Article Review

Galactomannan Test in Suspected Invasive Pulmonary Aspergillosis Patients: An Evidence-Based Case Report

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Abstract

Background: Invasive pulmonary aspergillosis is a severe fungal infection with a high mortality rate. However, because the clinical and radiological images are non-specific, and culture results take a long time and yield unsatisfactory results, rapid, high-accuracy tests are needed. Consequently, the diagnosis of invasive pulmonary aspergillosis remains difficult. The objective of this study was to assess the galactomannan (GM) test as a diagnostic tool for patients with suspected invasive pulmonary aspergillosis.

Methods: Articles were searched through three databases (PubMed, Embase, and Cochrane) using keywords based on PICO components related to suspected invasive pulmonary aspergillosis and the GM test. Titles and abstracts were screened, duplicates were removed, and articles were filtered according to inclusion and exclusion criteria. The critical appraisal was performed using methods recommended by the Center for Evidence-Based Medicine at the University of Oxford.

Results: Three studies reported serum GM test sensitivities ranging from 71% to 88%, suggesting that this assay may be suitable as a screening tool due to its adequate true positive detection rate. The specificity values in these studies ranged from 89% to 98%, indicating good accuracy in correctly identifying true negative cases. However, considerable heterogeneity was observed across the studies.

Conclusion: The GM test is a promising rapid diagnostic tool for suspected invasive pulmonary aspergillosis, enabling earlier and more accurate antifungal treatment. However, further studies are needed to standardize its cut-off values and interpretation to ensure consistent clinical application.

Keywords: diagnosis, galactomannan, invasive pulmonary aspergillosis

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INTRODUCTION

Invasive pulmonary aspergillosis (IPA) is a respiratory infection caused by Aspergillus infection, which is widespread in the environment.[1] Epidemiological investigations show that nearly 200,000 patients develop Aspergillus infection annually, with a mortality rate ranging from 30% to 90%.[2,3] IPA is classified mainly into invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), and allergic bronchopulmonary aspergillosis (ABPA). IPA is a serious opportunistic infectious disease with high morbidity and mortality, particularly in immunocompromised and hospitalized patients.[4]

The diagnosis of invasive pulmonary aspergillosis is made by detecting fungal elements through biopsy and fungal culture examination. By reason of biopsy is an invasive procedure and fungal culture takes a long time with low sensitivity,[5] alternative diagnostic tests have been developed to detect fungal biomarkers such as the galactomannan antigen.[6]

The GM test detects the presence of GM antigen in blood and other body fluids. GM is a polysaccharide component of the fungal cell wall that is released during fungal growth. The GM test offers faster results along with high sensitivity and specificity, enabling earlier diagnosis and timely administration of fungus-specific therapy. Consequently, it also helps reduce the incidence, morbidity, and mortality associated with Aspergillus infections.[6,7]

Therefore, this evidence-based clinical review (EBCR) evaluates the diagnostic accuracy of the GM test using the EORTC/MSG (European Organization

for Research and Treatment of Cancer/Mycoses Study Group) Aspergillosis criteria as the reference standard.

CLINICAL SCENARIO

A 45-year-old male patient came to the emergency room with complaints of cough, fever, and chills accompanied by night sweats for 2 weeks. He was a blood cancer patient and was still undergoing chemotherapy. On physical examination, the results were within normal limits. Laboratory investigations of type count showed neutropenia. On chest x-ray examination, consolidation was seen accompanied by bilateral halo signs. The ECG examination was within normal limits. Patients were cared for and treated according to patient condition standards. After several days of treatment, the patient's condition worsened, and so he was transferred to the ICU. The doctor then suspected a fungal infection and intended to perform a galactomannan (GM) test.

The clinical question for that case is “Is the GM test good for diagnosing invasive pulmonary aspergillosis?” with respondents who are patients with suspected invasive pulmonary aspergillosis. Index test uses the GM test with comparison EORTC/MSG criteria. The output to be observed is the diagnosis of aspergillosis.

METHOD

The literature search was conducted on October 14, 2023, in PubMed, Embase, and Cochrane using PICO-based keywords (Patient: suspected invasive pulmonary aspergillosis; Index test: GM; Comparison: EORTC/MSG criteria; Outcome: diagnosis). PubMed and Cochrane searches used MeSH terms and title/abstract filters, while Embase utilized the PICO interface with synonyms. Cochrane’s low yield (3 hits) resulted from strict systematic review filters. Iterative searches ensured completeness, retrieving 41 articles (Table 1).

Table 1. Article search results

Database	Search query	Hits
PubMed/ MEDLINE	(("Aspergillosis"[MeSH Terms] OR "Aspergillosis"[Title/Abstract] OR "invasive aspergillosis"[Title/Abstract]) AND ((((("aspergillu"[All Fields] OR "Aspergillus"[MeSH Terms] OR "Aspergillus"[All Fields]) AND ("antigen s"[All Fields] OR "antigene"[All Fields] OR "antigenes"[All Fields] OR "antigenic"[All Fields] OR "antigenically"[All Fields] OR "antigenicities"[All Fields] OR "antigenicity"[All Fields] OR "antigenized"[All Fields] OR "antigens"[MeSH Terms] OR "antigens"[All Fields] OR "Antigen"[All Fields])) AND "research design"[MeSH Terms]) OR "aspergillus antigen test"[Title/Abstract] OR "Galactomannan"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	31
Embase	(aspergillosis:ti,ab OR 'aspergillosis'/exp OR 'invasive aspergillosis':ti,ab OR 'invasive aspergillosis'/exp OR 'invasive pulmonary aspergillosis':ti,ab OR 'invasive pulmonary aspergillosis'/exp) AND ('galactomannan test':ti,ab OR 'aspergillus antigen':ti,ab OR 'galactomannan test'/exp OR 'aspergillus antigen'/exp) AND ('systematic review':ti,ab OR 'systematic review'/exp OR 'meta analysis':ti,ab OR 'meta analysis'/exp)	7
Cochrane	ID Search Hits	3
	#1 ("aspergillosis"):ti,ab,kw 583	
	#2 MeSH descriptor: [Aspergillosis] explode all trees 251	
	#3 (Invasive Aspergillosis):ti,ab,kw 296	
	#4 MeSH descriptor: [Invasive Pulmonary Aspergillosis] explode all trees 20	
	#5 #1 OR #2 OR #3 OR #4. 583	
	#6 (Aspergillus Antigen Test):ti,ab,kw 15	
	#7 Any MeSH descriptor in all MeSH products 0	
	#8 (Galactomannan):ti,ab,kw 107	
	#9 Any MeSH descriptor in all MeSH products 0	
	#10 #6 OR #7 OR #8 OR #9 119	
	#11 #5 AND #10 59	
	#12 #5 AND #10 in Cochrane Review 3	

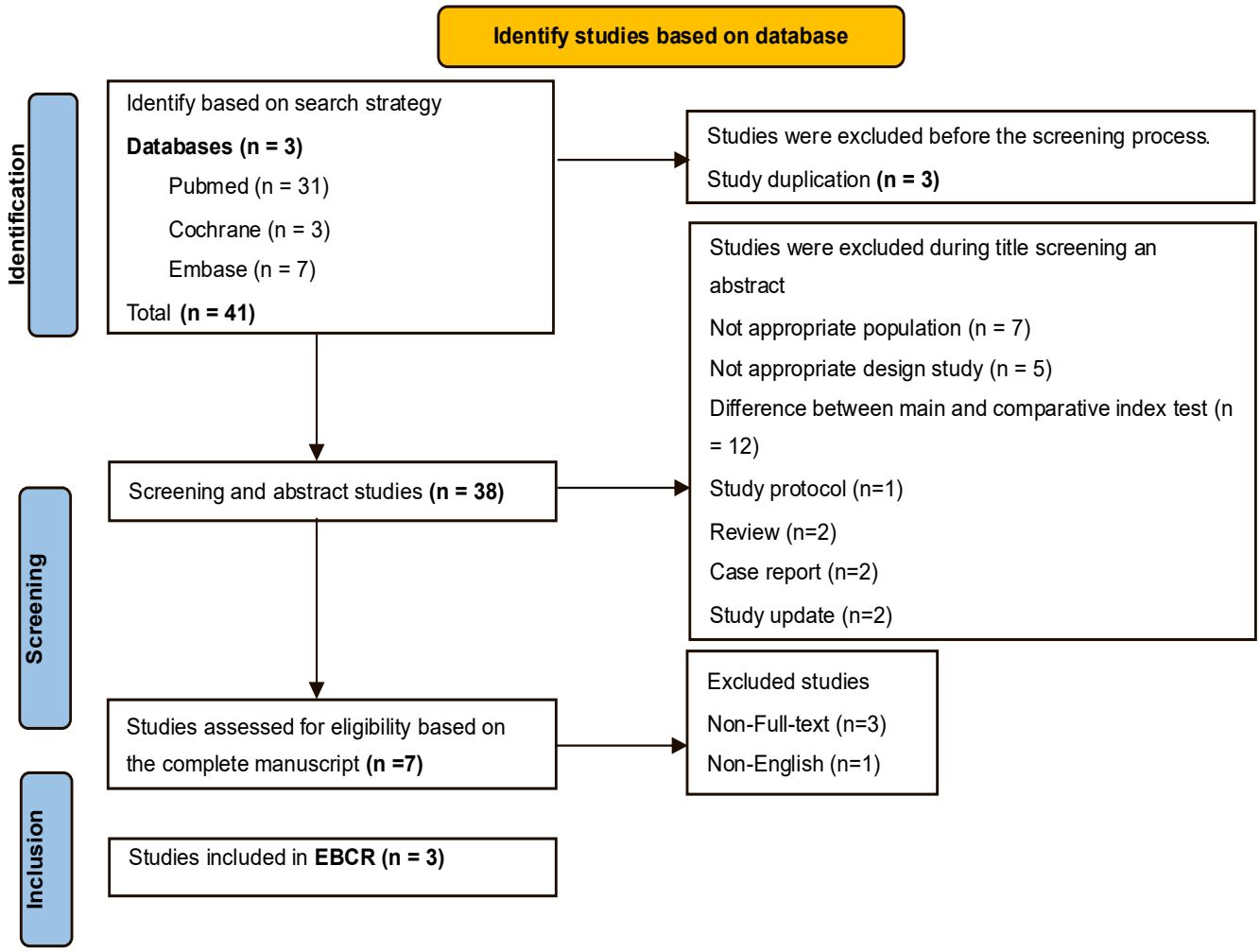

Figure 1. PRISMA *Flow chart* strategy in search and selection of results

Articles retrieved from the search engines were saved and imported into Mendeley Desktop and then filtered to remove duplicates based on identical titles. The remaining articles were further screened by reviewing their abstracts and titles and were ranked according to eligibility criteria.

Inclusion criteria were used that included studies involving samples from patients with suspected invasive aspergillosis, using the GM test as the index test. The comparison was based on the gold standard fungal culture, and the outcome was the diagnosis of invasive aspergillosis. Only systematic reviews and meta-analyses were included. Exclusion criteria excluded articles not written in Indonesian or English and those without free full-text access.

Selected articles were appraised using the QUADAS-2 tool as recommended by the Center for Evidence-Based Medicine, University of Oxford, for systematic reviews and meta-analyses. The assessment evaluated patient selection, the index test (GM), the reference standard (EORTC/MSG criteria), and the flow/timing for risk of bias and applicability. Two independent reviewers performed the appraisal (Cohen's kappa: $\kappa = 0.82$, indicating substantial agreement). Any discrepancies were resolved by consensus with a third reviewer, ensuring transparent evaluation.

RESULTS

The three included studies (Chang et al, Qusay et al, de Heer et al) demonstrated sensitivity values of 71–88% and specificity values of 89–98% for the serum GM test, indicating its potential as both a screening and confirmatory test. For bronchoalveolar lavage fluid (BALF) specimens, sensitivity ranged from 84% to 89% and specificity from 79% to 88%, suggesting higher diagnostic accuracy but greater invasiveness.

Table 2. Critical assessment of each study

Author, Year	Country	Study Design	Sample Size	Population	Sensitivity (Serum vs. BALF)	Specificity (Serum vs. BALF)
Chang L et al., 2022[12]	China	Meta-analysis	2,345	Hematological malignancies, immunocompromised	83% vs. 89%	90% vs. 79%
Qusay H et al., 2019[11]	USA	Systematic review	1,892	Hematological malignancies, bone marrow transplant recipients	71% vs. 84%	89% vs. 88%
de Heer K et al., 2019[13]	Netherlands	Meta-analysis	1,567	Immunocompromised, ICU patients	88% vs. 88%	98% vs. 81%

Due to the limited number of studies (n=3) and high heterogeneity—caused by differences in cut-off points, patient populations, and underlying diseases—a quantitative meta-analysis (e.g., pooled sensitivity/specificity or summary receiver operating characteristic [SROC] curves) was not performed. Instead, individual study results were synthesized narratively.

The quality of evidence was assessed using the GRADE approach and was rated as moderate due to high heterogeneity and the limited number of studies. No significant publication bias was detected, but imprecision was noted because of small sample sizes in some studies.

DISCUSSION

Invasive pulmonary aspergillosis remains a significant cause of morbidity and mortality, especially among immunocompromised patients such as those with hematological malignancies or undergoing hematopoietic cell transplantation. Diagnosis is challenging because clinical symptoms and radiological findings have limited sensitivity and specificity. Tissue biopsy, the gold standard for definitive diagnosis, is frequently contraindicated in critically ill patients due to high risks of bleeding and clinical instability. Therefore, non-invasive diagnostic tools such as the GM assay have been developed and extensively validated to enable earlier and more accurate detection of IPA.[8,9]

The GM test's accuracy has been benchmarked against the EORTC/MSG criteria, which classify IPA cases as proven, probable, or possible. Systematic reviews and meta-analyses consistently show that GM detection in BALF yields higher sensitivities (84–89%) and comparable specificities (79–88%) to serum specimens, which demonstrate a sensitivity of around 71% and a specificity of 89%.[6,10–13]

For instance, studies by Chang et al, Qusay et al, and de Heer et al reported BALF sensitivities of 89%, 84%, and 88%, with specificities of 79%, 88%, and 81%, respectively, whereas serum demonstrated a sensitivity of 71% and a specificity of 89%.[6,10–13] This superior sensitivity in BALF stems from direct sampling at the infection site, whereas serum testing relies on circulating antigen. However, BALF collection is invasive and often not feasible in critically ill or mechanically ventilated patients, making serum GM testing a more practical and safer alternative. Repeated serum testing once or twice weekly is recommended to capture the dynamic nature of antigenemia and to improve diagnostic confidence.[14–17]

Clinically, GM antigen detection in BALF significantly outperforms serum testing in sensitivity and offers comparable specificity, reinforcing its role as the preferred diagnostic specimen in immunocompromised populations.[6,10] Nevertheless, patient instability and the invasive nature of BALF sampling limit its use, positioning serial serum GM testing every 1–2 weeks as a valuable method to monitor fungal infection progression.[6,13] Optimal diagnostic performance is achieved at a GM cut-off value of 0.5, which balances between high sensitivity (around 89%) and early disease detection, compared to a cut-off of 1.0 that reduces sensitivity to approximately 78% while maintaining similar specificity.[12,13]

Importantly, early empiric antifungal therapy guided by GM results in high-risk patients, such as those with hematologic cancers or undergoing transplantation, can reduce aspergillosis-related mortality. However, prior antifungal treatment markedly lowers GM sensitivity —from 87.5% to

20%—underscoring the necessity of integrating therapy status into result interpretation.[18]

The accuracy of the GM test varies depending on the underlying condition, age, and assay cut-off values. In patients with hematological malignancies and those undergoing hematopoietic stem cell transplantation, pooled data demonstrated high diagnostic accuracy with a sensitivity of 83% (95% CI=74%–90%), a specificity of 90% (95% CI=82%–94%), a positive likelihood ratio (PLR) of 8.05 (95% CI=4.82–13.44), a negative likelihood ratio (NLR) of 0.19 (95% CI=0.12–0.29), a diagnostic odds ratio (DOR) of 42.64 (95% CI=24.35–74.67), and an area under the curve (AUC) of 0.93 (95% CI=0.91–0.95).[11]

Conversely, accuracy declined in solid organ transplant recipients and non-neutropenic ICU patients, mainly due to false-positive results caused by airway colonization, antibiotic cross-reactivity, or sample contamination, which reduced specificity.[9,10] Sensitivity is also generally lower in adults compared to children.[12]

Cut-off values strongly influence test performance. At thresholds of 0.5, 0.8, 1.0, 1.5, 2.0, and 3.0, the reported AUC values are 0.92, 0.86, 0.93, 0.89, 0.88, and 0.94, respectively. Although a cut-off of 3.0 yields the highest AUC (0.94), its sensitivity is notably low (35%), making it less suitable for screening. Conversely, a 0.5 cut-off offers a favorable sensitivity of 89%, significantly better than 78% at the 1.0 threshold, while maintaining comparable AUC values. This supports 0.5 as the most balanced and clinically practical threshold.[12,13]

Considerable heterogeneity exists across GM studies. For example, BALF collection techniques differ in lavage volume, fluid volume, and collection timing, all of which affect antigen detection and test reproducibility. Furthermore, the use of EORTC/MSG criteria that incorporate GM results in the case definition may introduce incorporation bias, making diagnostic accuracy appear higher than it actually is. Some studies address this limitation by restricting evaluation to “proven” cases without considering GM microbiological criteria or by applying double standards for comparison. However, such strategies have been inconsistently applied.[6,12,13,19] Additionally, shorter fever duration—reflecting early disease—and a high disease prevalence within the study population may further influence diagnostic accuracy.[13]

Alternative diagnostic tools were also developed to address the limitations of the GM test. Beta-D-glucan (BDG) assays offer a broader-spectrum marker, sensitive to multiple invasive fungal infections but less specific for Aspergillus, making them unsuitable for IPA diagnosis in isolation. Their diagnostic value increases when combined with the GM test, especially when either test yields borderline or conflicting results. Polymerase chain reaction (PCR) targeting Aspergillus DNA is often highly sensitive and, when used alongside the GM test and BDG assay, can substantially improve diagnostic accuracy. However, PCR performance is currently hampered by heterogeneity and the lack of standardized protocols across laboratories, which limits its standalone clinical reliability.[8,11]

Despite high accuracy in hematologic populations, the GM test shows lower performance in non-hematologic and non-neutropenic populations, particularly in ICU patients. In these settings, false positives due to airway colonization, antibiotic cross-reactivity, or contamination reduced diagnostic utility. Reported GM test sensitivity often falls below 70%, with specificities around 75–80% in ICU settings—substantially lower than in neutropenic, hematologic patients. These factors necessitate careful clinical and radiological correlation in non-hematologic patients. Contextual diagnostic tools, such as the AspICU scoring system, have been developed for ICU use but still require biomarker data to be interpreted in conjunction with clinical judgment and imaging. Thus, a multimodal approach—integrating multiple biomarkers (GM test, BDG, PCR), imaging, and clinical criteria—is essential for accurate diagnosis in this group.[1,12]

LIMITATION

This study is limited by the inclusion of only three studies, which reduces the strength and

generalizability of the findings. Potential publication bias may overestimate diagnostic accuracy, as studies with positive results are more likely to be published. Selection bias is also possible due to the predominance of hematology patients, limiting applicability to broader populations. Heterogeneity of varying cut-offs, specimen types, and prior antifungal therapy (as noted by Marr et al) further complicates interpretation. Future studies should use larger, multicenter cohorts, standardized protocols, and include unpublished data to minimize bias and improve evidence quality.

CONCLUSIONS

The GM test is a promising rapid diagnostic tool for suspected invasive pulmonary aspergillosis, allowing earlier and more accurate initiation of antifungal therapy. BALF specimens provide better sensitivity through direct sampling from the infection site, but their invasive collection limits use in critically ill patients. The serum GM test is a practical alternative with good specificity, particularly when repeated testing is employed. Further studies are needed to standardize assay cut-off values and interpretation to ensure consistent clinical application globally.

CONFLICT OF INTEREST

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