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Serum galactomannan for diagnosing invasive aspergillosis in pediatric patients: A meta-analysis

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ABSTRACT

Background: The serum galactomannan (GM) assay is used to diagnose invasive *aspergillosis* (IA). We conducted a systematic review and analysis to estimate the overall accuracy of the serum GM test for diagnosing pediatric IA.

Method: A systematic literature review was conducted of all relevant studies published in PubMed and EMbase databases up to March 10, 2017. We selected and assessed articles that reported diagnostic data related to serum GM for diagnosis of pediatric IA. Pooled diagnostic odds ratios (DORs) and summary receiver operating characteristics (SROCs) were constructed with a cutoff value of 0.5. Additionally, pooled sensitivity (SEN), specificity (SPE), and positive and negative likelihood ratios (PLR and NLR, respectively) were estimated for summarizing overall test performance.

Results: Seventeen studies were included in this systematic review. The total number of patients (age range 0–21 years old) was 1768, with 178 that had proven or probable IA. The pooled serum GM assay results, with a cutoff value of 0.5 for proven or probable IA, were DOR: 41.16 (95% confidence interval (CI) 21.48–78.86), SEN: 0.85 (95% CI 0.72–0.93), SPE: 0.88 (95% CI 0.80–0.93), PLR: 6.92 (95% CI 4.40–10.88), and NLR: 0.17 (95% CI 0.09–0.32). The SROC was 0.93.

Conclusion: Serum GM can be used to assist in diagnosis of proven or probable pediatric IA. However, serum GM test results should be interpreted in combination with clinical findings in pediatric IA cases, as the test results are not always sensitive or specific enough for pediatric IA.

1. Introduction

Invasive aspergillosis (IA) is the most common type of severe, opportunistic filamentous fungal infection in pediatric patients; this infection is mainly caused by *Aspergillus fumigatus*, as well as other *Aspergillus* species [1–5]. Rates of morbidity and mortality associated with IA infections have risen steadily in recent years, especially for recipients of pediatric hematopoietic stem cell transplants (HSCTs) and for pediatric oncology patients undergoing intensive chemotherapy [6–8].

Mortality for IA patients is in the range of 40%–90% and is mainly affected by the timing of initiation of therapy [9,10]. Unfortunately, early diagnosis of IA is still challenging in children, as conventional diagnosis is dependent on culture and histopathologic examination. Notably, microscopy and culture methods for analysis of sputum and bronchoalveolar lavage (BAL) are not sufficiently sensitive [11]. Although radiology can offer diagnostic clues, it lacks specificity. Blood, cerebrospinal fluid, and bone marrow specimens rarely yield *Aspergillus* species [7,12–15]. The galactomannan (GM) antigen detection test was introduced in 1995 and approved by the FDA in 2003. Galactomannan is a heat-stable polysaccharide found in the fungal wall of most *Aspergillus* and *Penicillium* species, and is released into bodily fluids as the mold grows [16]. Currently, the GM assay is becoming more common for diagnosis of IA in adult patients. Thus, incorporation of serum GM enzyme immunoassays may provide evidence of IA infection in pediatric patients [15,17]. However, the assay has not been thoroughly evaluated for diagnosis of IA in pediatric patients.

To date, several studies from single medical centers in a small number of countries have evaluated the diagnostic capability of serum GM testing for diagnosis of pediatric IA; however, the diagnostic value of the GM test in pediatric patients varies widely, primarily because of the small sample sizes utilized in many prior studies. Moreover, no systematic review has focused on the general value of the GM test in pediatric patients. Although Lehrnbecher et al. [18] recently assessed the diagnostic value of the GM test in pediatric cancer patients in a meta-analysis, that analysis was designed to investigate pediatric

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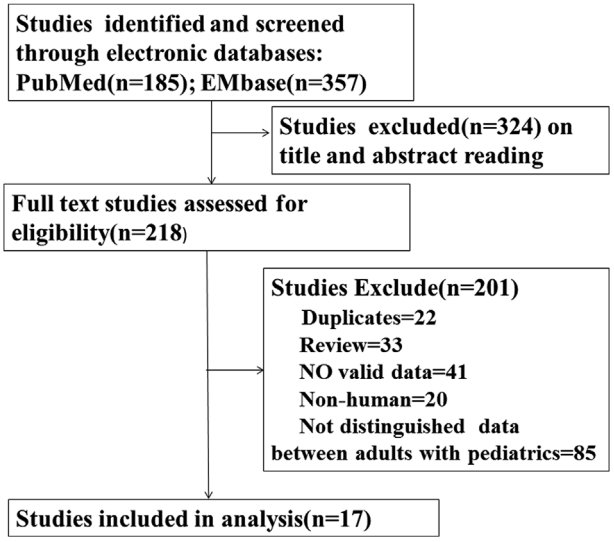

Fig. 1. Flow diagram of included studies.

invasive fungal disease (IFD), rather than pediatric IA; further, it mostly included studies that were published before April 2016. Therefore, we conducted a systematic review and meta-analysis to assess the diagnostic value of the GM test in cases of pediatric IA.

2. Methods

2.1. Search strategy

To identify eligible articles for this systematic review, two independent investigators (TT and SJL) searched entries in the PubMed and EMbase databases in all languages, from the inception of each database until March 10, 2017. Search terms included "(invasive aspergillus OR invasive aspergillosis OR IA)" AND "(galactomannan OR GM test)" AND "(pediatric OR children OR child)". As the analysis progressed, we improved the search strategies when necessary. To identify additional studies, all references cited in database-identified studies were also reviewed.

2.2. Inclusion and exclusion criteria

Inclusion criteria: this systematic review included all relevant studies that involved the diagnostic performance of the GM assay in

Table 1
Characteristics of the eligible studies.

Author, year	Study design	Region\period	Data Collection	Diagnosis criteria	Patients demographic			
					Male	Mean Age (Year MD)	Number (proven or probable IA)	disease
Gulhadiye Avcu, 2017	Case control study	Turkey\ 2006–2015	Retrospective	EORTC/ MSG2008	80	55month (0.25–17.3 years)	141(5)	IA/HM
Juergen Loeffler, 2017	Cohort study	Germany\ 2012–2015	Retrospective	EORTC/ MSG2008	24	9.5year (4–21 years)	39(4)	IA/HSCT
Shilan Mohammadi, 2015	Case-control study	Iran\ 2013.1–2014.3	Prospective	EORTC/ MSG2008	NA	NA	70(16)	IPA/IM
Aharon Gefen, 2015	Cohort study	Israel\ 2010.1–2011.12	Prospective	EORTC/ MSG2008	28	8.5 years (0–20 years)	46(5)	IA/HSCT
Veronique Dinand, 2013	Cohort study	India\ 2007.1–2011.12	Prospective	EORTC/ MSG2008	101	5years (0–18 years)	145(20)	IA/neutropenic
Soo-Han Choi, 2013	Cohort study	Korea\ 2007.7–2010.9	Retrospective	EORTC/ MSG2008	55	9.35years (0–18 years)	83(23)	IA/Cancer
Ajaya K. Jha, 2013	Cohort study	India\ 2010.7–2011.12	Prospective	EORTC/ MSG2002	74	6.1years (0–14years)	95(2)	IPA/HM
Mark de Mol, 2012	Cohort study	Netherlands\ 2002.7–2008.6	Retrospective	EORTC/ MSG2008	27	9.8years (1.1–18.2 years)	41(17)	IPA/HM
Parisa Badiee, 2012	Cohort study	Iran\ 2008.11–2009.11	Prospective	EORTC/MSG 2008	NA	9.3year (1–14 years)	62(10)	IA/HM
Brian T. Fisher, 2012	Cohort study	American\ 2004.5–2007.7	Prospective	EORTC/ MSG2002	121	7.8years (0–19 years)	195(0)	IA/HM
Veronique Dina, 2010	Cohort study	Indian\ 2006.10–2010.2	Prospective	EORTC/ MSG2008	NA	NA	109(22)	IA/febrile nuetropenia
E. castagnola, 2010	Cohort study	Italy\ 1999–2005	Retrospective	EORTC/ MSG2008	NA	9years (0.08–20 years)	195(22)	IA/HM
Rishi Desai, 2009	Cohort study	American\ 2006.11–2007.11	Retrospective	EORTC/ MSG2008	33	10.3years[a]	38(9)	IA/HM
Randall Hayden, 2008	case-control study	American\ 2008	Retrospective	EORTC/ MSG2002	NA	8.3year (0.25–18 years)	56(17)	IA/Cancer
Patrick C. Foy, 2007	Case-control study	American\ 2004	Retrospective	EORTC/NIAID	NA	NA	50(5)	IA/HSCT
William J. Steinbach, 2007	Cohort study	American\ 1999.11–2004.12	prospective	EORTC/ MSG2002	40	8years (0.5–21 years)	64(1)	IA/HSCT
Annie Sulahian, 2001	Cohort study	Frince\ 1995.1–1998.12	prospective	NA	NA	NA	347(9)	IA/HM

NA: not applicable.
HSCT: hematopoietic stem cell transplantation.
HM: hematological malignancy.
IA: invasive aspergillosis.
IPA: invasive pulmonary aspergillosis.
[a] Mean values for all the included patients.