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Original Article

Comparison of diagnostic efficacy of galactomannan lateral flow assay vs enzyme immunoassay: importance of storage conditions

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Abstract

Introduction: Galactomannan antigen is a valuable biomarker for diagnosing invasive aspergillosis. Traditional methods, such as enzyme immunoassays (EIA), require batch sampling, whereas lateral flow assays (LFA) provide a simpler and faster diagnostic process. This study aimed to compare the diagnostic efficacy of both testing methods.

Methodology: This prospective case-control study involved 192 serum samples categorized according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG criteria). LFA were conducted following the manufacturer's instructions, utilizing a cube reader. Receiver operating characteristic (ROC) analysis was performed to determine the optimal LFA threshold, and concordance analysis was conducted for both assays.

Results: The indicated sensitivity and specificity of LFA at the recommended galactomannan index threshold (GMI $\geq$ 0.5) were 15.3% (9/59) and 99% (132/133), respectively. Post-ROC analysis at a threshold of 0.4 revealed an area under the curve (AUC) of 0.685, with sensitivity, specificity, positive predictive value, and negative predictive value at 18%, 99%, 91%, and 73%, respectively. Qualitative agreement between the tests, assessed using the Kappa statistic, indicated a very low degree of agreement (κ = 0.18). In contrast, quantitative agreement, evaluated through Kendall's W-test, demonstrated a very high degree of agreement (W = 0.84).

Conclusions: Despite previous literature suggesting the efficacy of LFA, our study found it unsuitable for screening due to its low sensitivity. We recommend exercising caution regarding the manufacturer's storage recommendations until further studies on sample storage conditions are conducted.

Key words: aspergillosis; *Aspergillus*; diagnosis; galactomannan; serum.

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Introduction

Invasive aspergillosis is life-threatening, particularly in critically ill patients and immunocompromised individuals, such as those with hematologic malignancies [1]. It has a mortality rate of 50% even with treatment, which can rise to 99% if left untreated [2]. Invasive aspergillosis is not a notifiable disease; therefore, determining its global burden is challenging. Data from over 120 countries indicate that more than 2.1 million people develop invasive aspergillosis each year, with a crude annual mortality rate of 85.2% [3]. The incidence of invasive aspergillosis in patients with hematologic malignancies who develop neutropenia due to prolonged chemotherapy or undergo bone marrow transplantation typically ranges from 6% to 16% [4].

The primary factors influencing survival in invasive aspergillosis are early diagnosis and the selection of appropriate antifungal therapy [5]. In an autopsy study of 893 intensive care unit patients, only 40% were diagnosed with antemortem aspergillosis [6]. Definitive diagnosis of invasive aspergillosis typically relies on culture and histopathology; however, obtaining these diagnostic tests can be challenging in patients with hematologic malignancies, particularly due to thrombocytopenia. Furthermore, waiting for the results of these tests in this vulnerable population can increase the risk of mortality. Consequently, there is a growing need for rapid diagnostic methods [7].

Galactomannan is a component of the fungal cell wall. In clinical practice, testing for galactomannan antigen is performed on serum and bronchoalveolar lavage (BAL) samples using the enzyme immunoassay (EIA) method [8]. However, EIA test results generally have a slow turnaround time [9]. The recent *Aspergillus* galactomannan lateral flow assay (LFA) developed by IMMY® (Oklahoma, USA) has accelerated the

diagnostic process, with sample preparation and testing taking approximately 45 minutes per patient [10].

The aim of this study was to compare the diagnostic efficacy of galactomannan antigen detection in invasive aspergillosis among patients with hematologic malignancies, utilizing both EIA and the newly developed LFA. The overall objective was to expedite the diagnostic process, initiate early treatment, and reduce the morbidity and mortality associated with invasive aspergillosis.

Methodology

Patient selection

Our study was conducted prospectively with patients admitted to the hematology clinic of a single-center university hospital between 1 March 2022 and 30 November 2022. The study included patients aged 18 years or older who were diagnosed with hematologic malignancies and who underwent routine preemptive screening for galactomannan antigen using the EIA.

The study evaluated patients diagnosed with the following hematologic malignancies: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), myelofibrosis, myelodysplastic syndrome (MDS), multiple myeloma (MM), and aplastic anemia.

The patients were categorized according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria (updated in 2020) for the diagnosis of invasive aspergillosis [11]. Those diagnosed through tissue biopsy samples were included in the proven invasive aspergillosis group. In the case of the probable invasive aspergillosis group, hematologic malignancy served as the host factor, thoracic computed tomography (CT) findings as the clinical criterion, and a serum galactomannan enzyme immunoassay (GM-EIA) > 1 as the mycological criterion. The possible invasive aspergillosis group included the previously defined host factor and clinical criterion but did not include a mycological criterion. This group was assessed in conjunction with the probable cases because the number of proven cases were limited in number. The patients in the control groups were randomly selected from those who did not meet the EORTC/MSG criteria. The galactomannan lateral flow assay (GM-LFA) was not utilized in defining these groups.

Examination procedure

The study was conducted as a prospective case-control study involving samples from 192 patients who were routinely examined for invasive fungal diseases. The samples were collected over a 9 month period. All patients hospitalized with malignancies in the hematology clinic underwent routine weekly serum galactomannan antigen testing using the EIA method (Dynamiker® Biotechnology, Tianjin, China) for preemptive management [12].

After analyzing galactomannan antigen in serum samples using the EIA method, the same samples were subsequently tested for galactomannan antigen using the LFA method (IMMY® Diagnostics, Oklahoma, USA) within 72 hours. Throughout this 72-hour period, the serum samples were stored in a refrigerator at 4 °C in accordance with the manufacturer's recommendations [10].

The serum samples designated for analysis using the IMMY® *Aspergillus* galactomannan lateral flow test were pre-treated in accordance with the manufacturer's instructions. Specifically, 300 µL of serum sample was added to a heat-resistant tube containing 100 µL of pretreatment buffer solution. The mixture was then heated in a heat block at 120 °C for 6 minutes and subsequently centrifuged at 10,000 rpm for 5 minutes. Following centrifugation, 80 µL of the supernatant was transferred to a second tube, and 40 µL of running buffer solution was added to complete the pre-treatment process, which took approximately 15 minutes. The prepared sample was then immersed in the lateral flow strip and incubated for 30 minutes. A cube reader developed by the manufacturer was used for quantitative interpretation of the test results. Overall, the entire testing process, including sample preparation, yielded results within a total timeframe of 45 minutes.

Parameters

The demographic, biochemical, and clinical parameters routinely assessed in patients were recorded retrospectively from hospital records. The parameters examined included demographic data (age and gender); hematological diagnosis; neutropenia status; antifungal prophylaxis and treatments, culture and pathology results; CT images and reports of the thorax or paranasal sinuses; and galactomannan antigen levels obtained using both EIA and LFA methods.

Statistical analysis

The mean or median values for continuous variables were presented as descriptive statistics, and the number (n) and percentage (%) values were

recorded for categorical variables. A 95% confidence interval was used for proportional data. The suitability of the numerical variables to the normal distribution was tested using the Shapiro–Wilk test. The independent groups t test was used for intergroup comparison of variables that fit the normal distribution. Mann-Whitney U and Kruskal-Wallis tests were used for variables that did not fit the normal distribution. The relationship between numerical variables was evaluated using Spearman's rank correlation test. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated using a 2×2 table for diagnostic evaluation. Receiver operating characteristic (ROC) analysis was performed to determine the optimum positivity rate for LFA. Kendall's W and kappa tests were used to assess compatibility between the two tests. SPSS 26 (IBM, Armonk, NY, USA) software was used for statistical analyses. The results were considered significant at $p < 0.05$.

Ethical approval

Approval for the research was granted by the Clinical Research Ethics Committee at Gaziantep University. The ethics committee approved the study on 23 February 2022, under decision number 2022/71.

Results

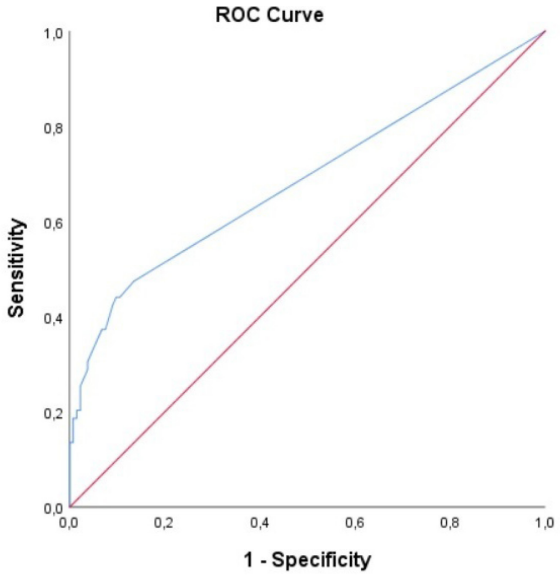
A total of 192 patients who met the inclusion criteria were included in the study. Among them, 112 (58.3%) were male and 80 (41.7%) were female. The mean age of the patients was 43.6 ± 18.2 years. When classified according to the EORTC/MSG criteria, two patients (1%) were defined as proven, 17 (8.9%) as probable, and 90 (46.9%) as possible invasive aspergilloses. 83 patients (43.2%) who did not meet the EORTC/MSG criteria were classified as the control group.

Galactomannan antigen positivity (GMI ≥ 0.5) was detected in 59 (30.7%) patients by EIA and in 10 (5.2%) patients by LFA. LFA positivity rate for proven or probable aspergillosis was 15.8% (3/19; 95% CI: 0–31.8), for possible invasive aspergillosis was 6.7% (6/90; 95% CI: 2.7–10), and for control group was 1.2% (1/83; 95% CI: 0–3.2) (Table 1).

As a gold standard test, sensitivity and specificity were analyzed using the Chi square test that included all patients and considered the threshold value of the GM-EIA test as 0.5 (Figure 1).

A positive and moderate correlation (r = 0.402, $p < 0.001$) was established between GM-EIA and GM-LFA according to the results of the Spearman's rank correlation test.

Figure 1. ROC curve of lateral flow test performance parameters (all patients).



Parameters	GMI (+) Threshold Value	
	0.4	0.5
Sensitivity (95% CI)	18% (9-27)	15% (6-24)
Specificity (95% CI)	99% (98-100)	99% (90-100)
Positive predictive value (95% CI)	91% (75-100)	90% (81-99)
Negative predictive value (95% CI)	73% (67-79)	72% (63-81)
Positive likelihood ratio	24.7	20.2
Negative likelihood ratio	0.81	0.85
The area under the curve	0.685 (0.596-0.774)	

CI: confidence interval; GMI: galactomannan index; ROC: receiver operating characteristic.

Table 1. Results of galactomannan antigen EIA and LFA.

	Proven/probable	Possible	Control
Population (n)	19	90	83
GM-EIA > 0.5 threshold (n/%)	19 (100%)	27 (30%)	13 (15.6%)
GM-EIA min	0.70	0.02	0.05
GM-EIA median	1.25	0.16	0.14
GM-EIA max	5.85	4.06	0.90
GM-LFA > 0.5 threshold (n/%)	3 (15.8%)	6 (6.7%)	1 (1.2%)
GM-LFA min	0.00	0.00	0.00
GM-LFA median	0.06	0.00	0.00
GM-LFA max	15.2	4.34	0.80

EIA: enzyme immunoassay; GM: galactomannan; LFA: lateral flow assay; max: maximum; min: minimum.

A high degree of agreement was determined in quantitative compatibility between the GM-EIA and GM-LFA (W = 0.84, $p = 0.000$), based on the results of Kendall's W test. When we examined the qualitative compatibility between GM-EIA and GM-LFA for a threshold value of 0.5, a low degree of compatibility was detected based on Cohen's kappa test (κ: 0.18, $p = 0.000$).

The characteristics of patients in the proven and probable group are presented in Table 2.

Discussion

In this study, we compared the diagnostic efficiency of the IMMY® *Aspergillus* galactomannan lateral flow test versus the galactomannan antigen test EIA (Dynamiker Biotechnology, Tianjin, China). Limited positive results were obtained with LFA in serum samples that were positive (GMI ≥ 0.5) for EIA. Only one serum sample was positive (GMI: 0.53) by LFA, but negative (GMI: 0.14) by EIA. All other positive LFA samples were also positive with EIA. The lower sensitivity of LFA compared to EIA suggests that LFA may not be suitable as a screening test for invasive aspergillosis.

The literature on this emerging diagnostic method is rapidly expanding. In a retrospective study conducted by White *et al*., serum samples from 132 patients, of which 32 were proven or probable cases, were analyzed using the LFA method. The study reported a sensitivity of 96.6% and a specificity of 98%. The AUC was 0.99, indicating successful diagnostic performance, with a threshold value of 0.5. Additionally, the study revealed a high agreement (κ = 0.69) between the LFA and EIA results, as assessed by Kappa statistics [13]. In a prospective study conducted by Mercier *et al.*, serum samples from 239 patients, of which 41 were proven or probable cases, were analyzed using the LFA method [14]. The study reported a sensitivity of 41%, specificity of 95%, and positive predictive value of 61%. AUC was 0.82, and at a threshold value of 0.5, the LFA method was determined to be a rapid and alternative approach for the detection of galactomannan [14]. In a prospective study conducted by Serin *et al.*, serum samples from 87 patients of which 11 were proven or probable cases, were analyzed using the LFA method [15]. The study reported a sensitivity of 90.9%, specificity of 90.8%, positive predictive value of 58.8%, negative predictive value of 98.6%. The AUC was 0.934. Based on a threshold value of 0.5, the study emphasized that the LFA method demonstrated strong diagnostic performance and can be effectively used in conjunction with other diagnostic tests [15]. In a prospective study conducted by Alhan *et al.*, serum samples from 171 patients of which 28 were proven or probable cases, were analyzed using the LFA method [16]. The sensitivity and specificity were 75% and 100%, respectively. AUC was 0.832, indicating successful diagnostic performance at a threshold value of 0.5. Additionally, the study found a moderate correlation ($p = 0.01$) and excellent agreement ($p < 0.001$) between the LFA and EIA methods [16]. A meta-analysis by Zhang *et al.* included BAL or serum samples from 2,838 patients in 19 studies in which the LFA method was applied [17]. The pooled sensitivity was 75%, and the pooled specificity was 87%. The positive likelihood ratio was 12.02, and the negative

Table 2. Proven and probable group patient characteristics.

Group	Culture	Lung biopsy	Thorax CT Findings	Malignancy	EIA	LFA
Proven	*Aspergillus*	*Aspergillus*	Normal	NHL	1.03	0.04
Proven	*Aspergillus*	*Aspergillus spp.*	Normal	AML	0.7	0
Probable	None	None	Nodule, tree in bud	Myelofibrozis	1.03	0.06
Probable	None	None	Nodule	ALL	1	0
Probable	Not detected	None	Consolidation	HL	3.9	0
Probable	None	None	Nodule, consolidation	NHL	1.06	0
Probable	None	None	Nodule	NHL	1.84	0.27
Probable	None	None	Nodule, consolidation	ALL	1.2	0
Probable	None	Mold	Nodule, consolidation	CLL	4.06	0.43
Probable	None	Mold	Nodule, consolidation	CLL	1.04	0.07
Probable	Not detected	None	Consolidation	AML	1.55	0.03
Probable	None	None	Nodule, consolidation	AML	1.17	0.19
Probable	None	Mold	Cavity, consolidation	CLL	1.08	0.07
Probable	Mold	Mold	Nodule, cavity	Aplastic anemia	1.58	0.06
Probable	None	None	Nodule	AML	3.8	1.28
Probable	Not detected	None	Cavity, nodule, consolidation	AML	1.68	0.43
Probable	Not detected	None	Nodule	HL	1.25	0
Probable	Not detected	None	Nodule, air-crescent, cavity, consolidation	AML	5.85	7.8
Probable	Not detected	None	Nodule, air-crescent, cavity, consolidation	AML	4.78	15.2

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BAL: bronchoalveolar lavage; CLL: chronic lymphocytic leukemia; CT: computer tomography; EIA: enzyme immunoassay; GM: galactomannan; HL: Hodgkin lymphoma; LFA: lateral flow assay; NHL: non-Hodgkin lymphoma; Tx: transplantation.

likelihood ratio was 0.27. AUC was 0.94, indicating that the LFA method was a useful diagnostic tool with a threshold value of 0.5 [17].

Our analyses of LFA and EIA demonstrated quantitative agreement but lacked qualitative concordance. As a result, we decided to adjust the threshold values of the tests. Despite modifications based on ROC analyses aimed at improving sensitivity and specificity, we were unable to achieve the desired sensitivity levels for screening purposes. Sensitivity increased only marginally from 15% to 18% even with a reduction of the threshold value to 0.4.

Since the test performance of not only proven or probable cases, but also possible cases and control groups is important, statistical analysis was conducted on the entire cohort. Although the number of possible cases in our study was substantial, these cases were not excluded from the analysis, as we believed that evaluating test performance across all groups would provide valuable insights.

In the aforementioned studies on the LFA, patient groups that did not receive antifungal treatment or prophylaxis were selected intentionally. However, it is important to note that in real life, these patient groups typically require antifungal treatment or prophylaxis in accordance with established guidelines [18]. Therefore, patients who received antifungal treatment or prophylaxis were not excluded from our study. This underscores the clear need for a rapid diagnostic test for early diagnosis, particularly given the real-world patient profiles in which such treatments are commonly administered.

Antifungal treatment or prophylaxis is commonly administered to patients with hematological malignancies, such as leukemia, who are at high risk of invasive aspergillosis during chemotherapy. Specifically, the use of mold-active treatment or prophylaxis significantly reduces the likelihood of galactomannan positivity [18]. In our study, potential confounding effects related to the use of antifungal therapy or prophylaxis were minimized by employing the same serum samples for both the EIA and LFA methods, which were analyzed simultaneously. Additionally, serum samples for the LFA were consistently evaluated by the same individual who conducted the tests using a cube reader. Quality control of the LFA kit was performed on a monthly basis using positive control samples. This ensured reliability and consistency of test performance. As a result, confounding factors associated with the LFA methodology were effectively mitigated.

When examining results that were inconsistent with the literature, we identified differences in storage conditions as a potential contributing factor. In many studies, the manufacturer's recommendation to store serum samples at 2–8°C for up to 5 days was not adhered to; instead, serum samples were preserved at – 70 °C or – 80 °C [13,19–22]. Consequently, we question the validity of the manufacturer's recommendation regarding 5-day storage at 2–8 °C. Therefore, comparative studies should be conducted to evaluate various storage conditions simultaneously, including storage at 2–8 °C, – 20° C, and – 80 °C. In a study by Hsiao *et al*., serum samples stored for 2 years were re-evaluated and compared using the EIA and lateral flow device (LFD) methods, revealing a decrease in positivity rates. Notably, when the LFD test was conducted 2–7 days after the EIA test, the agreement between the two methods significantly declined ($p < 0.05$). Consequently, it was determined that storage of serum samples for more than 2 days adversely affected the test results [23]. Given the similarities in the operating principles of the LFD and LFA methods, we believe that these results highlight the importance of storage conditions in our study.

The main limitation of our study was the inability to perform invasive diagnostic procedures in patients with hematological malignancies due to factors such as neutropenia, thrombocytopenia, high international normalized ratio (INR), and the unavailability of biopsy or culture results, which are considered gold standard tests. Consequently, while not a gold standard, the GM-EIA test was utilized as a reference in our study [24].

The EIA kit routinely used in our hospital is sourced from Dynamiker Biotechnology (Tianjin, China), while studies in the literature frequently utilize the Bio-Rad (California, USA) EIA kit [1,2,5,7,13,21]. It is important to note that different results may be obtained with different EIA kits. Additionally, it is crucial to acknowledge that EIA is not considered the gold standard diagnostic test for invasive aspergillosis.

Conclusions

Although LFA has been reported to be reliable or even superior to EIA in the literature, our study found LFA to be inappropriate for screening purposes due to its low sensitivity. It is advisable to refrain from adhering to the manufacturer’s recommendation of storing samples for 5 days at 2–8 °C until further studies on storage conditions are conducted.

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Conflict of interests
No conflict of interests is declared.

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