MAJOR ARTICLE

# Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis

**Christopher D. Pfeiffer,[1] Jason P. Fine,[2] and Nasia Safdar[1]**

Departments of [1]Medicine and [2]Biostatistics, University of Wisconsin Medical School, Madison, Wisconsin

**(See the editorial commentary by Rex on pages 1428–30)**

***Background.*** A double-sandwich enzyme-linked immunosorbent galactomannan assay has been approved for surveillance for invasive aspergillosis in immunocompromised patients. We undertook a meta-analysis to assess the accuracy of a galactomannan assay for diagnosing invasive aspergillosis.

***Methods.*** Studies of the galactomannan assay that used the European Organization for Research and Treatment of Cancer or similar criteria as a reference standard and provided data to calculate sensitivity and specificity were included. Pooled sensitivity and specificity and summary measures of accuracy, Q* (the upper left-most point on the summary receiver-operating characteristic curve), mean *D* (a log odds ratio), and Youden index were calculated. Subgroup analyses were performed to explore heterogeneity.

***Results.*** Twenty-seven studies from 1966 to 28 February 2005 were included. Overall, the galactomannan assay had a sensitivity of 0.71 (95% confidence interval [CI], 0.68–0.74) and specificity of 0.89 (95% CI, 0.88–0.90) for proven cases of invasive aspergillosis. The Youden index, mean *D,* and Q* were 0.54 (95% CI, 0.41–0.65), 2.74 (95% CI, 21.12–3.36), and 0.80 (95% CI, 0.74–0.86), respectively, indicating moderate accuracy. Subgroup analyses showed that the performance of the test differed by patient population and type of reference standard used. Significant heterogeneity was present.

***Conclusions.*** The galactomannan assay has moderate accuracy for diagnosis of invasive aspergillosis in immunocompromised patients. The test is more useful in patients who have hematological malignancy or who have undergone hematopoietic cell transplantation than in solid-organ transplant recipients. Further studies with attention to the impact of antifungal therapy, rigorous assessment of false-positive test results, and assessment of the utility of the test under nonsurveillance conditions are needed.

Invasive aspergillosis (IA) occurs in 8%–15% of patients undergoing allogeneic stem cell transplantation and in 5%–15% of patients undergoing solid-organ transplantation [1]. Despite advances in therapy, IA is associated with considerable morbidity and mortality, ranging from 30% to 70% in transplant recipients [2]. Diagnosis of IA is challenging, because clinical and radiologic signs are very insensitive or nonspecific. Tissue biopsy as a means of making the diagnosis is invasive and is not always possible, especially among patients with thrombocytopenia. Early diagnosis leading to prompt institution of appropriate therapy may result in improved patient outcomes.

Much attention has been focused on developing a noninvasive test for diagnosing IA, particularly methods to detect galactomannan [1]. Galactomannan is a polysaccharide cell-wall component that is released by aspergillus during growth. Initial diagnostic assays including latex agglutination (Pastorex *Aspergillus;* Sanofi Diagnostics Pasteur) had poor sensitivity. More recently, a double-sandwich ELISA that incorporates the B 1–5 glactofuranose–specific EBA2 monoclonal antibody as both the detector and acceptor for galactomannan showed a high sensitivity with a threshold of 0.5 ng/mL and has been approved by the US Food and Drug Administration for use with serum samples (Platelia; Bio-Rad). However, results of test performance have been variable, and a systematic analysis of the overall accuracy of the test for surveillance of IA in high-risk populations has not been undertaken.

The goal of this meta-analysis was to characterize

Received 8 November 2005; accepted 19 December 2005; electronically published 14 April 2006.

Presented in part: 43rd Annual Meeting of the Infectious Diseases Society of America, San Francisco, California, 6–9 October 2005 [abstract 284].

Reprints or correspondence: Dr. Nasia Safdar, University of Wisconsin Hospital and Clinics, H4/572 CSC, 600 Highland Ave., Madison, WI 53792 (ns2@medicine.wisc.edu).

**Clinical Infectious Diseases 2006; 42:1417–27**



1058-4838/2006/4210-0011$15.00

the clinical utility of the Platelia galactomannan assay for surveillance of IA in high-risk patient populations and to evaluate which variables affect its performance.

## METHODS

***Literature search.*** Two investigators (C.D.P., N.S.) independently searched the published English- and Spanish-language literature using the Medline, PubMed, Cumulative Index to Nursing and Allied Health, and Cochrane Collaboration databases from inception to February 2005. Search terms included "*Aspergillus,*" "Aspergillosis," "Platelia," "galactomannan," "diagnosis," and combinations of these 5 terms. Abstracts of meetings of the Infectious Diseases Society of America, Focus on Fungal Infections, and InterScience Conference on Antimicrobial Agents and Chemotherapy were also reviewed. References from recent published reviews [1, 3] and from included studies were also perused. Authors of the original studies were contacted for additional information if data needed to calculate sensitivity and specificity were not provided.

***Study selection criteria.*** We defined criteria for the inclusion of studies before reviewing specific reports. Studies of series of patients that used the European Organization of the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria or similar criteria for diagnosis of *Aspergillus* infection [4] (table 1) and that provided data to calculate both sensitivity and specificity were included. Case reports and review articles were excluded. If a study appeared to meet selection criteria but had a patient population that appeared to be the same as or to overlap with the patient population of a similar study [5, 6], we chose to include the larger of the studies [6]. Studies that provided data only on serum samples, rather than patients, were excluded. Studies evaluating the performance of the galactomannan assay on specimens other than serum samples were excluded, as were all studies that assessed the performance of galactomannan assays other than the Platelia assay.

***Data extraction.*** We used a standard form to extract data on relevant characteristics. The Standards for Reporting of Diagnostic Accuracy statement was used to assess study quality [7]. However, studies were not excluded on the basis of quality.

We evaluated studies for all of the following characteristics: description of the study population, type of study (prospective or retrospective), the use of EORTC/MSG diagnostic criteria as the reference standard for case definition versus other similar criteria, the number of case patients and control subjects, the number and frequency of serum samples obtained, cutoff values for definition of a positive Platelia test result, the blinding of investigators to results, prevalence of IA, sensitivity, specificity, the use of antifungal therapy during testing, and the presence of bias that may have influenced results, particularly incorporation bias (i.e., using a positive galactomannan test result as part of the diagnostic criteria for IA).

***Statistical analysis.*** We calculated pooled sensitivity and specificity with 95% CIs separately for proven IA and proven or probable IA. Cases of possible IA were considered to be negative for the purposes of analysis. Heterogeneity in the estimates of sensitivity and specificity was assessed using the Pearson $\chi^2$ test or Fisher's exact test.

To summarize the overall diagnostic ability of the tests, we computed the Youden index ($\text{sensitivity} + \text{specificity} - 1$) and $D$ for each study. The Youden index is a summary measure of accuracy incorporating both sensitivity and specificity. We averaged these measures across studies and computed 95% CIs based on these averages.

D is a log OR that is the ratio of the odds that a person who has IA will have a positive test result to the odds that a person who does not have IA will have a positive test result. To account for heterogeneity, we also fit a summary receiver-operating characteristic (ROC) curve using the methodology proposed by Moses et al. [8] by linear regression of $D$ on S. $D = \text{logit(TPR)} - \text{logit(FPR)}$, and $S = \text{logit(TPR)} + \text{logit(FPR)}$, where TPR is the true positive rate or sensitivity, and FPR is the false-positive rate or $1 - \text{specificity}$. With use of these results, we then calculated Q*, where sensitivity = specificity on the summary ROC curve, corresponding to the upper left-most point on the summary ROC, and a 95% CI for Q* [9]. The summary measure Q* has been advocated over area under the ROC curve, because it is meaningful in the ROC region of greatest interest [9]. The higher the values of the Youden index, $D$, and Q*, the greater the accuracy of the test.

Finally, we computed positive predictive value and negative predictive value on the basis of the pooled estimates of the sensitivity and specificity. With use of a range of prevalences of 0.05–0.20, as reported in the literature and summarized by Wheat et al. [3], we examined how positive predictive value and negative predictive value changed for prevalences of 0.05, 0.10, 0.15, and 0.20.

We explored the reasons for heterogeneity by performing subgroup analyses. We examined whether characteristics of the patient population (e.g., presence of hematological malignancy, receipt of solid-organ transplant, or receipt of bone marrow transplant) affected the diagnostic accuracy of the Platelia assay. We also studied the performance of the test relative to the reference standard by stratifying studies according to those that used the EORTC/MSG criteria versus those that used similar (but not identical) criteria. Analyses were stratified by age to estimate the performance of the test for children and adults. For each analysis, we compared summary statistics across subgroups using 1-way analysis of variance. All statistical analyses were performed using S-PLUS software (MathSoft).

**Table 1. European Organization of the Research and Treatment of Cancer/Mycoses Study Group criteria for diagnosis of invasive aspergillosis.**

| Diagnosis or type of diagnostic criteria | Criteria |
|---|---|
| Diagnosis | |
| Proven invasive FI | Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging); or positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes |
| Probable invasive FI | At least 1 host factor criterion; 1 microbiological criterion; and 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection |
| Possible invasive FI | At least 1 host factor criterion and 1 microbiological or 1 major (or 2 minor) clinical criteria from abnormal site consistent |
| Type of diagnostic criteria | |
| Host factors | Neutropenia (<500 neutrophils/$mm^3$ for >10 days); persistent fever for >96 h refractory to appropriate broad-spectrum antibacterial treatment in high-risk patients; body temperature either >38°C or <36°C and any of the following predisposing conditions: prolonged neutropenia (>10 days) in previous 60 days, recent or current use of significant immunosuppressive agents in previous 30 days, proven or probable invasive FI during previous episode of neutropenia, or coexistence of symptomatic AIDS; signs and symptoms indicating graft-versus-host disease, particularly severe (grade ⩾2) or chronic extensive disease; prolonged (>3 weeks) use of corticosteroids in previous 60 days |
| Microbiological | Positive result of culture for aspergillus from sputum or bronchoalveolar lavage fluid samples; positive result of culture or findings of cytologic/direct microscopic evaluation for *Aspergillus* species from sinus aspirate specimen; positive findings of cytologic/direct microscopic evaluation for aspergillus from sputum or bronchoalveolar lavage fluid samples; positive result for *Aspergillus* antigen in specimens of bronchoalveolar lavage fluid, CSF, or ⩾2 blood samples; positive findings of cytologic or direct microscopic examination for fungal elements in sterile body fluid samples |
| Clinical | Must be related to site of microbiological criteria and temporally related to current episode |
| LRTI | |
| Major | Any of the following new infiltrates on CT imaging: halo sign, air-crescent sign, or cavity within area of consolidation[a] |
| Minor | Symptoms of LRTI (cough, chest pain, hemoptysis, or dyspnea); physical finding of pleural rub; any new infiltrate not fulfilling major criterion; pleural effusion |
| Sinonasal infection | |
| Major | Suggestive radiological evidence of invasive infection in sinuses (i.e., erosion of sinus walls or extension of infection to neighboring structures, and extensive skull base destruction) |
| Minor | Upper respiratory symptoms (e.g., nasal discharge and stuffiness); nose ulceration or eschar of nasal mucosa or epistaxis; periorbital swelling; maxillary tenderness; black necrotic lesions or perforation of hard palate |
| CNS infection | |
| Major | Radiological evidence suggesting CNS infection (e.g., mastoiditis or other parameningeal foci, extradural empyema, intraparenchymal brain, or spinal cord mass lesion) |
| Minor | Focal neurological symptoms and signs (including focal seizures, hemiparesis, and cranial nerve palsies); mental changes; meningeal irritation findings; abnormalities in CSF biochemistry and cell count (provided that CSF is negative for other pathogens by culture or microscopy and negative for malignant cells) |
| Disseminated FI | Papular or nodular skin lesions without any other explanation; intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis |

**NOTE.** FI, fungal infection; LRTI, lower respiratory tract infection. Adapted from Ascioglu et al. [4].

[a] In the absence of infection by organisms that may lead to similar radiological findings including cavitation, such as *Mycobacterium, Legionella,* and *Nocardia* species.

## RESULTS

### Overall Analysis

We identified 139 studies from our literature search. Of these, 29 reports encompassing 27 studies met our inclusion criteria. Figure 1 shows the literature search leading to selection of the final 27 articles. Tables 2 and 3 show detailed characteristics of these studies. If the study included both children and adults but was stratified by age, data are presented separately for children and adults.

Fifteen studies included only adults as the population under study, 2 provided data on children separately, 7 included both children and adults, and 5 did not provide data. Six studies were limited to bone marrow transplant recipients, 3 were limited to solid-organ transplant recipients, and 17 were limited

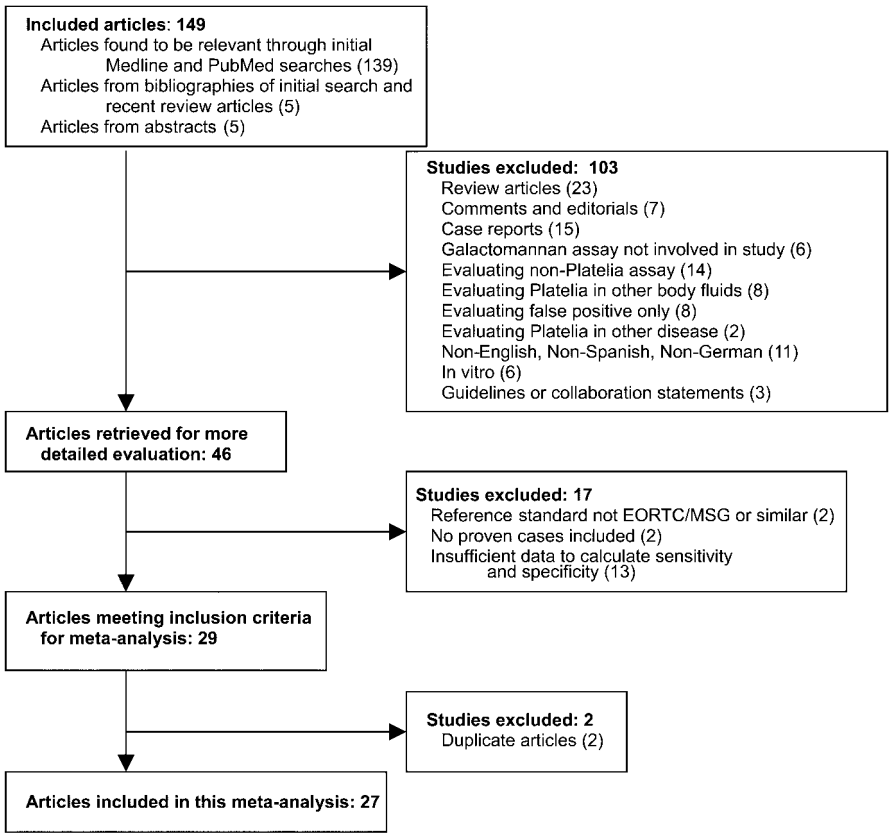


**Figure 1.** Summary of study assessment and inclusion in a meta-analysis of studies involving diagnosis of invasive aspergillosis using a galactomannan assay. EORTC, European Organization of the Research and Treatment of Cancer; MSG, Mycoses Study Group.

to patients with hematological malignancy. One study did not specify the population under study but mentioned that the patients were immunocompromised.

Five studies reported the threshold for positivity as 0.5, whereas 13 studies used a threshold of 1.0, and 11 studies used a threshold of 1.5. Four studies reported whether the assessment was done in a blinded manner, whereas that information was not reported in 3 studies, and blinding was not done in the remainder. Antifungal therapy was mentioned in 4 studies, but only 1 study analyzed the effect of prior or current antifungal therapy on the performance of the test.

Nineteen studies used the EORTC/MSG criteria, whereas 10 studies used criteria that were similar to but not identical with EORTC/MSG criteria. Most studies showed some degree of incorporation bias, because *Aspergillus* galactomannan forms part of the reference standard for diagnosing IA in the EORTC/MSG criteria. However, this was present only for the probable cases, because a positive galactomannan test result is not part of the EORTC/MSG criteria for proven IA.

The test was used for surveillance of IA in all of the included studies. The frequency of sampling ranged from once per week to twice per week. Twenty-six studies reported data separately for proven cases and probable cases of IA, whereas 3 studies provided data only on combined proven and probable cases of IA.

Table 4 shows the pooled sensitivity and specificity of the galactomannan assay overall and in the prespecified subgroups. Overall, the sensitivity of the test was 0.71 (95% CI, 0.68–0.74), and the specificity was 0.89 (95% CI, 0.88–0.90) for proven cases. For proven and probable cases, the sensitivity was 0.61 (95% CI, 0.59–0.63), and the specificity was 0.93 (95% CI, 0.92–0.94).

We found considerable heterogeneity among the studies ($P < .0001$). Summarizing across studies, for proven cases, the mean sensitivity was 0.73 (95% CI, 0.61–0.85), and the median sensitivity was 0.77 (interquartile range [IQR], 0.61–1.0). The mean specificity was 0.81 (95% CI, 0.76–0.87), and the median specificity was 0.81 (IQR, 0.72–0.93) for proven cases. For proven or probable cases, the mean sensitivity was 0.69 (95% CI, 0.59–0.79), and the median sensitivity was 0.69 (IQR, 0.52–0.87). The mean specificity was 0.89 (95% CI, 0.84–0.94), and the median specificity was 0.93 (IQR 0.81–0.97).

To summarize the overall diagnostic ability of the galactomannan test, we computed the Youden index, $D$, and Q*. The results are shown in table 5. The mean Youden index for proven cases was 0.54 (95% CI, 0.41–0.65), and the median Youden

**Table 2. Characteristics of studies included in the meta-analysis of diagnosis of invasive aspergillosis using a galactomannan assay.**

| Study | Year | Patient population | Age group | Study design | Purpose of study | Reference standard | Blinded | Threshold for positive test result[a] | No. of samples required for positivity | Antifungal therapy reported |
|---|---|---|---|---|---|---|---|---|---|---|
| Becker et al. [19] | 2003 | Patients with hematological malignancy | Adult | Prospective | Surveillance | EORTC/MSG | Yes | 1 | 2 | No |
| Platelia package insert [20] | 2003 | Patients with hematological malignancy | NR | Pospective | Surveillance | EORTC/MSG | Yes | 0.5 | 2 | No |
| Bretagne et al. [21] | 1997 | Patients with hematological malignancy | All | Prospective | Surveillance | Other | No | 1 | 2 | No |
| Bretagne et al. [22] | 1998 | Bone marrow transplant recipients | All | Retrospective | Surveillance | Other | No | 1 | 2 | No |
| Buchheidt et al. [23] | 2004 | Patients with hematological malignancy | Adult | Prospective | Surveillance | EORTC/MSG | No | 1.5 | 2 | No |
| Challier et al. [24] | 2004 | Immunocompromised | Adult | Prospective | Surveillance | EORTC/MSG | NR | 1 | 1 | No |
| Challier et al. [24] | 2004 | Immunocompromised | Pediatric | Prospective | Surveillance | EORTC/MSG | NR | 1 | 1 | No |
| Costa et al. [25] | 2002 | Patients with hematological malignancy | Adult | Retrospective | Surveillance | EORTC/MSG | No | 1.5 | 1 | No |
| Fortun et al. [26] | 2001 | Solid-organ transplant recipients | Adult | Retrospective | Surveillance | Other | Yes | 1 | 1 | No |
| Herbrecht et al. [27] | 2002 | Patients with hematological malignancy | All | Prospective | Surveillance | EORTC/MSG | No | 1.5 | 1 | No |
| Husain et al. [28] | 2004 | Solid-organ transplant recipients | Adult | Prospective | Surveillance | EORTC/MSG | No | 0.5 | 1 | No |
| Jarque et al. [29] | 2003 | Patients with hematological malignancy | Adult | Prospective | Surveillance | EORTC/MSG | NR | 1.5 | 2 | No |
| Kami et al. [30] | 2001 | Patients with hematological malignancy | Adult | Prospective | Surveillance | Other | Yes | 1.5 | 2 | No |
| Kwak et al. [31] | 2004 | Solid-organ transplant recipients | Adult | Prospective | Surveillance | EORTC/MSG | no | 0.5 | 2 | Yes |
| Machetti et al. [32] | 1998 | Bone marrow transplant recipients | NR | Prospective | Surveillance | Other | No | 1.5 | 2 | No |
| Maertens et al. [33] | 1999 | Patients with hematological malignancy | All | Prospective | Surveillance | Other | No | 1 | 2 | No |
| Maertens et al. [6] | 2002 | Bone marrow transplant recipients | Adult | Prospective | Surveillance | EORTC/MSG | No | 1 | 2 | No |
| Maertens et al. [34] | 2004 | Patients with hematological malignancy | Adult | Prospective | Surveillance | EORTC/MSG | Yes | 0.5 | 2 | No |
| Marr et al. [16] | 2004 | Patients with hematological malignancy | All | Prospective | Surveillance | EORTC/MSG | No | 1 | 1 | Yes |
| Moragues et al. [35] | 2003 | Patients with hematological malignancy | Adult | Retrospective | NR | EORTC/MSG | No | 1.5 | 2 | No |
| Pazos et al. [36] | 2003 | Patients with hematological malignancy | NR | Prospective | Surveillance | EORTC/MSG | NR | 1.5 | 2 | No |
| Pinel et al. [37] | 2003 | Patients with hematological malignancy | All | Pospective | Surveillance | EORTC/MSG | No | 1.0 | 2 | No |
| Rovira et al. [38] | 2004 | Bone marrow transplant recipients | Adult | Prospectivw | Surveillance | EORTC/MSG | NR | 1.5 | 1 | No |
| Suhalian et al. [39] | 2001 | Bone marrow transplant recipients | Adult | Prospective | Surveillance | Other | No | 1.5 | 1 | No |
| Sulahian et al. [40] | 1996 | Bone marrow transplant recipients | NR | Prospective | Surveillance | Other | Yes | 1 | 1 | No |
| Sulahian et al. [39] | 2001 | Patients with hematological malignancy | Pediatric | Prospective | Surveillance | Other | No | 1.5 | 2 | Yes |
| Ulusukarya et al. [41] | 2000 | Patients with hematological malignancy | All | Retrospective | Surveillance | Other | No | 1 | 1 | No |
| Verweij et al. [42] | 1995 | Patients with hematological malignancy | Adult | Retrospective | Surveillance | Other | No | 1 | 2 | No |
| Yoo et al. [43] | 2005 | Patients with hematological malignancy and bone marrow transplant recipients | Adult | Prospective | Surveillance | EORTC/MSG | NR | 0.5 | 2 | No |

**NOTE.** EORTC/MSG, European Organization of the Research and Treatment of Cancer/Mycoses Study Group; NR, not reported.

[a] Cutoff value for defining a positive test result.

**Table 3. Characteristics and results of studies included in the meta-analysis of diagnosis of invasive aspergillosis using a galactomannan assay.**

| Study | Date | Proven cases | Probable cases | Proven cases | | | | | | | Proven or probable cases | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Prevalence | TP | FN | FP | TN | Sensitivity | Specificity | TP | FN | FP | TN | Sensitivity | Specificity |
| Becker et al. [19] | 2003 | 2 | 11 | 0.02 | 1 | 1 | 17 | 68 | 0.50 | 0.80 | 6 | 7 | 12 | 62 | 0.46 | 0.84 |
| Platelia package insert [20] | 2003 | NR | NR | … | NR | NR | NR | NR | … | … | 25 | 6 | 16 | 132 | 0.81 | 0.89 |
| Bretagne et al. [21] | 1997 | 3 | 3 | 0.06 | 3 | 0 | 13 | 34 | 1.00 | 0.72 | 6 | 0 | 10 | 34 | 1.00 | 0.77 |
| Bretagne et al. [22] | 1998 | 6 | 12 | 14.63 | 6 | 0 | 13 | 22 | 1.00 | 0.63 | 14 | 4 | 5 | 18 | 0.78 | 0.78 |
| Buchheidt et al. [23] | 2004 | 6 | 3 | 3.39 | 1 | 5 | 3 | 168 | 0.17 | 0.98 | 3 | 6 | 1 | 167 | 0.33 | 0.99 |
| Challier et al. [24] | 2004 | 3 | 11 | 7.89 | 2 | 1 | 8 | 27 | 0.67 | 0.77 | 9 | 5 | 1 | 23 | 0.64 | 0.96 |
| Challier et al. [24] | 2004 | 4 | 8 | 12.5 | 3 | 1 | 16 | 12 | 0.75 | 0.43 | 11 | 1 | 8 | 12 | 0.92 | 0.60 |
| Costa et al. [25] | 2002 | 4 | 16 | 13.33 | 4 | 0 | 16 | 10 | 1.00 | 0.38 | 20 | 0 | 0 | 10 | 1.00 | 1.00 |
| Fortun et al. [26] | 2001 | NR | NR | … | NR | NR | NR | NR | … | … | 5 | 4 | 2 | 31 | 0.56 | 0.94 |
| Herbrecht et al. [27] | 2002 | 31 | 67 | 4.25 | 20 | 11 | 62 | 704 | 0.65 | 0.92 | 31 | 67 | 51 | 648 | 0.32 | 0.93 |
| Husain et al. [28] | 2004 | 9 | 3 | 12.85 | 2 | 7 | 14 | 47 | 0.22 | 0.77 | 3 | 9 | 15 | 46 | 0.25 | 0.75 |
| Jarque et al. [29] | 2003 | NR | NR | … | NR | NR | NR | NR | … | … | 8 | 4 | 3 | 85 | 0.67 | 0.97 |
| Kami et al. [30] | 2001 | 33 | 0 | 27.04 | 19 | 14 | 3 | 86 | 0.58 | 0.97 | NR | NR | NR | NR | NR | NR |
| Kwak et al. [31] | 2004 | 0 | 1 | 0.0 | 0 | 0 | 21 | 133 | … | 0.86 | 1 | 0 | 20 | 133 | 1.00 | 0.87 |
| Machetti et al. [32] | 1998 | 1 | 3 | 4.54 | 1 | 0 | 5 | 16 | 1.00 | 0.76 | 3 | 1 | 3 | 15 | 0.75 | 0.83 |
| Maertens et al. [33] | 1999 | 27 | NR | 14.51 | 25 | 2 | 2 | 42 | 0.93 | 0.95 | NR | NR | NR | NR | NR | NR |
| Maertens et al. [6] | 2002 | 5 | 8 | 5.00 | 5 | 0 | 13 | 82 | 1.00 | 0.86 | 11 | 2 | 7 | 82 | 0.85 | 0.92 |
| Maertens et al. [34] | 2004 | 16 | 13 | 15.38 | NR | NR | NR | NR | … | … | 28 | 1 | 2 | 93 | 0.97 | 0.98 |
| Marr et al. [16] | 2004 | 13 | 11 | 19.40 | 8 | 5 | 16 | 38 | 0.62 | 0.70 | 13 | 11 | 11 | 32 | 0.54 | 0.74 |
| Moragues et al. [35] | 2003 | 3 | 1 | 5.55 | 2 | 1 | 1 | 50 | 0.67 | 0.98 | 2 | 2 | 1 | 49 | 0.50 | 0.98 |
| Pazos et al. [36] | 2003 | 5 | 3 | 3.24 | 5 | 0 | 5 | 144 | 1.00 | 0.97 | 7 | 1 | 3 | 143 | 0.88 | 0.98 |
| Pinel et al. [37] | 2003 | 3 | 31 | 0.37 | 0 | 3 | 34 | 770 | 0.0 | 0.96 | 17 | 17 | 17 | 756 | 0.50 | 0.98 |
| Rovira et al. [38] | 2004 | 1 | 5 | 1.31 | 1 | 0 | 5 | 68 | 1.00 | 0.93 | 4 | 2 | 2 | 66 | 0.67 | 0.97 |
| Suhalian et al. [39] | 2001 | 22 | 22 | 4.88 | 17 | 5 | 32 | 396 | 0.77 | 0.93 | NR | NR | NR | NR | NR | NR |
| Sulahian et al. [40] | 1996 | 25 | NR | 11.52 | 19 | 6 | 53 | 138 | 0.76 | 0.72 | NR | NR | NR | NR | NR | NR |
| Sulahian et al. [39] | 2001 | 5 | 4 | 1.44 | 5 | 0 | 38 | 304 | 1.00 | 0.89 | NR | NR | NR | NR | NR | NR |
| Ulusukarya et al. [41] | 2000 | 10 | 6 | 7.40 | 8 | 2 | 9 | 116 | 0.80 | 0.93 | 11 | 5 | 6 | 113 | 0.69 | 0.95 |
| Verweij et al. [42] | 1995 | 6 | 0 | 0.09 | 5 | 1 | 19 | 36 | 0.83 | 0.65 | NR | NR | NR | NR | NR | NR |
| Yoo et al. [43] | 2005 | 2 | 12 | 1.56 | 1 | 1 | 36 | 90 | 0.50 | 0.71 | 12 | 2 | 25 | 89 | 0.86 | 0.78 |
| Overall | | … | … | … | 163 | 66 | 454 | 3601 | … | … | 250 | 157 | 221 | 2839 | … | … |

**NOTE.** FN, no. of cases with false-negative result; FP, no. of cases with false-positive result; NR, not reported; TN, no. of cases with true-negative result; TP, no. of cases with true-positive result.

**Table 4. Pooled sensitivity and specificity of the galactomannan assay for diagnosis of invasive aspergillosis (IA).**

| Studies | Cases of proven IA | | | | Cases of proven or probable IA | | | |
|---|---|---|---|---|---|---|---|---|
| | TP/(TP + FP) | Pooled sensitivity (95% CI) | TN/(TN + FP) | Pooled specificity (95% CI) | TP/(TP + FN) | Pooled sensitivity (95% CI) | TN/(TN + FP) | Pooled specificity (95% CI) |
| All | 163/229 | 0.71 (0.68–0.74) | 3601/4055 | 0.89 (0.88–0.90) | 250/407 | 0.61 (0.59–0.63) | 2839/3060 | 0.93 (0.92–0.94) |
| Studies limited to patients with hematological malignancy | 106/152 | 0.70 (0.62–0.77) | 2570/2808 | 0.92 (0.90–0.93) | 177/304 | 0.58 (0.52–0.64) | 2324/2457 | 0.95 (0.94–0.96) |
| Studies limited to patients undergoing BMT | 49/60 | 0.82 (0.70–0.90) | 722/843 | 0.86 (0.83–0.88) | 32/49 | 0.65 (0.60–0.78) | 17/26 | 0.65 (0.44–0.83) |
| Studies limited to solid-organ transplant recipients | 2/9 | 0.22 (0.03–0.60) | 180/215 | 0.84 (0.78–0.88) | 9/22 | 0.41 (0.21–0.64) | 210/247 | 0.85 (0.80–0.89) |
| Studies using EORTC/MSG criteria | 74/116 | 0.64 (0.54–0.73) | 2549/2869 | 0.89 (0.88–0.90) | 211/354 | 0.60 (0.54–0.65) | 2628/2823 | 0.93 (0.92–0.94) |
| Studies not using EORTC/MSG criteria | 89/113 | 0.79 (0.70–0.86) | 1052/1186 | 0.89 (0.87–0.90) | 39/53 | 0.74 (0.60–0.85) | 211/237 | 0.89 (0.84–0.93) |
| Studies involving pediatric population only | 8/9 | 0.89 (0.51–1.00) | 316/370 | 0.85 (0.85–0.89) | 11/12 | 0.92 (0.82–1.00) | 12/20 | 0.60 (0.36–0.81) |
| Studies involving adult population only | 58/93 | 0.62 (0.52–0.72) | 1211/1398 | 0.87 (0.85–0.88) | 102/140 | 0.73 (.46-.61) | 802/889 | 0.90 (.88–0.92) |
| Studies of both pediatric and adult populations | 70/93 | 0.75 (0.65–0.84) | 1726/1875 | 0.92 (0.91–0.93) | 92/196 | 0.47 (0.40–0.54) | 1601/1701 | 0.94 (0.93–0.95) |
| Studies using a cutoff value of 0.5 for defining positivity | 3/11 | 0.27 (0.06–0.61) | 27/341 | 0.79 (0.74–0.83) | 69/87 | 0.79 (0.69–0.87) | 493/571 | 0.86 (0.83–0.89) |
| Studies using a cutoff value of 1.0 for defining positivity | 85/107 | 0.79 (0.71–0.87) | 1385/1598 | 0.87 (0.85–0.88) | 103/159 | 0.65 (0.57–0.72) | 1163/1242 | 0.94 (0.92–0.95) |
| Studies using a cutoff value of 1.5 for defining positivity | 75/111 | 0.68 (0.58–0.76) | 1946/2116 | 0.92 (0.91–0.93) | 78/161 | 0.48 (0.41–0.56) | 1183/1247 | 0.95 (0.93–0.96) |

**NOTE.** BMT, bone marrow transplantation; EORTC/MSG, European Organization of the Research and Treatment of Cancer/Mycoses Study Group; FN, no. of cases with false-negative result; FP, no. of cases with false-positive result; TN, no. of cases with true-negative result; TP, no. of cases with true-positive result.

index was 0.55 (IQR, 0.31–0.74). For proven or probable cases, the mean Youden index was 0.57 (95% CI, 0.47–0.67), and the median Youden index was 0.60 (IQR, 0.48–.073). For proven cases, the mean *D* was 2.74 (95% CI, 2.12–3.36), and the median *D* was 2.59 (IQR, 1.55–3.79). For proven or probable cases, the mean *D* was 2.49 (95% CI, 1.81–3.17) and the median *D* was 2.76 (IQR 0.02–3.82). The values of the Youden index, *D,* and Q* are consistent with moderate accuracy of the test.

The Q* estimate was 0.80 (95% CI, 0.74–0.86) for proven cases and 0.85 (95% CI, 0.79–0.91) for proven or probable cases. A summary ROC plot, summarizing the performance of the galactomannan test for patients with proven cases and patients with proven or probable cases, is shown in figure 2.

The positive and negative predictive values across a range of prevalences are shown in table 6. As expected, the positive predictive value increased as prevalence increased for both proven cases and proven or probable cases. Negative predictive values were very similar for proven cases and proven or probable cases, whereas positive predictive value appeared to be somewhat higher for proven or probable cases than it was for proven cases alone.

### Subgroup Analyses of Proven Cases

***Underlying disease.*** The sensitivity and specificity of the test for patients with hematological malignancy was 0.70 (95% CI, 0.62–0.77) and 0.92 (95% CI, 0.90–0.93), respectively. The mean Youden index, *D,* and Q* were 0.54, 3.13, and 0.83, respectively. For bone marrow transplant recipients, the sensitivity and specificity were 0.82 (95% CI, 0.70–0.90) and 0.86 (95% CI, 0.83–0.88), respectively. The mean Youden index, *D,* and Q* were 0.73, 3.02, and 0.82, respectively. For recipients of solid-organ transplants, the sensitivity and specificity of the test were 0.22 (95% CI, 0.03–0.60) and 0.84 (95% CI, 0.78–0.88), respectively. The limited numbers of studies precluded robust estimates of overall accuracy. The results of the test for heterogeneity were statistically significant. Overall, the performance of the test varied by type of transplantation, with a much poorer performance among solid-organ transplant recipients, compared with among bone marrow transplant recipients or patients with hematological malignancy.

***Choice of reference standard.*** When stratifying by reference standard, we found that, when analyses were limited to studies using EORTC/MSG criteria, the sensitivity and specificity of the test were 0.64 (95% CI, 0.54–0.73) and 0.89 (95% CI, 0.88–0.90), respectively. Studies not using the EORTC/MSG criteria found that the sensitivity and specificity of the galactomannan assay were 0.79 (95% CI, 0.70–0.86) and 0.89 (95% CI, 0.87–0.90), respectively. The mean Youden index, *D,* and Q* values were 0.43, 2.30, and 0.75, respectively, in studies using the EORTC/MSG criteria. The mean Youden index, *D,*

**Table 5. Summary measures of accuracy and and subgroup analyses for the galactomannan assay for diagnosis of invasive aspergillosis, compared with reference standard.**

| Proven cases or proven and probable cases, studies | Youden index | | | D value | | | Q* value (95% CI) |
|---|---|---|---|---|---|---|---|
| | Mean (95% CI) | SD | Median (IQR) | Mean (95% CI) | SD | Median (IQR) | |
| Proven cases of IA | | | | | | | |
| All | 0.54 (0.41–0.65) | 0.30 | 0.55 (0.31–0.74) | 2.74 (2.12–3.36) | 1.51 | 2.59 (1.55–3.79) | 0.80 (0.74–0.86) |
| Studies limited to patients with hematological malignancy | 0.54 (0.38–0.70) | 0.29 | 0.55 (0.34–0.73) | 3.13 (2.31–3.95) | 1.53 | 2.89 (1.77–4.27) | 0.83 (0.75–0.91) |
| Studies limited to patients undergoing BMT | 0.73 (0.61–0.87) | 0.16 | 0.73 (0.65–0.84) | 3.02 (2.29–3.75) | 0.90 | 3.16 (2.33–3.63) | 0.82 (0.76–0.88) |
| Studies using EORTC/MSG criteria | 0.43 (0.26–0.60) | 0.32 | 0.38 (0.20–0.61) | 2.30 (2.19–3.11) | 1.57 | 1.91 (1.33–3.17) | 0.75 (0.65–0.85) |
| Studies not using EORTC/MSG criteria | 0.70 (0.61–0.79) | 0.14 | 0.72 (0.63–0.76) | 3.46 (2.70–4.22) | 1.14 | 3.66 (2.75–3.94) | 0.83 (0.79–0.87) |
| Studies limited to pediatric population | 0.54 (−0.17 to 1.25) | 0.50 | 0.54 (0.36–0.71) | 2.60 (−0.99 to 6.19) | 2.54 | 2.60 (1.70–3.48) | 0.76 (0.66–0.84) |
| Studies of adults | 0.45 (0.28–0.62) | 0.29 | 0.44 (0.26–0.62) | 2.30 (1.52–3.08) | 1.31 | 2.25 (1.50–3.28) | 0.83 (0.75–0.91) |
| Studies of both pediatric and adult populations | 0.54 (0.31–0.77) | 0.31 | 0.63 (0.44–0.73) | 3.00 (1.88–4.12) | 1.48 | 3.01 (2.04–3.49) | NA |
| Studies using a cutoff of 0.5 for defining positivity | 0.10 (−0.12 to 0.32) | 0.16 | 0.10 (0.04–0.16) | 0.50 (−0.32 to 1.32) | 0.58 | 0.50 (0.29–0.70) | 0.67 (NA) |
| Studies using a cutoff of 1.0 for defining positivity | 0.50 (0.34–0.66) | 0.28 | 0.48 (0.31–0.72) | 2.42 (1.55–3.28) | 1.50 | 1.99 (1.34–3.24) | 0.78 (0.71–0.85) |
| Studies using a cutoff of 1.5 for defining positivity | 0.65 (0.49–0.81) | 0.26 | 0.67 (0.54–0.85) | 3.44 (2.49–4.39) | 1.50 | 3.56 (2.68–3.93) | 0.84 (0.78–0.90) |
| Proven or probable cases of IA | | | | | | | |
| All | 0.54 (0.41–0.65) | 0.30 | 0.55 (0.31–0.74) | 2.74 (2.12–3.36) | 1.51 | 2.59 (1.55–3.79) | 0.85 (0.79–0.91) |
| Studies limited to patients with hematological malignancy | 0.59 (0.44–0.73) | 0.26 | 0.63 (0.58–0.67) | 3.95 (2.93–4.97) | 1.83 | 3.79 (3.53–4.43) | 0.89 (0.83–0.94) |
| Studies limited to patients undergoing BMT | 0.64 (0.55–0.73) | 0.09 | 0.61 (0.58–0.67) | 3.40 (2.5–4.3) | 0.90 | 3.94(2.66–4.17) | 0.81 (0.75–0.87) |
| Studies limited to patients undergoing SOT | 0.46 (−0.04 to 0.96) | 0.43 | 0.49 (0.25–0.68) | 1.86 (0.01–3.70) | 1.60 | 2.59 (1.31–2.78) | 0.76 (0.34–1.00) |
| Studies using EORTC/MSG criteria | 0.57 (0.44–0.70) | 0.27 | 0.62 (0.37–0.75) | 3.57 (2.40–4.44) | 1.83 | 3.76 (2.84–4.18) | 0.86 (0.78–0.94) |
| Studies not using EORTC/MSG criteria | 0.61 (0.52–0.70) | 0.10 | 0.58 (0.56–0.64) | 3.12 (2.61–3.62) | 0.56 | 2.96 (2.71–3.71) | 0.83 (0.79–0.87) |
| Studies limited to pediatric population | 0.52 (NA) | NA | 0.52 (NA) | 2.80 (NA) | NA | 2.80 (NA) | 0.89 (0.81–0.97) |
| Studies of adults | 0.59 (0.41–0.77) | 0.30 | 0.64 (0.41–0.82) | 3.68 (2.44–4.92) | 2.06 | 3.72 (2.78–4.31) | 0.80 (0.70–0.90) |
| Studies of both pediatric and adult populations | 0.50 (0.34–0.66) | 0.20 | 0.52 (0.33–0.62) | 2.80 (1.89–3.71) | 1.11 | 3.12 (1.96–3.72) | NA |
| Studies using a cutoff of 0.5 for defining positivity | 0.63 (0.30–0.96) | 0.37 | 0.69 (0.64–0.87) | 3.19 (1.12–5.25) | 2.30 | 2.97 (2.86–3.45) | 0.89 (0.75–1.00) |
| Studies using a cutoff of 1.0 for defining positivity | 0.54 (0.43–0.64) | 0.17 | 0.54 (0.48–0.63) | 2.85 (2.23–3.46) | 0.97 | 3.02 (2.39–3.32) | 0.80 (0.74–0.86) |
| Studies using a cutoff of 1.5 for defining positivity | 0.59 (0.41–0.77) | 0.25 | 0.61 (0.44–0.69) | 3.93 (2.81–5.05) | 1.58 | 3.85 (3.21–4.40) | 0.92 (0.85–0.99) |

**NOTE.** For definition of Youden index, *D* value, and Q* value, see Methods. BMT, bone marrow transplantation; IQR, interquartile range; NA, not available.

and Q* values were 0.70, 3.46, and 0.84, respectively, in studies not using EORTC/MSG criteria. Differences in the accuracy of the galactomannan assay when stratified by type of reference standard were statistically significant ($P = .007$ for Youden index and $P = 0.049$ for *D*).

***Age.*** When analyses were restricted to studies including only adults, the sensitivity was 0.62 (95% CI, 0.52–0.72), and the specificity was 0.87 (95% CI, 0.85–0.88). The mean Youden, *D,* and Q* for studies of adults was 0.45, 2.30, and 0.83, respectively. For studies providing data on children, the sensitivity was 0.89 (95% CI, 0.51–1.00), and the specificity was 0.85 (95% CI, 0.85–0.89). The results of the test for heterogeneity were significant. The mean Youden, *D*, and Q* values were 0.54, 2.60, and 0.76, respectively. The number of studies providing data for children was far fewer (2 studies) than the number of studies providing data for adults.

***Choice of cutoff values for defining positivity.*** Analyses stratified by 3 cutoff definitions for positivity (0.5, 1.0, and 1.5)

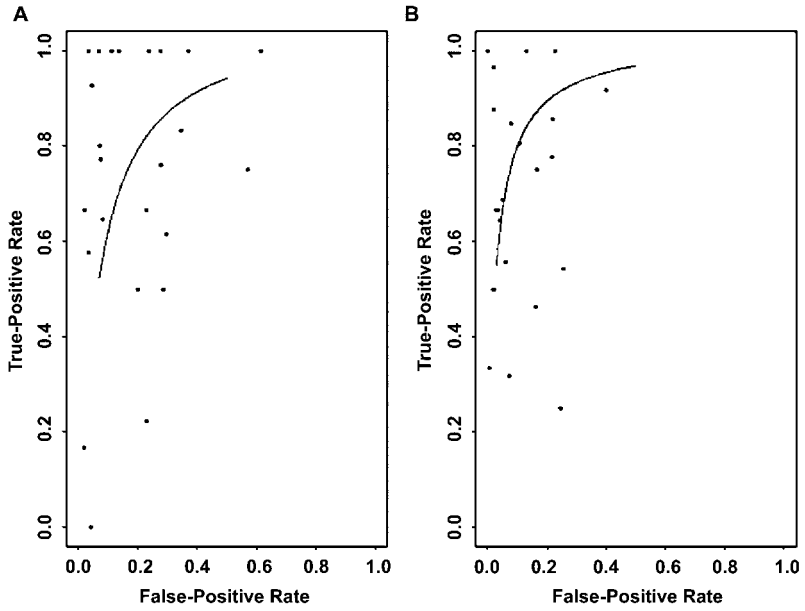


**Figure 2.** Summary receiver-operating characteristic curve for the galactomannan assay (Platelia; Bio-Rad), compared with reference standard, for proven cases of invasive aspergillosis *(A)* and both proven or probable cases of invasive aspergillosis *(B)*. Each dot represents a study.

showed that, overall, the accuracy of the galactomannan test improved with a higher threshold. However, the differences were statistically significant only for the $D$ values ($P = .016$).

***Proven or probable cases.*** The performance of the galactomannan test when probable cases were included with proven cases for the analyses is shown in tables 4 and 5. Overall, the results were not markedly different, comparing with those obtained for proven cases alone.

## DISCUSSION

IA is a leading cause of death among immunocompromised patients, especially among those patients with hematological malignancy or those who undergo hematological or solid-organ transplantation [10–12]. Clinical and radiologic diagnosis of IA has limited sensitivity and specificity [13]. In patients with thrombocytopenia, a tissue diagnosis carries the risk of bleeding and is usually not advisable.

The use of a biological marker as an adjunct for screening for IA in high-risk patients is attractive, because it is noninvasive and may detect evidence of IA prior to the appearance of clinical signs and symptoms. Galactomannan is a polysaccharide cell-wall component that is released by *Aspergillus* species. Among the many tests that have been developed for detection of galactomannan, the double-sandwich ELISA (Platelia; Bio-Rad), which incorporates the B 1–5 galactofuranose–specific EBA2 monoclonal antibody as both the acceptor and the detector for galactomannan, has the most promise.

Although numerous studies have been performed to determine the sensitivity and specificity of the assay in various patient populations, the results are variable. The goal of our meta-analysis was to synthesize the existing literature on screening for IA in high-risk patients with use of the galactomannan assay and to calculate summary measures of accuracy.

Our main finding was that the assay was moderately useful for surveillance of IA in patients with hematological malignancy or hematological transplant recipients. However, the performance of the test dropped sharply for solid-organ transplant recipients, for whom it had poor sensitivity and specificity. Subgroup analyses showed that the sensitivity of the test was higher when a reference standard other than the EORTC/MSG criteria was used. However, the differences were small, probably reflecting the exclusion from our analysis of studies that used reference standards very different from the EORTC/MSG-proposed criteria.

We examined the effect of prevalence of IA on the performance of the assay. The pretest probability greatly influences the predictive values of any test, and not surprisingly, our analysis found that positive predictive value increased with increasing prevalence. The galactomannan assay should be used only when there is a high pretest probability of IA, such as in high-risk populations with neutropenia and malignancy or populations that have undergone transplantation.

Our analysis has limitations stemming from the heterogeneity in the design of the studies we analyzed. A recent review has elegantly summarized the challenges of evaluating the accuracy of the galactomannan assay [14]. We attempted to minimize heterogeneity arising from the choice of reference standard by requiring that all included studies use the EORTC/

**Table 6. Predictive values of the galactomannan assay for diagnosis of invasive aspergillus (IA), by prevalence.**

| | Cases of proven IA | | Cases of proven or probable IA | |
|---|---|---|---|---|
| Prevalence | Positive predictive value (95% CI) | Negative predictive value (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
| 0.05 | 0.25 (0.23–0.28) | 0.98 (0.97–0.99) | 0.31 (0.28–0.35) | 0.98 (0.97–0.99) |
| 0.10 | 0.42 (0.39–0.45) | 0.96 (0.95–0.97) | 0.49 (0.45–0.53) | 0.96 (0.95–0.97) |
| 0.15 | 0.53 (0.50–0.56) | 0.95 (0.94–0.96) | 0.61 (0.57–0.64) | 0.93 (0.92–0.94) |
| 0.20 | 0.62 (0.59–0.65) | 0.92 (0.91–0.94) | 0.69 (0.65–0.72) | 0.91 (0.89–0.92) |

MSG criteria or criteria that were similar to the EORTC/MSG criteria for diagnosis of IA. The choice of cutoff value for defining a positive test result deserves mention. At the initial launch of the ELISA in Europe a decade ago, a cutoff serum ratio of 1.5 was recommended in the manufacturers' manual. Over the past several years, many studies have reported using a cutoff value of 1.0, and the US Food and Drug Administration–approved ELISA in the United States recommends a cutoff value of 0.5. We found that the accuracy of the test improved with a higher threshold. Incorporation bias is also a concern when the test under study is part of the reference standard [15]. The EORTC/MSG criteria include a positive galactomannan test result for defining probable but not proven cases; thus, incorporation bias would not be of concern for analysis of proven cases.

We also performed subgroup analyses to explore the reasons for the heterogeneity found in the main analyses. A major cause of variable test performance may be prior antifungal therapy, which may be expected to result in lower sensitivity and specificity of the galactomannan assay by decreasing fungal bioburden. Marr et al. [16] found that, for proven IA in hematopoietic cell transplant recipients, the sensitivity of the Platelia assay varied from 87.5 in those patients not receiving antifungal therapy to 20% in those patients receiving antifungal therapy. However, too few other studies included in our analysis reported whether patients were receiving or had received antifungal therapy at the time that blood samples were obtained for galactomannan testing, and we were unable to perform a subgroup analysis to explore this finding further. Other sources of false-positive galactomannan test results have recently been reported, particularly concurrent piperacillin-tazobactam treatment [17, 18].

It is important to acknowledge that, in all of the studies included in our analysis, the galactomannan test was used for surveillance for IA with repeated serum sampling in a high-risk patient population during a defined period of high risk. The usefulness of the galactomannan test for the diagnosis of IA in patients with signs and symptoms suggestive of IA needs study and cannot be inferred from results involving the study populations in our analysis. We also did not examine the performance of the galactomannan assay for samples other than serum samples. Additional studies are needed to examine test characteristics in other specimen types.

Finally, the most important outcome in studies of diagnostic tests is whether diagnosis impacts patient outcomes with regard to mortality and morbidity. That information was not provided in any of the included studies, and additional research is needed to determine the impact of early diagnosis (and presumably, earlier treatment) of IA on mortality. Additional research should focus on the impact of antimicrobial therapy on test performance, more-rigorous assessment of false-positive test results, and assessment of the usefulness of the test for improving patient outcomes in nonsurveillance conditions.

## Acknowledgments

***Potential conflicts of interest.*** All authors: no conflicts.

## References

1. Singh N, Paterson DL. *Aspergillus* infections in transplant recipients. Clin Microbiol Rev **2005**; 18:44–69.
2. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood **2003**; 102: 827–33.
3. Wheat LJ. Rapid diagnosis of invasive aspergillosis by antigen detection. Transpl Infect Dis **2003**; 5:158–66.
4. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis **2002**; 34:7–14.
5. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood **2001**; 97: 1604–10.
6. Maertens J, Van Eldere J, Verhaegen J, Verbeken E, Verschakelen J, Boogaerts M. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. J Infect Dis **2002**; 186:1297–306.
7. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med **2003**; 138:40–4.
8. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med **1993**; 12: 1293–316.

9. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med **2002**; 21:1237–56.
10. Singh N. Fungal infections in the recipients of solid organ transplantation. Infect Dis Clin North Am **2003**; 17:113–34, viii.
11. Singh N. Invasive aspergillosis in organ transplant recipients: new issues in epidemiologic characteristics, diagnosis, and management. Med Mycol **2005**; 43(Suppl 1):S267–70.
12. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **2002**; 34:909–17.
13. Patterson TF. Approaches to fungal diagnosis in transplantation. Transpl Infect Dis **1999**; 1:262–72.
14. Marr KA, Leisenring W. Design issues in studies evaluating diagnostic tests for aspergillosis. Clin Infect Dis **2005**; 41(Suppl 6):S381–6.
15. Reid MC, Lachs MS, Feinstein AR. Use of methodological standards in diagnostic test research: getting better but still not good. JAMA **1995**; 274:645–51.
16. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis **2004**; 190:641–9.
17. Adam O, Auperin A, Wilquin F, Bourhis JH, Gachot B, Chachaty E. Treatment with piperacillin-tazobactam and false-positive *Aspergillus* galactomannan antigen test results for patients with hematological malignancies. Clin Infect Dis **2004**; 38:917–20.
18. Sulahian A, Touratier S, Ribaud P. False-positive test for aspergillus antigenemia related to concomitant administration of piperacillin and tazobactam. N Engl J Med **2003**; 349:2366–7.
19. Becker MJ, de Marie S, Willemse D, Verbrugh HA, Bakker-Woudenberg IA. Quantitative galactomannan detection is superior to PCR in diagnosing and monitoring invasive pulmonary aspergillosis in an experimental rat model. J Clin Microbiol **2000**; 38:1434–8.
20. Platelia [package insert]. Hercules, CA: Bio-rad, **2003**.
21. Bretagne S, Marmorat-Khuong A, Kuentz M, Latge JP, Bart-Delabesse E, Cordonnier C. Serum *Aspergillus* galactomannan antigen testing by sandwich ELISA: practical use in neutropenic patients. J Infect **1997**; 35:7–15.
22. Bretagne S, Costa JM, Bart-Delabesse E, Dhedin N, Rieux C, Cordonnier C. Comparison of serum galactomannan antigen detection and competitive polymerase chain reaction for diagnosing invasive aspergillosis. Clin Infect Dis **1998**; 26:1407–12.
23. Buchheidt D, Hummel M, Schleiermacher D, et al. Prospective clinical evaluation of a LightCycler-mediated polymerase chain reaction assay, a nested-PCR assay and a galactomannan enzyme-linked immunosorbent assay for detection of invasive aspergillosis in neutropenic cancer patients and haematological stem cell transplant recipients. Br J Haematol **2004**; 125:196–202.
24. Challier S, Boyer S, Abachin E, Berche P. Development of a serum-based Taqman real-time PCR assay for diagnosis of invasive aspergillosis. J Clin Microbiol **2004**; 42:844–6.
25. Costa C, Costa JM, Desterke C, Botterel F, Cordonnier C, Bretagne S. Real-time PCR coupled with automated DNA extraction and detection of galactomannan antigen in serum by enzyme-linked immunosorbent assay for diagnosis of invasive aspergillosis. J Clin Microbiol **2002**; 40: 2224–7.
26. Fortun J, Martin-Davila P, Alvarez ME, et al. *Aspergillus* antigenemia sandwich-enzyme immunoassay test as a serodiagnostic method for invasive aspergillosis in liver transplant recipients. Transplantation **2001**; 71:145–9.
27. Herbrecht R, Letscher-Bru V, Oprea C, et al. *Aspergillus* galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol **2002**; 20:1898–906.
28. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia *Aspergillus* galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant **2004**; 4:796–802.
29. Jarque I, Andreu R, Salavert M, et al. Value of *Aspergillus* galactomannan antigen detection in the diagnosis and follow-up of invasive aspergillosis in hematological patients [in Spanish]. Rev Iberoam Micol **2003**; 20:116–8.
30. Kami M, Fukui T, Ogawa S, et al. Use of real-time PCR on blood samples for diagnosis of invasive aspergillosis. Clin Infect Dis **2001**; 33:1504–12.
31. Kwak EJ, Husain S, Obman A, et al. Efficacy of galactomannan antigen in the Platelia *Aspergillus* enzyme immunoassay for diagnosis of invasive aspergillosis in liver transplant recipients. J Clin Microbiol **2004**; 42:435–8.
32. Machetti M, Feasi M, Mordini N, et al. Comparison of an enzyme immunoassay and a latex agglutination system for the diagnosis of invasive aspergillosis in bone marrow transplant recipients. Bone Marrow Transplant **1998**; 21:917–21.
33. Maertens J, Verhaegen J, Demuynck H, et al. Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for hematological patients at risk for invasive aspergillosis. J Clin Microbiol **1999**; 37: 3223–8.
34. Maertens J, Theunissen K, Verbeken E, et al. Prospective clinical evaluation of lower cut-offs for galactomannan detection in adult neutropenic cancer patients and haematological stem cell transplant recipients. Br J Haematol **2004**; 126:852–60.
35. Moragues MD, Amutio E, Garcia-Ruiz JC, Ponton J. Usefulness of galactomannan detection in the diagnosis and follow-up of hematological patients with invasive aspergillosis [Spanish]. Rev Iberoam Micol **2003**; 20:103–10.
36. Pazos C, del Palacio A. Early diagnosis of invasive aspergillosis in neutropenic patients with bi-weekly serial screening of circulating galactomannan by Platelia Aspergillus [Spanish]. Rev Iberoam Micol **2003**; 20:99–102.
37. Pinel C, Fricker-Hidalgo H, Lebeau B, et al. Detection of circulating *Aspergillus fumigatus* galactomannan: value and limits of the Platelia test for diagnosing invasive aspergillosis. J Clin Microbiol **2003**; 41: 2184–6.
38. Rovira M, Jimenez M, De La Bellacasa JP, et al. Detection of *Aspergillus* galactomannan by enzyme immunoabsorbent assay in recipients of allogeneic hematopoietic stem cell transplantation: a prospective study. Transplantation **2004**; 77:1260–4.
39. Sulahian A, Boutboul F, Ribaud P, Leblanc T, Lacroix C, Derouin F. Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. Cancer **2001**; 91:311–8.
40. Sulahian A, Tabouret M, Ribaud P, et al. Comparison of an enzyme immunoassay and latex agglutination test for detection of galactomannan in the diagnosis of invasive aspergillosis. Eur J Clin Microbiol Infect Dis **1996**; 15:139–45.
41. Ulusakarya A, Chachaty E, Vantelon JM, et al. Surveillance of *Aspergillus* galactomannan antigenemia for invasive aspergillosis by enzyme-linked immunosorbent assay in neutropenic patients treated for hematological malignancies. Hematol J **2000**; 1:111–6.
42. Verweij PE, Stynen D, Rijs AJ, de Pauw BE, Hoogkamp-Korstanje JA, Meis JF. Sandwich enzyme-linked immunosorbent assay compared with Pastorex latex agglutination test for diagnosing invasive aspergillosis in immunocompromised patients. J Clin Microbiol **1995**; 33: 1912–4.
43. Yoo JH, Choi JH, Choi SM, et al. Application of nucleic acid sequence-based amplification for diagnosis of and monitoring the clinical course of invasive aspergillosis in patients with hematologic diseases. Clin Infect Dis **2005**; 40:392–8.