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Original Article

Comparison of 1,3-Beta-D-Glucan & Galactomannan Antigens in Early Diagnosis of Invasive Fungal Infections

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Abstract

Objective: To compare the efficacy of 1,3-beta-D-glucan & galactomannan antigens for early diagnosis of invasive fungal infections (IFIs).

Methods: This was a comparative cross-sectional study conducted at Pathology department, King Edward Medical University, Lahore for 6 months. 37 confirmed patients of IFIs were enrolled. Venous samples were taken carefully in sterile serum cups from all patients and samples were divided in 2 groups on the basis of antigen biomarker applied i.e. BDG and Galactomannan. BDG of >80 pg/ml was declared positive while galactomannan index > 0.5 was taken as positive. Data was analyzed in SPSS-26.

Results: The mean age was 42.43±14.83 years. Out of 37, 26 (70.27%) were males and 11 (29.73%) females. Candida was seen in 21 (56.76%), mucor in 8 (21.62%), aspergillus in 6 (16.22%) and trichosporon in 2 (5.41%) patients. BDG showed positive for 23 (62.16%) and negative for 14 (37.84%) IFIs while Galactomannan was positive for 6 (16.22%) and negative for 31 (83.78%) IFIs. The sensitivity of BDG was 62.16% and Galactomannan was 16.22%. The comparison between two biomarkers was significant (p=0.037).

Conclusion: BDG was more effective than galactomannan for early diagnosis of IFIs.

Key words: Invasive Fungal Infections, comparison, 1,3-beta-D-Glucan, Galactomannan.

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Introduction

Invasive fungal infections (IFIs) had been critical and fatal complications in immunocompromised patients. These are systemic, generalized, deeply seated, visceral, and disseminated very dangerous infections.[1] Worldwide fungal pathogens are responsible for at least 13 million infections with 6.5 million invasive infections leading to annual 1.5 million deaths globally primarily in immunocompromised population.[2] Asia had the largest burden of fungal disease in the world and here the incidence of IFI is 3 to 15 times higher compared with international data.[3] In Pakistan around 3,280,549 (1.78%) people are affected annually excluding fungal sinusitis, tineas and oral candidiasis. However, the true burden of the disease is still unknown.4 Despite this, IFIs have been underdiagnosed still in our set up. Common predisposing factors are chemotherapy, corticosteroid therapy, asthma, cancers and organ transplantation.[2]

IFIS have been a threat globally for immunocompromised patients. The wider use of steroids, chemotherapy, transplants and invasive devices such as central venous catheters have become the cause of mortality and morbidity.[5]

Many fungi such as aspergillus produce polysaccharides i.e. 1,3-β-D-glucan and galactomannan of their cell walls released from the expanding aspergillus hyphae.[6] This act as key biomarkers for quick, non-invasive and readily avilable IFIs analysis in these patients.[7]

Cultures and histopathology are the conventional gold standard for diagnosis of fungal infections but the slow turnaround time and delayed treatment make the clinical condition worse and at times demise of patient. As a result, early and improved diagnostic approaches for

IFIs are needed. Early detection of fungal biomarkers like BDG and GM from cell wall components or fungal DNA, have been critical to the rapid diagnosis of IFIs.[8] IFI patients' prognosis is dependent on early fungal isolation and effective antifungal therapy and subsequent monitoring.[9]

In a research, sensitivity and specificity of Galactomannan were 54.6% and 90% respectively while BDG's sensitivity and specificity of BDG were 97.4% and 96.6% respectively.[10] Similarly BDG had 91.6% sensitivity and 86.44% specificity, whereas Galactomannan had 80.67% sensitivity and 76.27% specificity in another study.[11]

IFIs are deep seated and challenging to diagnose. These necessitates invasive technique to obtain specimens for histological analysis; hence biomarker tests are safe, quick and non- invasive method of diagnosing IFIs.[12]

The objective was to compare efficacy of 1,3-beta-D-glucan & galactomannan antigens (biomarkers) in early diagnosis of IFIs. This may improve patient care, mortality and morbidity. Therefore the aim of this study is to compare the efficacy of 1,3-beta-D-glucan & galactomannan antigens in early diagnosis of IFIs.

Methods

This was a comparative cross-sectional study conducted at pathology department, King Edward Medical University, Lahore from 1st August 2020 to 31st January 2021 vide IRB letter No 433/RC/KEMU dated 03-07-2020. 37 patients aged 15-80 years of either gender with confirmed IFIs on the basis of the European Organization for Research and Treatment of Cancer (EORTC) were included by non-probability convenient sampling.[13] IFIs were taken as confirmed isolation of a fungus by blood culture, or histopathology from a deep seated site or tissue specimen. Patients confidentially were maintained. Sample size was estimated by using 5% level of significance, 90% power of test with expected mean values of BDG as 81% and Galactomannan as 49%.[4] Patients with probable and suspected IFIs, superficial fungal infections and endemic mycoses were major exclusion. Informed consent was taken. Demographic data like name, age, gender, address) was noted. Patient co-morbid like diabetes mellitus, organ transplantation, and cancer chemotherapy, steroids and antibiotics were also noted.

All confirmed IFIs patients' 5ml blood sample were drawn in disposable syringes. All samples were divided into 2 sterile serum cups A & B and were stored carefully. On sample A, BDG kit was applied using gold stream Fungus (1,3)-BDG by chromogenic method (GCT-1101T) and on sample B, Galactomannan kit was applied using the Fungi Xpert Aspergillus Galactomannan ELISA Detection method. So, all patients had both markers tested at a time.

After 2hrs ELISA plates were assessed and results were obtained and noted in the proforma. BDG level ≥80 pg/ml was taken as positive. For galactomannan, ≥0.5 index was taken as positive. All positive and negative result values were recorded on a predesigned proforma.

Data was analyzed by using SPSS-v26. Quantitative variables like age in years, fungal biomarkers values were taken as mean + standard deviation. Qualitative variables like gender, comorbid conditions were presented as frequency and percentages. Shapiro-Wilk test was also applied to determine the distribution of BDG and Galactomannan levels. Chi Square test was applied to compare the two antigen tests i.e. BDG and galactomannan, taking P value < 0.05 as significant.

Results

The mean age was 42.43±14.83 years. The minimum and maximum ages recorded were 18 and 73 years respectively. There were 26 (70.27%) males and 11 (29.73%) females. 23 (62.16%) cases were positive for IFI on BDG, while 14 (37.84%) showed negative test results. Distribution of BDG values were determined by Shapiro-Wilk test and p-value was significant ($p<0.05$) showing BDG level did not follow normal distribution. So non-parametric means were used to present this variable. The median BDG value was 124.02 with interquartile range of 496.95. 6 cases (16.22%) were positive for IFI On Galactomannan biomarker, while 31 (83.78%) cases results were negative. Distribution of Galactomannan values was determined by Shapiro-Wilk test and p-value was significant ($p<0.05$) showing Galactomannan level did not follow normal distribution. So non-parametric means were used to present this variable too. The median Galactomannan was 0.02 with interquartile range of 0.01. (Table 1)

In 23 BDG positive cases, Galactomannan was positive only in 6 cases while 17 showed negative results. In 14 BDG negative cases, all 14 (100%) cases showed negative results for Galactomannan. The difference was significant ($p<0.05$). (Table 2)

Candida was seen in 21 (56.76%) cases, mucor in 8 (21.62%) cases ,aspergillus was found in 6 (16.22%) cases and trichosporon in 2 (5.41%) cases. (Fig 1)

Data stratification was done for type of fungus. Mean BDG level was 95.52±12.69 in aspergillus cases, 322.48 ± 222.34 in candida cases, 7.81±0.00 in mucor cases and 228.99±13.03 in trichosporon cases. The difference was highly significant ($p<0.05$) in all groups. In patients with aspergillus, mean Galactomannan level was 0.78

±0.11. In patients with candida, mean Galactomannan level was 0.02±0.004. In patients with mucor, mean Galactomannan level was 0.02±0.01. Mean Galactomannan level was 0.02±0.01 in trichosporon cases. The difference was highly significant (p<0.05) in all groups. (Table 3)

Table 1: *Descriptive Statistics of patients*

Age (years)	**n**	**37**
	Mean	42.43
	Standard Deviation	14.83
	Minimum	18
	Maximum	73
BDG Levels	Shapiro-Wilk	0.762
	p-value	0.000
	Mean	230.99
	Standard Deviation	223.11
	Median	124.02
	Interquartile range	496.95
	Minimum	7.81
	Maximum	523.44
Galactomannan Levels	Shapiro-Wilk	0.482
	P-value	0.000
	Mean	0.14
	Standard Deviation	0.29
	Median	0.02
	Interquartile range	0.01
	Minimum	0.01
	Maximum	0.97

Table 2: *Comparison of IFI diagnosed on BDG and Galactomannan Antigens*

Variable outcomes		IFI on BDG		Total
		Positive	Negative	
IFI on Galactomannan	Positive	6	0	6
		26.1%	0.0%	16.2%
	Negative	17	14	31
		73.9%	100%	83.8
Total		23	14	37
		100%	100%	100%

Chi-Square Test = 4.359 P-value = 0.037 (Significant)

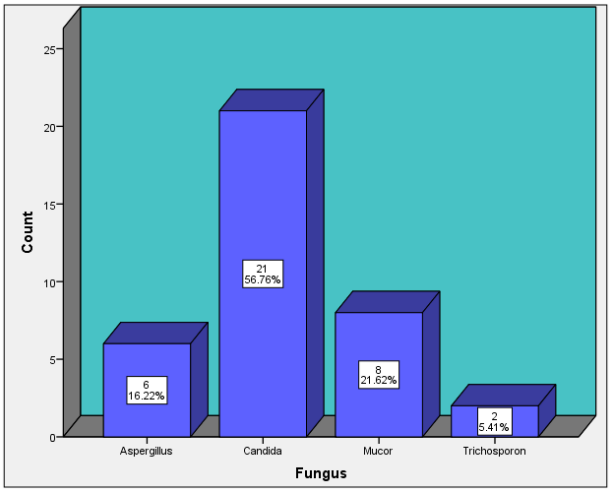

Figure 1: *Distribution of fungus type involved among patients*

Discussion

In our study, 23 cases were detected positive on BDG kit with a test sensitivity of 62.16%. On the other hand, 6 cases were found positive on Galactomannan kit with a test sensitivity of 16.22%. The comparison between BDG and Galactomannan was detected significant (p=0.037). This is supported from literature.

Total positivity of BDG and galactomannan in a study by Hoenigl M et.al. were 12 of 13 (92%) and 5 of 13 (38%) patients, respectively. Patients didn't go for residual lesion surgery. The total death rate of invasive fungal infections was 12 percent hence greater sensitivity with BDG as compared to GM as in our results.[14]

In a study by Singh et. al. it was concluded that the sensitivity and specificity of BDG was 97.4% and 96.6% respectively while the sensitivity and specificity of Galactomannan was 56.4% and 90% respectively for the diagnosis of IFIs.[15] This result is consistent with our results.

Sulahian et al. in their study concluded that sensitivity and specificity of BDG were 81% and 82%, respectively, whereas Galactomannan's were 49% and 97% respectively.[16] This also strengthens our study results.

Su et al. demonstrated the Predictive performance of BDG in endotracheal aspirate and bronchoalveolar lavage fluid for the detection of Candida pneumonia.

Table 3: *Comparison of BDG and Galactomannan levels in type of fungus*

Variable		Type of fungus				P-value
		Aspergillus	Candida	Mucor	Trichosporon	
Frequency		6	21	8	2	
BDG level	Mean	95.52	322.48	7.81	228.99	0.012
	Standard Deviation	12.69	222.34	0.00	13.03	
Galactomannan level	Mean	0.78	0.02	0.02	0.02	0.001
	Standard Deviation	0.11	0.004	0.01	0.01	

They demonstrated the sensitivity and specificity were 67 % and 82% respectively at 120pg/ml cut and 89% and 86% (both P 0.05), respectively for 130 pg/ml cut-off for areas under the receiver operating characteristic curve of 0.833% and 0.939%(both p<0.05), respectively.[17]

Serum BDG results in 229 patients with connective tissue disorders were observed by Kato et al. BDG levels were 129.7 to 207.6 pg/mL for fungal infections, whereas 10.5 to 8.6 pg/mL. range for non-fungal infections. It was concluded that 15 pg/ml cut off had the highest sensitivity (92.3 percent) and specificity (81.3%).[18] In our study, mean BDG level was 95.52±12.69 and 322.48 ±222.34 in in aspergillus and Candida cases, favoring higher rates in Candida.

In a study by Lahmer et al., it was concluded that the sensitivity and specificity of BDG was 73% and 83% for invasive aspergillosis and 77% and 53% for candidemia.[19]

In a study by Wei Z et.al. on 294 patients with hematological diseases with IFIs at Peking University People's Hospital, it was found that 122 were had positive result. It was concluded that BDG had higher sensitivity (64.4% vs 47.5%, P = 0.008), while the Galactomannan had higher specificity (93.0% vs 83.1%, P = 0.003).[20]

These Biomarkers made a rapid method of detection of IFIs for early diagnosis and treatment initiation reducing mortality and limitations of our study were a small population size and single centered.

Conclusion:

Detection of fungal biomarkers (BDG and galactomannan) is the more rapid method of confirming IFIs. BDG was found to be more effective than galactomannan in early diagnosis of IFIs. Hence these biomarkers can detect IFIs in just 2 hours' time and antifungal treatment can be started timely reducing mortality. Therefore, in future, these biomarkers can be used to diagnose IFIs in critically ill, immunocompromised patients in order to start early treatment and decrease mortality in IFIs patients.

Ethical Approval: The IRB/EC approved this study via letter no. 433/RC/KEMU dated July 03, 2020.

Conflict of Interest: None

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Authors' Contribution

TK, HB: Conception.

SUM, SI: Design of the work.

AMG, IUH: Data acquisition, analysis, or interpretation.

SUM, AMG, SI, IUH: Draft the work.

TK, HB: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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