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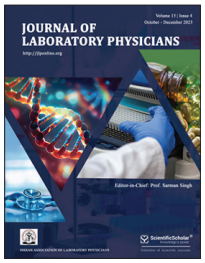
Journal of Laboratory Physicians

Article in Press



Original Article

Diagnostic performance of the newer automated chemiluminescence assay for fungal biomarkers in diagnosing invasive aspergillosis

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Received: 20 October 2024
Accepted: 03 April 2025
EPub Ahead of Print: 03 June 2025
Published:

DOI
10.25259/JLP_273_2024

Quick Response Code:

ABSTRACT

Objectives: The objective of this study was to study the performance of fully automated chemiluminescence immunoassay (FACIS) for fungal biomarkers to diagnose invasive aspergillosis (IA) and the associated confounding factors.

Materials and Methods: This prospective study was conducted in the Department of Microbiology over 1 year. Adult patients admitted with suspicion of IA, whose requisition for galactomannan (GM) assay received, were included. Appropriate samples of these patients were processed for microscopy and fungus culture as per standard methods. Serum GM assay and (1–3) β-d-glucan (BDG) assay were done as per kit literature on FACIS.

Statistical analysis: Statistical analyses were performed using the Statistical Package for the Social Sciences software version 21.0 on Microsoft Windows.

Results: A total of 1941 cases, predominantly males (64.8%) with a mean age of 55.7 ± 16.42 years were studied. Among the samples received, 25% were detected positive by GM assay and 34.7% by BDG assay. The cases were characterized as possible (25.2%) probable (10.2%), and proven (0.1%) as per European Organization for Research and Treatment of Cancer and Mycoses Study Group case definitions criteria. The sensitivity (51.9%, 62.9%) and specificity (77.1%, 87.8%) of the GM assay were determined considering culture and EORTC criteria as gold standard, respectively. The sensitivity of combined assays (GM and BDG) was higher as compared to GM alone. No significant association was observed between GM positivity and the confounding factors.

Conclusions: The study demonstrated that combined GM assay and BD assay are useful diagnostic modalities for IA. The FACIS is associated with fewer false-positive results.

Keywords: 1-3 β-d glucan, Culture, Fungus, Galactomannan, Invasive aspergillosis

INTRODUCTION

Fungal infections are increasing worldwide and the annual incidence of invasive aspergillosis (IA) in India is reported to be 17.9/lakh population.[1] IA is linked to significant mortality and morbidity, particularly in immunocompromised patients. The important risk factors associated are chronic steroid use, neutropenia, solid organ transplantation, and malignancy.[2,3] The primary pathogens causing aspergillosis include *Aspergillus fumigatus* (60–90%), *Aspergillus flavus, Aspergillus niger,* and *Aspergillus terreus.*[4,5]

The symptoms of IA are usually non-specific such as cough, fever, sputum production, hemoptysis, dyspnea, and pleuritic chest pain. Sometimes patients present with fever that does not respond to, or recurs despite, antibiotic treatment, the primary factors influencing survival are early diagnosis and timely treatment.[6]

The mainstay of diagnosis involves radiology which is non-specific, microbiological cultures associated with low positivity and long turnaround time, histopathology is invasive, and good samples are difficult to obtain. Nowadays, fungal biomarkers such as (1–3)-β-D-glucan (BDG) and galactomannan (GM) are available for faster diagnosis as they can be detected in blood before the clinical symptoms appear and help in the timely treatment of IA. These are non-invasive tests that provide results within hours, and can be used as prognostic markers also, though their use is limited due to high cost. GM assay is primarily used to detect IA. The cell wall of *Aspergillus* contains GM antigen, which is released into fluids and blood as the fungus invades the organs. GM test has been included in the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria for diagnosis of IA.[7]. The other marker BDG detects *Candida spp, Aspergillus* spp, and *Pneumocystis jirovecii*, but not the *Mucorales* and *Cryptococcus* spp.[8]

Various national and international studies have evaluated commercially available enzyme-linked immunosorbent assay (ELISA)-based methods (Platelia: Bio-Rad, France, Dynamiker Biotech: China) and various Lateral flow assays for GM antigen detection, while Fungitell (Associate of Cape Code, Falmouth, MA, USA) based on colorimetric method, Wako BDG assay (Wako Pure Chemical Industries, Osaka, Japan) based on turbidimetric, and Dynamiker BDG assay (Dynamiker Biotechnology Ltd, Tianjin, China) based on the spectrophotometric method have been evaluated for BDG assay.[9-11]

However, some confounding factors such as broad-spectrum antibiotics, other mold infections, immunoglobulins, dialysis, cellulose dressings, and breach in gastric mucosa have been reported as causes of false-positive results with these assays.[12]

Recently, a fully automated Chemiluminescence Immunoassay assay (FACIS, GenBio Pharmaceutical Co. Ltd, Tianjin, China) was commercially introduced to detect GM antigen and BDG where a single test can be performed and batch testing is not required. As the system is recently introduced literature is not available. The development and utilization of reliable tests to detect fungal biomarkers remain important in improving clinical decision-making and patient care. Hence, the study was planned to assess the performance of CLIA-based FungiXpert assay (GenBio Pharmaceuticals Co. Ltd, China) for detecting fungal biomarkers in high-risk patients of IA.

MATERIALS AND METHODS

This prospective study was conducted for 1 year from November 2022 in the Department of Microbiology, after the approval by the Ethical Committee of the Dayanand Medical College and Hospital, Ludhiana. Adult patients aged 18 years and above who were admitted with suspicion of IA, and their requisition for GM assay received in the microbiology department were included in the study.

Demographic and clinical details of the patients were recorded. Relevant clinical samples were collected and subjected to microscopy (potassium hydroxide [KOH] wet mount), fungal culture on Sabouraud dextrose agar (SDA), and GM and BDG assay. The cases were classified based on EORTC/MSG case definitions criteria as proven, probable, possible, and No IA cases using clinical, radiological, serological, and mycological findings.[13]

EORTC criteria

Host criteria: Patients with solid organ transplantation, prolonged corticosteroids or immunosuppressants use, immunodeficiency diseases, malignancy, and neutropenia

Clinical criteria: Presence of 1 of the following three signs on computed tomography.

(1) Dense, well-circumscribed lesion with or without a halo, (2) air-crescent sign and cavity, and (3) consolidation.

Mycological criteria: Positive microscopy or culture from a respiratory sample, positive GM antigen test or *Aspergillus* in serum or bronchoalveolar lavage, and cerebrospinal fluid.

Proven IA: Positive mycology (microscopy or culture) or histopathology of a sterile sample obtained in a sterile manner

Case definitions of IA as per EORTC criteria

Probable IA - One microbiological criterion, one host criterion, and clinical criteria

Possible IA - Host criteria, and presence of microbiological criteria, or clinical criteria.

KOH mount and fungal culture

Samples, including sputum, endotracheal secretions, and fluids such as bronchoalveolar lavage, bronchial brushings, pleural fluid, ascitic fluid, bile, drain fluid, and biopsy tissue were inoculated into two sets of SDA tubes, one containing cycloheximide and the other without cycloheximide. One set was incubated at 25°C while the other was incubated at 37°C.

The tubes were incubated for at least 3 weeks. During the 1st week, the tubes were examined daily, followed by alternate-day examinations in the 2nd and 3rd weeks. Any growth observed was identified based on colony morphology, microscopic examination using lactophenol cotton blue stain, and biochemical reactions.

GM Assay and (1-3) β-d glucan assay test was performed

The tests were performed on serum samples using FungiXpert® *Aspergillus* GM detection kit and Fungus 1–3 BDG detection kit (Genobio Pharmaceutical Co. Ltd., Tianjin, China) on the fully automated chemiluminescence immunoassay system (FACIS) system. The tests were performed as per kit protocol. Results were interpreted as index <0.5μg/L was negative and ≥ 0.5 μg/L was considered positive for GM antigen, While for BDG assay ≥ 0.1 ng/mL of serum concentration was considered positive, ≤ 0.06 ng/ml as negative, and any value in between these as indeterminate.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., Chicago, IL, USA) on Microsoft Windows. The data were summarized using the range, mean ± standard deviation, and, relevant, percentages and counts. The Chi-square test was used to compare categorical data, with the Fisher exact test applied when the expected frequency was below 5. The GM assay's sensitivity, specificity, predictive values, and diagnostic accuracy were calculated considering culture (method C) and EORTC criteria (Methods A and B) as the gold standard. In Method A, all cases (possible, probable, and proven) under EORTC criteria were considered true positives for IA. In Method B, the proven and probable categories were considered true positive and patients with No IA were true negative.

A receiver operating characteristic (ROC) curve was constructed, and the criterion value was determined based on the sensitivity and specificity of GM assay, calculated at various cutoffs by comparing with culture.

RESULTS

A total of 1941 samples were received from suspected IA cases for the GM assay test. Males were predominant (1257; 64.8%) and the maximum patients were from the age group of 51 to 70 years (853; 43.9%) with a mean age of 55.71 years ± 16.42 years [Table 1].

The majority were admitted in the wards (1517; 78.2%) with clinical manifestations as fever (994; 51.2%), followed by cough (992; 51.1%), dyspnea (586, 30.2%), and chest pain (315, 16.2%). The common risk factors were chronic steroid use and solid organ transplant which showed a significant association ($P < 0.05$) with GM positivity [Table 1].

Radiological findings were noted as reticulonodular opacifications (434; 22.4%), followed by consolidation (360; 18.5%), pleural effusion (340, 17.5%), and cavitation (94, 4.8%) in high-resolution computed tomography/chest X-ray. A significant association was seen between cavitation in radiological findings and GM positivity.

Out of 1941 samples, 485 (25%) serum samples were detected GM positive and received predominantly from male patients (64.8%). The 1-3 BGG assay and fungal culture/fungal smear from relevant samples were performed as per requisition [Figure 1]. Both fungal markers were detected positive in 11.6 % (154) patients. *Aspergillus* spp. isolation in various samples is shown in Table 2. Septate hyphae with acute angle branching were seen in two histopathological samples including lung tissue and kidney tissue [Figure 2]. Among the confounding factors studied, there was no significant association which was observed between the use of piperacillin and tazobactam, amoxicillin and clavulanic acid, and meropenem and dialysis with GM positivity but the use of piperacillin and tazobactam had shown significant association with 1-3 BDG positivity ($P < 0.05$), while antifungal usage showed a significant association with both the fungal biomarkers (1-3 BDG assay and GM assay) positivity. Patients with suspicion of IA were further categorized as Proven IA 2 (0.1%), Probable IA (199 [10.2%]), Possible IA (490 [25.2%]), and No IA (1450 [74.7%]) as per EORTC criteria.

The specificity and sensitivity of GM assay were calculated at various cutoffs considering fungal culture as the gold standard and ROC was plotted [Figure 3]. The area under the curve of 0.663 indicated the highest diagnostic accuracy. Specificity, sensitivity, negative predictive value, positive predictive value, and diagnostic accuracy of GM assay were calculated using different gold standards [Table 3]. Out of 1941 patients enrolled in our study, 71.0% were discharged satisfactorily whereas 4.7% of patients could not survive.

DISCUSSION

At present, there is a significant focus on detecting fungal biomarkers to enhance the accuracy of diagnosing invasive fungal infections. In this study, a total of 1941 suspected IA cases enrolled had an average age of t 55.71 years ± 16.42 with an age ranging from 18 to 98 years which was concordant with the observation made by Khorvash *et al*. in their study, where the average age of the patients was 54.95 ± 18.82 years, ranging from 20 to 86 years.[14] Similar to many other studies in our study, male predominance among suspected IA was observed.[15]

The commonest risk factor among these patients was chronic steroid use (26%), followed by alcohol consumption (7.3%)

Table 1: Demographic details of patients suspected of IA and GM-positive patients (*n*=1941).

	Suspected IA patients (*n*=1941) (%)	GM positive patients (485) (%)	*P*-value
Sex			
Males	1257 (64.8)	308 (63.5)	0.592
Females	684 (35.2)	177 (36.5)	
Age (years)			0.395
18–30	165 (8.5)	35 (7.2)	
31–40	248 (12.8)	62 (12.8)	
41–50	295 (15.2)	80 (16.5)	
51–60	406 (20.9)	113 (23.3)	
61–70	447 (23)	109 (22.5)	
>70	3801 (9.6)	86 (17.7)	
Mean age (years)	55.71±16.42	55.41	
Risk factors			
Chronic steroid use	523 (26.9)	257 (52.9)	0.001
Alcohol consumption	143 (7.3)	26 (53.6)	0.056
History of Tuberculosis	91 (4.6)	21 (4.3)	0.712
Solid organ Transplantation	73 (3.8)	36 (7.4)	0.001
Smoking	63 (3.2)	14 (2.8)	0.766
Neutropenia	30 (1.5)	10 (2.0)	0.292
HIV infection	10 (0.5)	2 (0.4)	0.715

IA: Invasive aspergillosis, GM: Galactomannan, HIV: Human immunodeficiency virus

Table 2: Sample-wise distribution of fungal isolates (*n*=1159).

Sample	*Aspergillus* spp. *n* (%)
Sputum (579)	36 (6.2)
Endotracheal secretions (311)	13 (4.1)
Bronchoalveolar lavage fluid (6)	0 (0)
Nasal mucosa (14)	3 (21.4)
Urine (34)	1 (3.2)
Tissue (11)	1 (9.0)
Pus (15)	0 (0)
Fluids (189)	0 (0)
Total (1159)	54 (4.6)

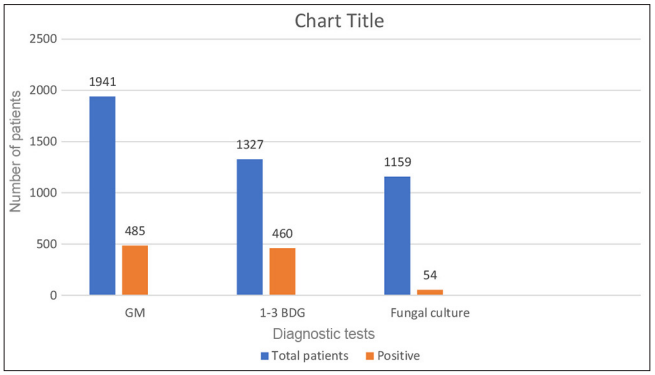

Figure 1: Distribution of samples in suspected cases of invasive aspergillosis and their positivity.

and solid organ transplantation (3.8%), and a significant association was seen between chronic steroid use and solid organ transplant. Likely, a study from the USA also reported steroid use (69%) as the most common risk factor followed by intensive care unit stay (56%), use of immunosuppressive agents (39%), solid organ transplant (33%), diabetes (28%), and mechanical ventilation (28%).[16] While, in a study by Herbrecht *et al.*, the majority of patients (63.2%) had hematological malignancies, followed by hematopoietic stem cell transplantation (21.3%).[17] Like our study, Meyer *et al.* also identified fever as the most frequent symptom in their research while the study conducted by Tutar *et al.* observed dyspnea as the most common clinical presentation.[18,19]

There is variability in radiological presentations of IA. In our study, reticulonodular opacification was the most common chest radiological finding, present in 22.40% of cases which were followed by consolidation at 18.50% and pleural effusion at 17.50% but in a previous study conducted at our institute on suspected cases of IA, 70% of the cases had consolidation.[12] A study by Huang *et al.*, also identified consolidation as the most common chest radiological finding, occurring in 23.8% of their cases.[20]

Table 3: Sensitivity, specificity, predictive values, and diagnostic accuracy of GM assay according to different estimates.

	Gold standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value (%)	Diagnostic accuracy (%)
Method A	EORTC criteria (Proven, Probable and Possible patients)	62.93	87.86	63.71	87.50	81.56
Method B	EORTC criteria (Probable and Proven patients)	93.97	82.99	38.72	99.18	84.12
Method C	Fungal culture	51.85	77.10	9.96	97.04	78.93
Cumulative (GM+1-3 BDG)	Fungal culture	66.67	60.54	7.63	97.38	60.83

GM: Galactomannan, BDG: β-d-glucan, EORTC: European organization for research and treatment of cancer

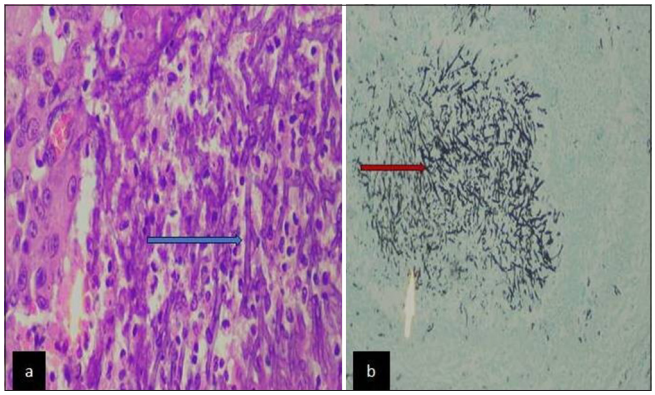

Figure 2: Specimen: Lung tissue from upper lobe. (a) Septate hyphae with acute angle branching (shown with blue arrow) and mixed inflammatory cells seen in Hematoxylin and eosin (H&E) stain, X40: (b) Septate fungal hyphae seen (shown with red arrow) in Gomori methenamine silver (GMS) stain x40.

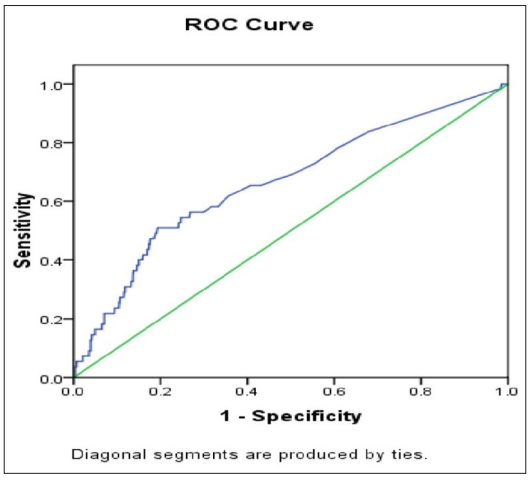

Figure 3: The AUC of 0.663 indicated the diagnostic accuracy. ROC: Reciever operating curve, AUC: Area under the curve.

In this study, lower GM positivity (25%) was observed as compared to a similar study conducted at our institute in 2018 using Platelia GM assay, which reported a 40.5% positivity rate among patients suspected of IA. Furthermore, a study from Delhi using serum and bronchoalveolar lavage samples reported 33.6% GM antigen positivity.[21] The increased positivity rate in these studies may be attributed to the manual ELISA methods used for GM detection. Hence, the possibility of a greater number of false positive results with that method. However, a research study from Brazil reported lower positivity where 19.2% GM positivity.[22]

BDG assay is included in EORTC criteria for diagnosis of invasive candidiasis. Hence, most of the studies of BDG assay are done for invasive candidiasis. In the present study, 34.7% of samples of suspected IA cases were detected positive by BDG assay. While another study reported (1-3)-BDG assay positivity rate of 70% by Fungitell assay.[23]

In our study, *Aspergillus* was grown in 4.6% samples only. Similarly, 7.3% *Aspergillus* culture positivity was observed by De Oliveira Cunha D *et al.*[22] However, few other studies have reported relatively higher culture positivity of 14–20%.[21,24] Possible factors attributed to variable culture positivity are empiric use of antifungals, contamination of cultures, quantity and quality of the samples, and incubation conditions.

According to the EORTC/MSG criteria, in our study, out of a total of 1941 suspected of invasive Aspergillosis, 0.10% was identified as proven IA, 10.20% as probable IA, 25% as possible IA, and 74.70% as no IA. A research study from All India Institute of Medical Sciences (AIIMS) Chhattisgarh observed 0.4% proven IA cases, 8.89% probable cases, and 3.81% possible cases.[24] However, A study from Brazil reported slightly higher proven IA cases (7.3%), followed by probable cases (6.4%) and possible cases (5.1%),[22]

Varied sensitivity and specificities of GM assay have been reported by many studies as they have used different methods (ELISA/LFA) gold standards (culture, EORTC criteria), and population (immunosuppressed, hematologic malignancies, etc.). In our study, sensitivity (62.93%) and specificity (87.86%), positive predictive value (63.71%), negative predictive value (87.50%), and diagnostic accuracy (81.56%)

of GM assay were calculated considering EORTC criteria as a gold standard. When only proven and probable cases were considered as reference standards, the sensitivity (93.97%) and diagnostic accuracy (84.12%) of the assay were increased. Similarly, a meta-analysis study reported a sensitivity of 76% and specificity of 92% of GM assay, considering proven/probable as standard and lower sensitivity (45%) if total (possible/probable/proven) cases were included in the study. A meta-analysis study by Pfeiffer *et al*. reported sensitivity (64%) and specificity (89%) using EORTC criteria.[25]

We have calculated the sensitivity (51.85%) and specificity (77.10%) of the GM assay with fungal culture as well. Also, a study on chronic pulmonary aspergillosis conducted at All India Institute of Medical Sciences, Raipur has reported sensitivity (77%) and specificity (78%) of Galactomannan Assay using fungal culture of sputum samples as standard.[24]

If BDG was used with GM assay for diagnosis of IA, the cumulative sensitivity (66.67%) of biomarkers was increased. Similarly, another meta-analysis study observed the improved sensitivity of combined biomarkers as compared to alone GM assay or BDG assay.[26]

The ROC curve was evaluated at different cutoff points to assess the test's performance. The area under the ROC curve (AUC), which indicates the diagnostic accuracy, was found to be 0.663. Similarly, a study from Delhi AIIMS reported an AUC of 0.636, while a study from South Korea observed the best diagnostic accuracy at 0.742.[27,28]

Furthermore, we observed very good negative predictive value (>97%) in both tests which further helped in ruling out IA. The same is reported by other research studies.[29]

Various studies have shown confounding factors associated with fungal markers' positivity. In our study, the use of piperacillin-tazobactam, amoxicillin-clavulanic acid, and meropenem did not show a significant association with the GM test results. In another study, a significant association was found between GM (Platelia) positivity and the administration of β-lactams in a past study from the same institute.[12] Several other studies have reported GM false-positive results in patients treated with piperacillin/tazobactam.[18] We found a significant association between piperacillin and tazobctam (PT) use and BDG positivity while a study on invasive fungal infections (IFI) using 1-3 beta D glucan (BDG) based on ELISA (Enzyme Linked Immunosorbent Assay) as a diagnosis method reported an association with PT use and dialysis.[29] From our experience with the recently introduced, chemiluminescence immunoassay-based system positivity of fungal markers is less affected by the reported confounding factors which further reduces the false positivity.

The limitation of this study was that samples for fungus culture and BDG tests were not obtained from all the patients and repeat tests were not received for follow-up as serial testing may increase the specificity.

CONCLUSIONS

IA is a major cause of morbidity and mortality in high-risk patients. The study indicated that fungal biomarkers are effective diagnostic modalities that provide rapid diagnosis of IA and help in timely treatment which further reduces morbidity and mortality combining both tests for the diagnosis of IA increases the sensitivity. The use of a CLIA-based automated system may reduce the impact of confounding factors and lead to fewer false-positive results.

Author contribution: S: Literature search, data collection, data analysis, statistical analysis, and manuscript preparation; JC: Study concept/design, literature search,data analysis, data interpretation, statistical analysis, manuscript preparation,editing, review and final approval; VG: Study concept, design, manuscript review; AS: Study concept, design, and manuscript review.

Ethical approval: The research/study was approved by the Institutional Review Board at Dayanand Medical College and Hospital, Ludhiana, Punjab, approva'l number DMCH/4/35-2021(8231), dated 15th October 2024.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The author confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Sabri, Chaudhary J, Gupta V, Singh A. Diagnostic performance of the newer automated chemiluminescence assay for fungal biomarkers in diagnosing invasive aspergillosis. J Lab Physicians. doi: 10.25259/JLP_273_2024