

Galactomannan Antigen Test for Early Diagnosis of Invasive Aspergillus Infection in Pediatric Febrile Neutropenia

Invasive aspergillosis is a major concern in neutropenic patients. We studied the utility of Galactomannan antigen detection test in serum using ELISA technique for early detection of invasive aspergillosis. Diagnostic accuracy of Galactomannan index (GMI) test was maximum at a cut-off of > 1.5 with a negative predictive value of more than 95%.

Keywords: Cancer chemotherapy, Immunosuppression.

Invasive Aspergillosis (IA) infection is a major diagnostic concern in immunosuppressed children. For the diagnosis of IA, simultaneous histopathologic/cytological and culture examination of tissue and fluid specimens is recommended [1]. In sick children, biopsy is not always possible and culture of respiratory specimens have a poor yield. The double sandwich ELISA Galactomannan antigen test has been developed and validated as useful for diagnosis of IA. The high mortality associated with IA makes the galactomannan antigen test a promising test for early initiation of therapy, especially in children with acute leukemia [2].

We studied the diagnostic accuracy of various cut-offs of Galactomannan antigen test in children with febrile neutropenia. Out of 74 episodes of febrile neutropenia, 17 children had invasive aspergillosis by European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) 2008 criteria (3 Proven, 11 Probable and 3 Possible). Galactomannan antigen test was done with immuno-enzymatic sandwich microplate assay in serum samples (Platelia® Aspergillus,

TABLE I DIAGNOSTIC EFFICACY OF GMI IN INVASIVE ASPERGILLOSIS IN PEDIATRIC FEBRILE NEUTROPENIA

Cut-off	Sensitivity	Specificity	PPV	NPV
0.5	100% (11/11)	47.7% (30/63)	25% (11/44)	100% (30/30)
1	81.8% (9/11)	66.7% (42/63)	30% (9/30)	95.5% (42/44)
1.5	81.8% (9/11)	92.1% (58/63)	64.2% (5/14)	96.7% (58/60)

PPV and NPV: Positive and Negative Predictive Value; GMI: Galactomannan Index.

Bio-Rad Laboratories, Hercules, CA). All 11 isolates had positive serum Galactomannan antigen test expressed as “galactomannan index” (GMI >0.5). All the probable infections that grew Aspergillus also had evidence of fungal infection on computed tomogram of the chest. **Table I** shows various diagnostic accuracy parameters at different cut-off points of GM antigen test. We plotted ROC curves for various cut-off’s (**Fig. 1**) to identify optimal cut-off value for GMI. GMI cut-off of 1.5 had the best diagnostic accuracy (Area under curve 0.869).

Different studies have used different positive cut-off for GMI ranging from 0.5 to 1.5 [3]. Recent EORTC guidelines do not recommend any specific cut-off value for positive result [4]. US Food and Drug Administration approved ELISA in the United States recommends a cut-off value of 0.5 [5].

There is heterogeneity in sensitivity and specificity in various systematic reviews and meta-analysis done on galactomannan assay. Our study showed no false negative at a cut-off of 0.5. Increasing the cut-off to 1.0 or 1.5 increased the specificity but at the expense of decrease in sensitivity (**Table I**). In our study negative predictive value of GM antigen was 95-100%. Our study shows that a GMI cut-off of 1.5 has a good specificity with reasonable sensitivity and seems to be optimal cut-off in diagnosis of invasive aspergillosis which is also consistent with other studies discussed in literature [6].

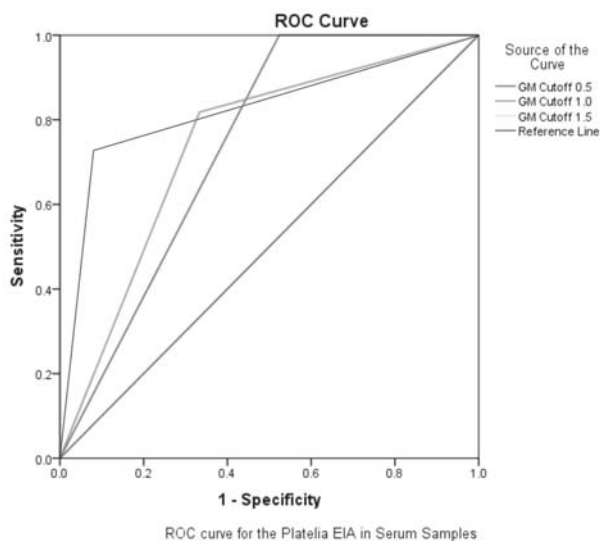


FIG. 1 ROC curve for various ODI cut-offs of Galactomannan antigen test for diagnosis of Invasive aspergillosis.

Our study has certain limitations like the effect of confounders giving false positive GM antigen test results like use of antibiotics (*e.g.* piperacillin-tazobactam) and dietary contamination (formulae milk) which were not excluded. For suspected invasive pulmonary aspergillosis bronchoscopy with BAL is recommended but it was not done in any patient due to presence of significant thrombocytopenia. A small sample size was another major limitation.

Our study highlights the usefulness of serum GM antigen test in the early diagnosis of IA and suggests a GMI cut-off of 1.5 as it have highest diagnostic accuracy. Early institution of specific therapy will prevent unnecessary use of antifungal therapy and development of resistance.

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