2005	Canada	Adult and Children HM	42.3	46	Randomized and Case-control	Prospective and Retrospective	Uncertain
Pazos et al. [25]	2005	Spain	Adult HM	44	42.5	Cohort	Retrospective	Random
Maertens et al. [26]	2004	Belgium	Adult HM	49	38.7	Cohort	Prospective	Consecutive
Kawazu et al. [27]	2004	Japan	Adult HM	45	30.2	Cohort	Prospective	Consecutive
Rovira et al. [28]	2004	Spain	Adult AHSCT	37	39.1	Cohort	Prospective	Consecutive
Buchheidt et al. [29]	2004	Germany	Adult HM	46	40	Cohort	Prospective	Uncertain
Pinel et al. [30]	2003	France	Adult and Children HM	?	?	Cohort	Prospective	Uncertain
Maertens et al. [31]	2002	Belgium	Adult AHSCT	35.6	33	Cohort	Prospective	Consecutive
Ulusakarya et al. [32]	2000	France	Adult and Children HM	41	52.5	Cohort	Retrospective	Consecutive
Kami et al. [33]	2001	Japan	Adult HM	48.3	23.7	Case-control	Prospective and Retrospective	Uncertain
Sulahian et al. [34]	2001	France	Adult and Children AHSCT	?	?	Cohort	Prospective	Consecutive
Maertens et al. [35]	1999	Belgium	Adult and Children HM	44	37.6	Cohort	Prospective	Consecutive

HM: Hematologic malignancy; AHSCT: Allogeneic hematopoietic stem cell transplantation.

Table 1 outlines the general characteristics of the publications included in the meta-analysis.

Figure 2 displays the methodological quality assessment of the studies included in the meta-analysis. In just two studies, it was stated that the patients had received mold-effective antifungal treatment while the assessment of serum GM. Although certain patients received antifungal therapy in fifteen studies, the specifics of the period of pre-test treatment or the number of patients treated remain unclear. Two studies identified that patients did not receive antifungal treatment prior to the test, whereas seven studies omitted any mention of treatment. Likewise, only four studies indicated that antifungal prophylaxis effective against molds was delivered, although in eleven studies, some patients received mold-effective prophylaxis and others received non-mold-effective prophylaxis. Consequently, the impact of antifungal treatment or mold-active antifungal prophylaxis on serum GM sensitivity or specificity was unable to be assessed.



	Flow and Timing	Index Test	Reference Standard	Patient Selection
High	7	3	0	7
Low	16	12	22	18
Unclear	3	11	4	1

High Low Unclear

Figure 2. Overall quality assessment of included studies using the QUADAS-2 tool

Pooled Sensitivity and Specificity Results For Serum GM ELISA

Comparisons were conducted between the proven and probable IA group and the group including solely proven IA patients. The pooled sensitivity and specificity were calculated for cut-off values of 0.5, 1.0, and 1.5 ODI. Separate subgroup analyses were conducted for articles that deemed a single positive result significant and those that required at least two consecutive positive results for significance.

In the group with proven/probable versus no-IA and a cut-off of 0.5 ODI, the overall pooled sensitivity and specificity were 80% and 78% (AUC: 0.892), respectively. The overall sensitivity and specificity were 74% and 96% (AUC: 0.959) for 1.0 ODI and 70% and 96% (AUC: 0.964) for 1.5 ODI, respectively.

Pooled sensitivity and specificity for the proven IA group were derived from 18 studies utilizing 2x2 tables. In the group with proven versus no-IA, the overall pooled sensitivity and specificity were 94% and 76% (AUC: 0.922) for the cut-off of 0.5 ODI, 86% and 96% (AUC: 0.979) for 1.0 ODI and 70% and 96% (AUC: 0.974) for 1.5 ODI, respectively. The pooled sensitivity and specificity per cut-off value were presented in Table 2. Forest plots of sensitivity and specificity per cut-off value are presented in supplementary document.

DISCUSSION

Invasive aspergillosis is one of the leading causes of morbidity and mortality, particularly in patients with hematological malignancies or those who have undergone hematopoietic stem cell transplantation, thus early detection is critical [36]. To prevent delays in diagnosis, empirical antifungal treatment is employed; however, toxicity and high costs may restrict its utilization. Consequently, the significance of non-invasive tests for facilitating early diagnosis is increasing [37]. GM and PCR in serum and BAL fluid represent the most extensively researched methods in this context. The purpose of this meta-analysis was to establish the diagnostic accuracy of the serum GM (Platelia) test in patients at high risk for IA.

Table 2. Pooled Sensitivity and Specificity Results For Serum Galactomannan

	Cut-off value	Number of studies	AUC	SEN I^2 (%)	Pooled SEN	SPE I^2 (%)	Pooled SPE
Proven and Probable IA vs no IA	**0.5 overall**	22	0.892	84.2	0.80	96.6	0.78
	0.5 single sample	11	0.859	81.1	0.85	96.9	0.68
	0.5 two consecutive samples	11	0.921	85.1	0.72	92.8	0.89
	1.0 overall	10	0.959	82.8	0.74	92.9	0.96
	1.0 single sample	6	0.954	86.2	0.76	88.5	0.91
	1.0 two consecutive samples	4	0.973	80.4	0.71	66.3	0.99
	1.5 overall	12	0.964	78.1	0.70	72.4	0.96
	1.5 single sample	7	0.957	79.9	0.71	77.4	0.95
	1.5 two consecutive samples	5	0.978	80.3	0.70	24.3	0.97
Proven IA vs no IA	**0.5 overall**	11	0.922	0	0.94	97.7	0.76
	0.5 single sample	6	0.936	3.4	0.93	97.8	0.67
	0.5 two consecutive samples	5	0.911	0	0.96	96.5	0.89
	1.0 overall	8	0.979	80.7	0.86	93.1	0.96
	1.0 single sample	4	0.979	85.2	0.82	86.2	0.91
	1.0 two consecutive samples	4	0.990	79.6	0.89	70.4	0.99
	1.5 overall	9	0.974	74.0	0.70	60.6	0.96
	1.5 single sample	5	0.986	73.6	0.78	65.8	0.95
	1.5 two consecutive samples	4	0.974	76.1	0.64	42.7	0.97

IA: Invasive aspergillosis; AUC:Area under curve; SEN: Sensitivity; SPE: Specificity.

Table 3. Comparison of pooled analysis results with the literature

	Cut-off	Dikmeer		Leeflang		Pfeiffer	
		SEN	SPE	SEN	SPE	SEN	SPE
Proven and Probable IA vs no IA	**0.5**	0.80	0.78	0.79	0.82	0.79	0.86
	1.0	0.74	0.96	0.71	0.90	0.65	0.94
	1.5	0.70	0.96	0.62	0.95	0.48	0.95
Proven IA vs no IA	**0.5**	0.94	0.76	-	-	0.27	0.79
	1.0	0.86	0.96	-	-	0.79	0.87
	1.5	0.70	0.96	-	-	0.68	0.92

SEN: Sensitivity; SPE: Specificity

A substantial level of heterogeneity (I^2) was observed with the exception of proven IA cases at 0.5 ODI. Limiting the population of patients to individuals with hematological cancer was anticipated to decrease heterogeneity. Nevertheless, the inclusion of studies involving patients with hematological cancer alongside with other lower-risk host factors for IA such as solid organ transplantation, long-term steroid use, immunosuppressive drug use, and HIV, as well as those at the highest risk, such as allogeneic stem cell transplantation, and inclusion of both adult and pediatric populations, might have contributed to increased heterogeneity. In these studies, it was not possible to isolate data specifically for patients with hematological malignancies and the adult patient cohort, with the exception of one study that examined adult data separately; thus, subgroup analysis could not be conducted.

In patients with proven and probable IA, serum GM revealed a sensitivity of 80% and specificity of 78% at the 0.5 ODI, 74% sensitivity and 96% specificity at the 1.0 ODI, and 70% sensitivity and 96% specificity at the 1.5 ODI. Increasing the cut-off value resulted in a gradual decrease in sensitivity and a corresponding increase in specificity. The specificity remained unchanged between the 1.0 and 1.5 cut-off values. In the proven IA group, serum GM sensitivity and specificity were determined to be 94% and 76% at 0.5 ODI, 86% and 96% at 1.0 ODI, and 70% and 96% at 1.5 ODI, respectively (Table 3). As the cut-off value increased, sensitivity decreased while specificity increased, remaining

constant after the cut-off of 1.0 ODI. These findings suggested that the optimal cut-off value for serum GM in both proven IA and proven/probable IA groups were 1.0 ODI. This outcome is significant as it aligns with the EORTC/MSG recommendations revised in 2020 [8].

A meta-analysis conducted by Pfeiffer in 2006, including 27 studies, determined the sensitivity and specificity for proven and probable IA patients as follows: 79% and 86% at 0.5 ODI, 65% and 94% at 1.0 ODI, and 48% and 95% at 1.5 ODI, respectively [38] (Table 3). In patients with proven IA, the sensitivity and specificity were 27% and 79% at the 0.5 ODI, 79% and 87% at the 1.0 ODI, and 68% and 92% at the 1.5 ODI, respectively. In our study, while the results for the 0.5 ODI were comparable in the proven and probable patient group, it was noted that sensitivity had increased at the 1.0 and 1.5 ODI. The application of the EORTC/MSG 2002 criteria as the diagnostic standard for IA in Pfeiffer's meta-analysis, along with variations in patient characteristics, may have influenced the sensitivity. The 2002 EORTC/MSG diagnostic criteria define the possible IA group as encompassing a wider population than the 2008 EORTC/MSG guideline, which classify the probable IA group as covering a more narrower range of patients. The exclusion of possible IA patients from the meta-analysis and implementation of the 2008 EORTC/MSG criteria in six studies may have affected the outcomes of our study. The inclusion of patients who received solid organ transplantation in the meta-analysis by Pfeiffer might have contributed to the observed lower sensitivity. Our analysis revealed that the sensitivity of proven IA patients was greater than that reported by Pfeiffer. The disparity could be attributed to the significantly smaller number of proven IA patients in the study conducted by Pfeiffer compared to our research.

Another meta-analysis conducted by Leeflang in 2008, including 29 studies, revealed that the sensitivity and specificity for proven and probable IA patients were 79% and 82% for 0.5 ODI, 71% and 90% for 1.0 ODI, and 62% and 95% for 1.5 ODI, respectively [39] (Table 3). Seperate analysis was not conducted for patients with only proven IA group. The results align with the findings of our study.

A meta-analysis by Bukkems in 2023, encompassing studies on adult HM patients, revealed a sensitivity of 92% and a specificity of 84% for 0.5 ODI [40]. They could not provide pooled results for 1.0 and 1.5 ODI values due to the availability of data from only a single study for these cut-off values. The higher sensitivity and specificity for 0.5 ODI in comparison to our findings might be because the 2008 EORTC/MSG criteria were employed as the reference standard in all of the studies that were analyzed in the aforementioned meta-analysis.

This study presents certain limitations. The sole screening of the MEDLINE database, the date of the database scan being outdated, and the selection of English publications may have resulted in the exclusion of relevant research. The main obstacle of IA diagnostic accuracy studies has been the challenge of utilizing the gold standard approach as a reference for all patients. Consequently, in the literature, including our research, the EORTC/MSG criteria have been employed as the reference standard. A notable source of bias worthy of discussion is incorporation bias. The EORTC/MSG criteria implement the value of GM for the diagnosis of probable IA, hence introducing the possibility of incorporation bias. This meta-analysis's strengths include the exclusion of low-risk IA patients and the comparison of patients alone with proven IA patients with no-IA patients.

CONCLUSION

This meta-analysis concluded that the serum GM test could be utilized in diagnosing IA at a 1.0 ODI cut-off value, which is consistent with current EORTC/MSG recommendations. Consequently, it is necessary to conduct additional research, preferably multiple randomized controlled trials.

Author contribution

Study conception and design: AD, MDT, and SA; data collection: AD, and SA; analysis and interpretation of results: AD, and SA; draft manuscript preparation: AD, MDT, and SA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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