



SERUM B-D-GLUCAN AS AN EARLY DIAGNOSTIC BIOMARKER FOR INVASIVE FUNGAL INFECTION IN NEONATES ADMITTED TO A TERTIARY-LEVEL NEONATAL INTENSIVE CARE UNIT: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Invasive fungal infections (IFIs) are a significant cause of late-onset sepsis in neonatal intensive care units (NICUs), with mortality rates of 30%–60% in affected neonates. Conventional blood culture is limited by poor sensitivity and prolonged turnaround times. Serum (1→3)- β -D-glucan (BDG), a conserved pan-fungal cell wall polysaccharide, has emerged as a promising non-culture biomarker; however, its diagnostic performance in neonatal populations remains incompletely characterised.

Objective: To evaluate the diagnostic accuracy of serum β -D-glucan for early identification of invasive fungal infection in high-risk neonates admitted to a tertiary-level NICU.

Methods: A prospective observational study was conducted over 18 months in the NICU of a tertiary academic hospital. Thirty neonates with clinically suspected late-onset sepsis (>72 h after birth) and ≥ 3 predefined IFI risk factors were enrolled. Serum BDG was quantified using the Fungitell® colorimetric assay (Associates of Cape Cod Inc., USA) based on the Limulus Amebocyte Lysate (LAL) reaction. Automated BACTEC blood cultures served as the reference standard. A BDG cutoff of ≥ 80 pg/mL was applied. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated using IBM SPSS v26.0.

Results: Of 30 neonates enrolled, 12 (40%) had confirmed IFI and 18 (60%) did not. Mean serum BDG was markedly higher in the IFI group (186.4 ± 52.8 pg/mL) than in the non-IFI group (48.6 ± 15.2 pg/mL; $p < 0.001$). At the ≥ 80 pg/mL threshold, BDG demonstrated sensitivity of 83.3%, specificity of 83.3%, PPV of 76.9%, NPV of 88.2%, and overall diagnostic accuracy of 83.3%. Baseline demographic parameters were comparable between groups (all $p > 0.05$); SpO_2 alone differed significantly ($p = 0.02$), attributed to greater respiratory support in the infected cohort.

Conclusion: Serum β -D-glucan demonstrates robust sensitivity, specificity, and negative predictive value for early detection of IFI in neonates. Integration into routine NICU sepsis workups may facilitate timely antifungal therapy and improved neonatal outcomes. Prospective multicentre studies are required to validate neonatal-specific cutoffs.

KEYWORDS: β -D-glucan, Invasive Fungal Infection, Neonatal Sepsis, NICU, Candida, Diagnostic Biomarker, Fungitell Assay, Neonatal Candidiasis, Non-culture Diagnostics, Diagnostic Accuracy.

Introduction

Invasive fungal infections (IFIs) represent one of the most clinically consequential complications encountered in neonatal intensive care units (NICUs) worldwide. Predominantly caused by *Candida* species, IFIs are responsible for approximately 9%–13% of all episodes of late-onset sepsis in very low birth weight (VLBW) neonates and carry mortality rates ranging from 30% to 60%[1]. In extremely low birth weight (ELBW) neonates weighing less than 1,000 g, incidence rises to as high as 20%[2]. The burden is particularly pronounced in India, where tertiary-level NICUs report IFI rates of 10%–15%, attributable to higher rates of broad-spectrum antibiotic use and limited antifungal prophylaxis[3].

The pathophysiological basis of neonatal susceptibility to IFI is multifactorial. Preterm neonates possess immature epidermal and mucosal barriers that facilitate fungal colonisation, while their innate immune systems demonstrate attenuated neutrophil chemotaxis, diminished complement-mediated opsonisation, and blunted pattern recognition receptor (PRR) signalling — particularly the dectin-1 pathway, which is central to β -D-glucan-mediated immune activation[4]. These deficits are compounded by the extensive use of central venous catheters, endotracheal tubes, parenteral nutrition, surgical interventions, and prolonged broad-spectrum antibiotic therapy[5].

Early diagnosis remains the foremost challenge in neonatal IFI management. Clinical features are non-specific, frequently mimicking bacterial sepsis. Blood culture — the reference standard — is critically limited: safe blood volumes rarely exceed 0.5–1.0 mL, fungal organisms grow slowly (3–5 days), and prior antifungal exposure reduces sensitivity to below 50%[6]. These limitations result in diagnostic delays directly associated with worsened outcomes[7]. Adjunctive biomarkers such as C-reactive protein and procalcitonin lack specificity for fungal aetiology.

Serum (1 $\rightarrow$ 3)- β -D-glucan (BDG), a high-molecular-weight polysaccharide constituting the primary structural scaffold of most pathogenic fungal cell walls, has attracted substantial interest as a pan-fungal, non-culture diagnostic biomarker. During active fungal invasion, BDG is shed into the circulation through cell wall turnover and hyphal fragmentation, with circulating concentrations correlating with fungal burden and disease severity[8]. The Fungitell® assay exploits BDG's ability to activate the LAL Factor G cascade, generating a colorimetric signal proportional to BDG concentration. Critically, BDG detects *Candida*, *Aspergillus*, *Pneumocystis jirovecii*, and *Fusarium* with a single test[9].

Published data from adult and paediatric populations support BDG's utility, with pooled sensitivities and specificities generally exceeding 70%–85%[10]. However, dedicated neonatal studies remain scarce, hampered by small cohort

sizes and heterogeneous cutoff thresholds[11]. Specific confounders in neonates — including glucan-containing gauze, certain antibiotics, blood products, albumin infusions, and parenteral nutrition — may generate false-positive BDG results and must be carefully accounted for[12]. Furthermore, neonatal physiology with altered protein-binding kinetics and immature renal clearance may fundamentally influence BDG dynamics, necessitating population-specific validation[13].

The present study was designed to address this evidence gap by prospectively evaluating serum BDG levels and their diagnostic accuracy in a well-characterised cohort of high-risk neonates in a tertiary NICU in northern India, and to determine whether BDG at the ≥ 80 pg/mL threshold offers clinically reliable diagnostic performance for identifying neonatal IFI.

Materials and Methods

Study Design, Setting, and Duration

This was a prospective observational study with a cross-sectional analytical design, conducted over an 18-month period in the Neonatal Intensive Care Unit of the National Institute of Medical Sciences and Research (NIMSR), NIMS University Rajasthan, Jaipur — a 950-bed tertiary-care academic medical centre serving northern and central Rajasthan, India.

Sample Size

A minimum sample size of 30 was determined by convenience sampling, appropriate for this pilot investigation designed to generate preliminary diagnostic performance estimates for BDG in a single tertiary NICU, pending validation in a larger multicentre cohort.

Inclusion and Exclusion Criteria

Neonates of any sex with clinically suspected late-onset sepsis (>72 hours after birth) fulfilling ≥ 3 predefined IFI risk criteria were included:

- Birth weight $<2,500$ g
- Hospitalisation duration >1 –3 weeks
- Mechanical ventilation requirement for >1 week
- Systemic antibiotic therapy for >72 hours
- History of major surgical procedure
- Receipt of total parenteral nutrition
- Persistent severe thrombocytopenia unresponsive to second-line antibiotics

Exclusion criteria:

- Prior antifungal therapy before enrolment
- Prior or concurrent amoxicillin-clavulanate administration
- Administration of intravenous immunoglobulins (IVIG), albumin, or plasma protein fractions within the preceding 72 hours (to mitigate false-positive BDG confounders)

Data Collection

Following written parental informed consent, a standardised proforma captured demographic data (gestational age, birth weight, sex, head circumference, age at enrolment), maternal obstetric history, mode of delivery, and NICU exposure risk factors. Clinical and vital parameters — heart rate, respiratory rate, capillary refill time, temperature, peripheral oxygen saturation (SpO₂), and blood pressure — were recorded at enrolment.

Laboratory Methods

Blood samples of 1–2 mL were collected aseptically for two simultaneous investigations:

1. **Blood Culture:** Automated blood culture using the BACTEC™ 9240 system (Becton Dickinson, USA) with Myco/F Lytic bottles incubated up to 14 days. Positive bottles were sub-cultured on Sabouraud Dextrose Agar and identified by colonial morphology, MALDI-TOF mass spectrometry, and conventional biochemical methods. A positive blood culture for a fungal pathogen in the presence of compatible clinical features constituted the reference standard for IFI.
2. **Serum β -D-Glucan:** Quantified using the Fungitell® assay (Associates of Cape Cod Inc., East Falmouth, MA, USA), a colorimetric method based on the LAL pathway, performed according to the manufacturer's instructions using pyrogen-free materials throughout. Results expressed in picograms per millilitre (pg/mL). A BDG level ≥ 80 pg/mL was classified as positive, consistent with the lower threshold range applied in mixed paediatric–neonatal populations[14].

The differential turnaround time between the two methods was a key rationale for incorporating serum BDG as the investigational biomarker in this study. Complete fungal

blood culture identification — encompassing automated incubation in the BACTEC™ system, sub-culture on Sabouraud Dextrose Agar, colony morphology assessment, and MALDI-TOF or biochemical confirmation — typically requires 1–2 weeks from specimen collection. In contrast, the Fungitell® colorimetric assay yields a reportable BDG result within 1–2 working days, with the assay itself completed in 40–60 minutes. This marked reduction in time-to-result is clinically critical in the neonatal setting, where delayed antifungal initiation is independently associated with increased morbidity and mortality.

Statistical Analysis

Data were analysed using IBM SPSS Statistics v26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean $\pm$ SD and compared using the independent-samples t-test; categorical variables by Pearson's chi-square or Fisher's exact test. Diagnostic performance at the ≥ 80 pg/mL threshold was characterised using 2 $\times$ 2 contingency table analysis. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Study Population and Demographic Characteristics

Thirty neonates meeting eligibility criteria were enrolled during the study period. On the basis of blood culture and clinical findings, 12 neonates (40.0%) were assigned to the IFI group and 18 neonates (60.0%) to the non-IFI group. Demographic characteristics are summarised in Table 1. No demographic parameter differed significantly between groups, confirming their comparability for the diagnostic analysis.

Box plots illustrating the distribution of demographic variables between groups are presented in Figures 1.1–1.4.

Table 1: Demographic Characteristics of Enrolled Neonates by Invasive Fungal Infection Status

Variable	IFI Group (n = 12)	Non-IFI Group (n = 18)	p-value
Age at enrolment (days), mean $\pm$ SD	13.75 $\pm$ 10.12	12.44 $\pm$ 6.91	0.68
Gestational age (weeks), mean $\pm$ SD	34.92 $\pm$ 3.41	35.78 $\pm$ 2.87	0.41
Birth weight (g), mean $\pm$ SD	2,183 $\pm$ 655	2,322 $\pm$ 612	0.52
Head circumference (cm), mean $\pm$ SD	30.42 $\pm$ 2.73	31.06 $\pm$ 2.54	0.47
Sex — Male, n (%)	5 (41.7%)	10 (55.6%)	0.44
Sex — Female, n (%)	7 (58.3%)	8 (44.4%)	0.44

SD = standard deviation. p-values: independent-samples t-test (continuous); chi-square (categorical). No variable reached significance at $p < 0.05$.

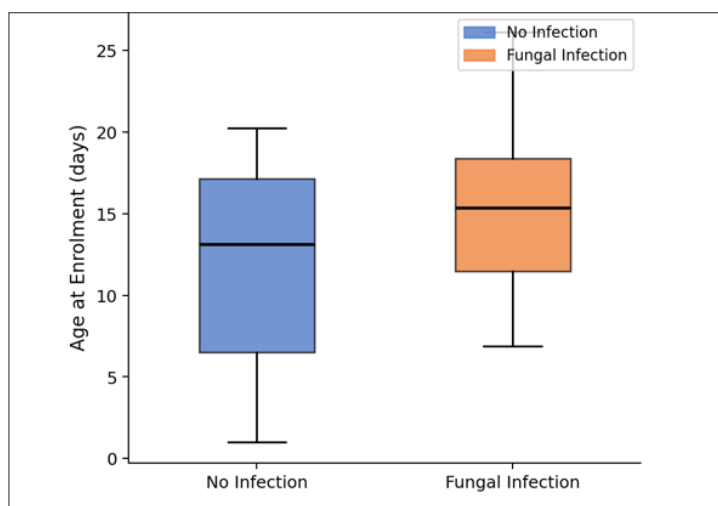


Figure 1.1: Box plot showing age at enrolment (days) between groups ($p = 0.68$).

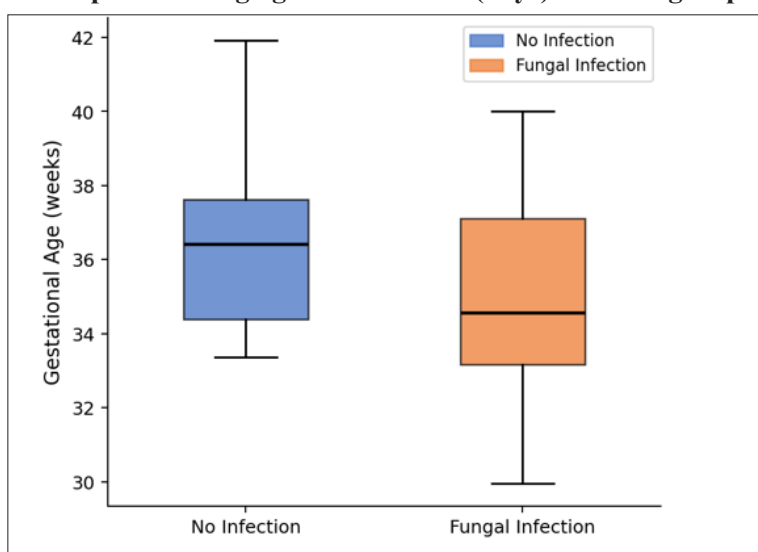


Figure 1.2: Box plot showing gestational age (weeks) between groups ($p = 0.41$).

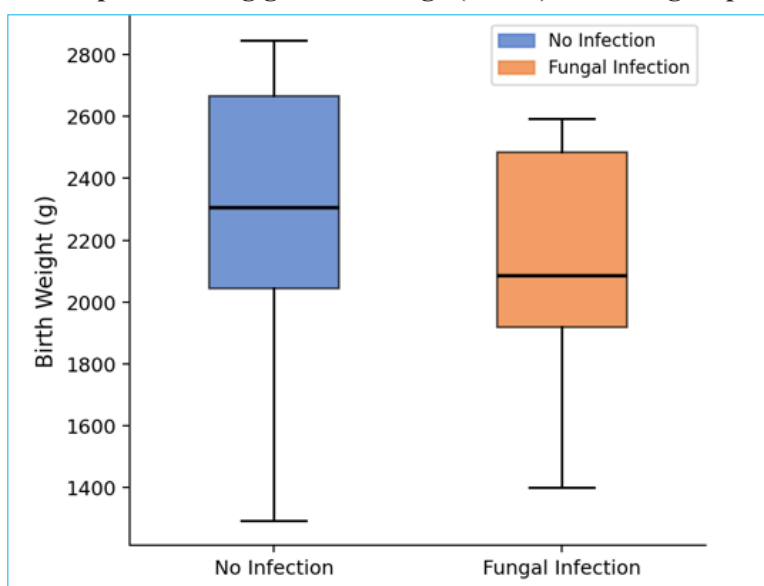


Figure 1.3: Box plot showing birth weight (g) between groups ($p = 0.52$)

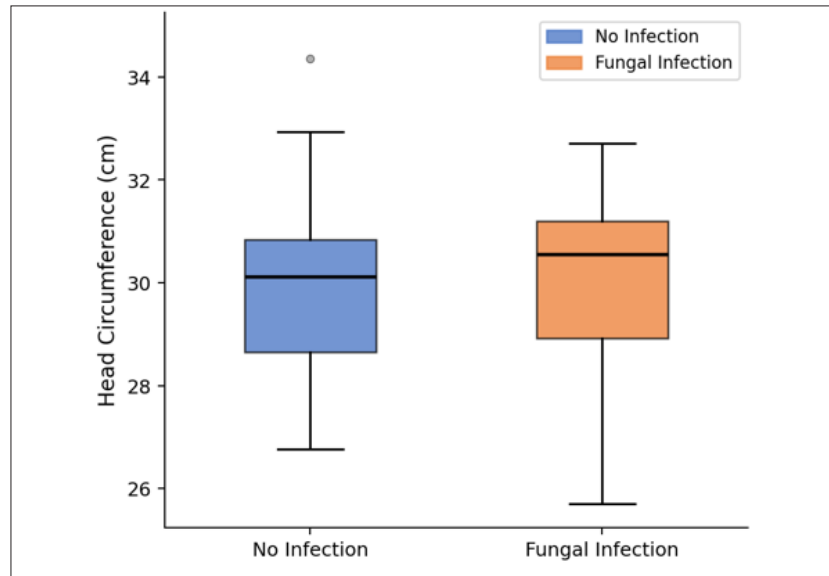


Figure 1.4: Box plot showing head circumference (cm) between groups ($p = 0.47$)

Sex Distribution

Males constituted 55.6% of the non-IFI group and 41.7% of the IFI group. The difference was not statistically significant ($p = 0.44$), indicating that sex was not a significant determinant of IFI in this cohort (Table 2, Figure 2).

Table 2: Sex Distribution Among Neonates With and Without Invasive Fungal Infection

Sex	IFI Group (n = 12), n (%)	Non-IFI Group (n = 18), n (%)	p-value
Male	5 (41.7%)	10 (55.6%)	0.44
Female	7 (58.3%)	8 (44.4%)	

p-value by chi-square test. Difference not statistically significant.

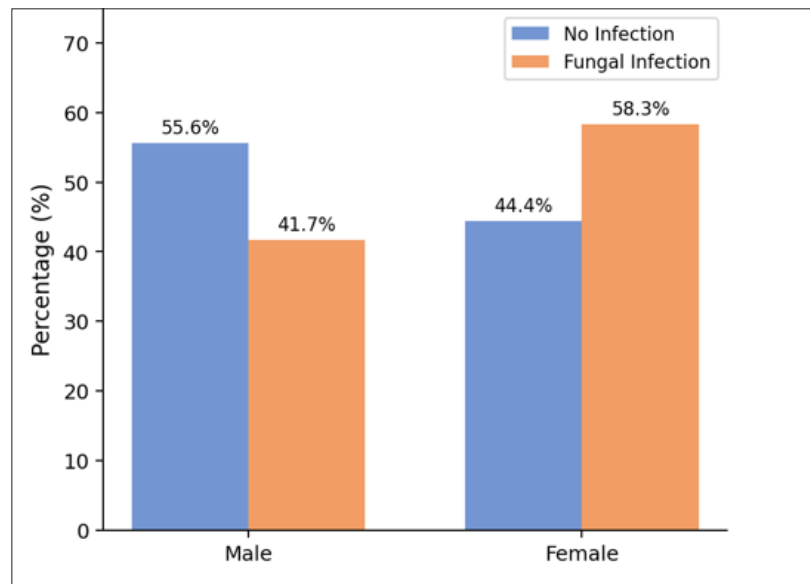


Figure 2: Bar graph showing sex distribution (%) between the Fungal Infection and No Infection groups ($p = 0.44$)

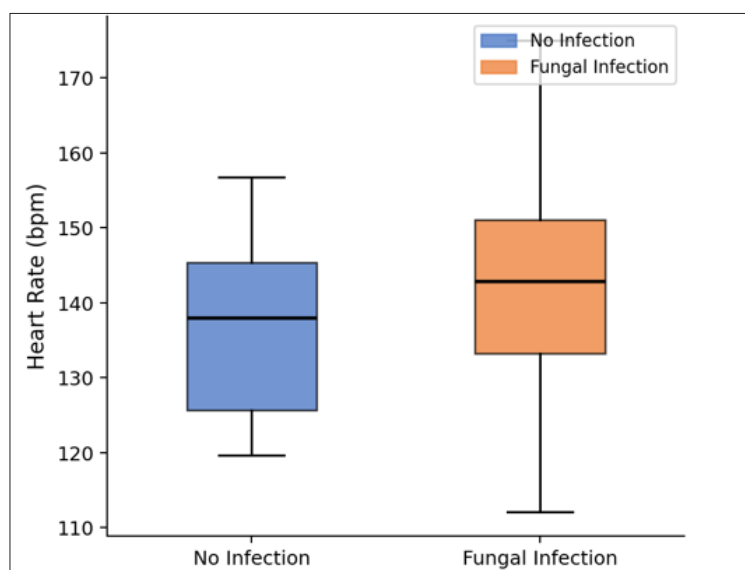
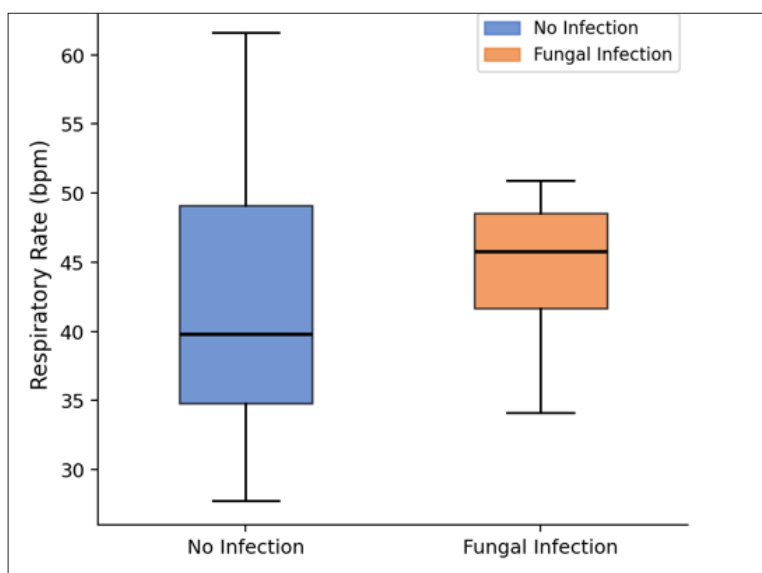
Clinical and Vital Parameters at Enrolment

Vital signs at enrolment are compared in Table 3 and Figures 3.1–3.5. Heart rate, respiratory rate, capillary refill time, and temperature did not differ significantly between groups. SpO_2 was the only parameter that differed significantly (IFI: $95.67 \pm 3.82\%$ vs. non-IFI: $91.17 \pm 4.76\%$; $p = 0.02$), most plausibly reflecting greater intensity of respiratory support in the infected cohort rather than any direct physiological effect of fungal infection.

Table 3: Comparison of Clinical and Vital Parameters at Enrolment Between Groups

Parameter	IFI Group (n = 12) Mean $\pm$ SD	Non-IFI Group (n = 18) Mean $\pm$ SD	p-value
Heart rate (bpm)	142.75 $\pm$ 14.38	138.22 $\pm$ 12.64	0.36
Respiratory rate (bpm)	46.58 $\pm$ 9.74	42.67 $\pm$ 8.91	0.28
Capillary refill time (s)	2.42 $\pm$ 0.67	2.11 $\pm$ 0.58	0.19
Temperature ($^{\circ}$ C)	36.80 $\pm$ 0.95	37.17 $\pm$ 1.03	0.31
SpO ₂ (%)	95.67 $\pm$ 3.82	91.17 $\pm$ 4.76	0.02*

bpm = beats/ breaths per minute; SpO₂ = peripheral oxygen saturation; SD = standard deviation. *Statistically significant ($p < 0.05$).


Figure 3.1: Box plot showing heart rate (bpm) between groups ($p = 0.36$)

Figure 3.2: Box plot showing respiratory rate (bpm) between groups ($p = 0.28$)

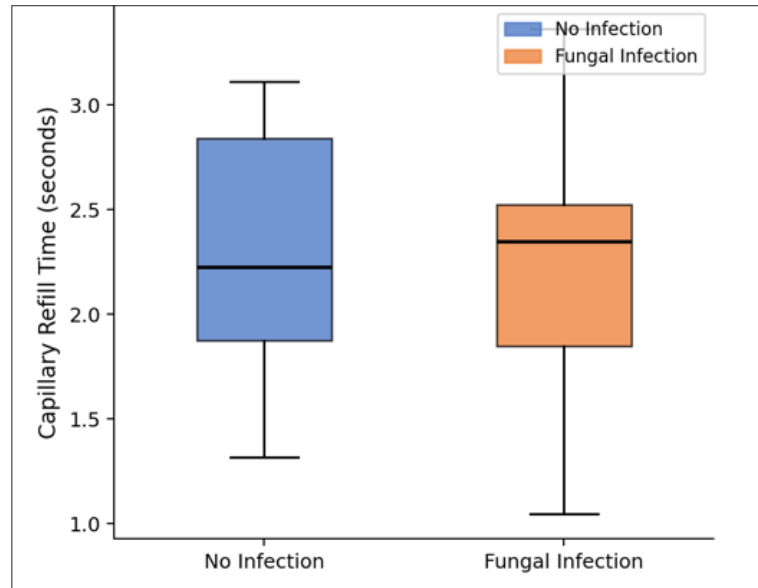


Figure 3.3: Box plot showing capillary refill time (seconds) between groups ($p = 0.19$)

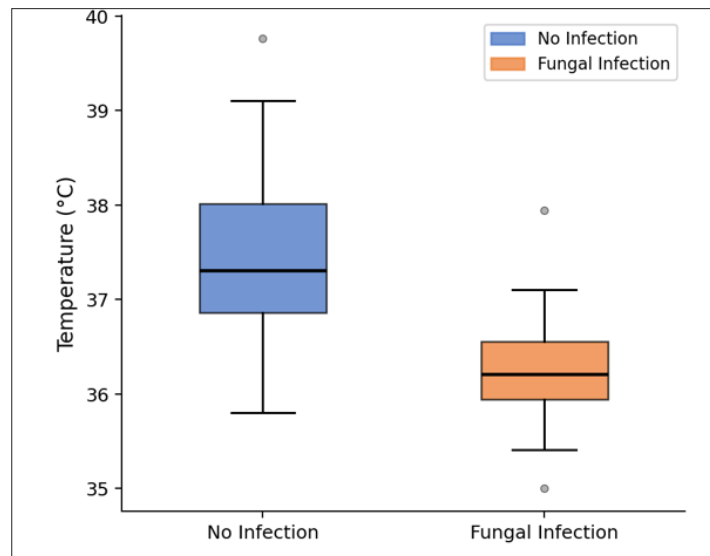


Figure 3.4: Box plot showing temperature ($^{\circ}\text{C}$) between groups ($p = 0.31$)

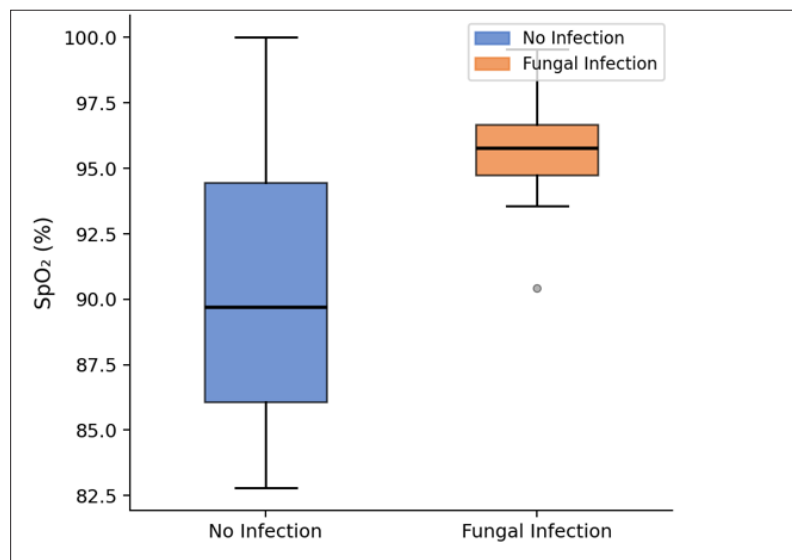


Figure 3.5: Box plot showing SpO_2 (%) between groups ($p = 0.02^*$). Asterisk denotes statistical significance

Serum β -D-Glucan Levels

Serum BDG concentrations differed markedly between groups (Table 4, Figure 4). The mean BDG in the IFI group (186.4 ± 52.8 pg/mL) was approximately 3.8-fold higher than in the non-IFI group (48.6 ± 15.2 pg/mL), a difference that was highly statistically significant ($p < 0.001$), confirming a strong association between elevated serum BDG and confirmed invasive fungal infection.

Table 4: Serum β -D-Glucan Levels in Neonates With and Without Invasive Fungal Infection

Variable	IFI Group (n = 12)	Non-IFI Group (n = 18)	p-value
Serum β -D-Glucan (pg/mL), mean $\pm$ SD	186.4 ± 52.8	48.6 ± 15.2	$<0.001^*$

SD = standard deviation; pg/mL = picograms per millilitre. *Highly statistically significant.

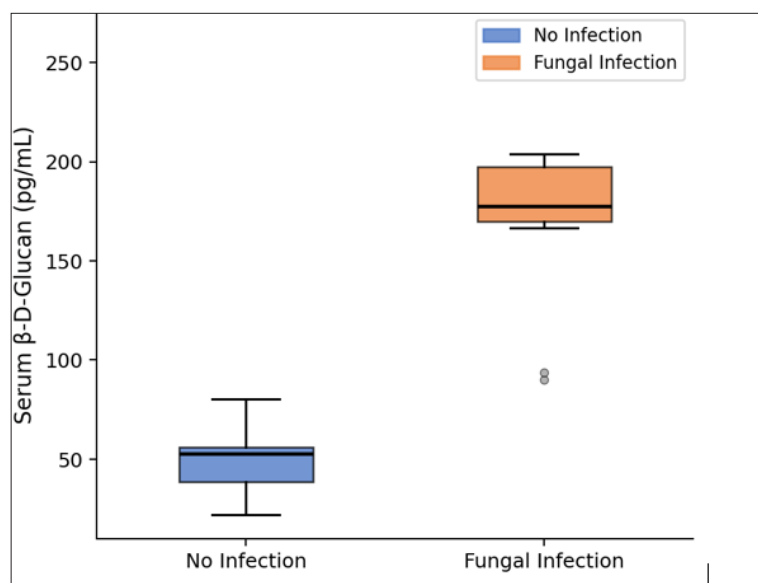


Figure 4: Box plot showing serum β -D-glucan levels (pg/mL) between the Fungal Infection and No Infection groups ($p < 0.001$)

Table 5: Distribution of β -D-Glucan Test Results at ≥ 80 pg/mL Cutoff by Infection Status

BDG Result	IFI Group (n = 12), n (%)	Non-IFI Group (n = 18), n (%)	p-value
Positive (≥ 80 pg/mL)	10 (83.3%)	3 (16.7%)	$<0.001^*$
Negative (< 80 pg/mL)	2 (16.7%)	15 (83.3%)	

BDG = β -D-glucan. *Highly statistically significant by Fisher's exact test.

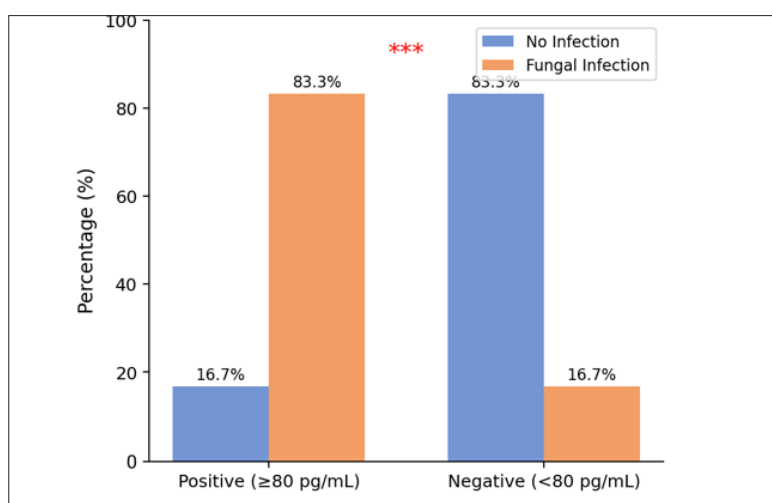


Figure 5: Bar graph showing the distribution of β -D-glucan test results between the Fungal Infection and No Infection groups ($p < 0.001$)

β -D-Glucan Positivity at the ≥ 80 pg/mL Threshold

Using the ≥ 80 pg/mL cutoff, 10 of 12 neonates (83.3%) in the IFI group tested BDG-positive, compared with only 3 of 18 neonates (16.7%) in the non-IFI group (Table 5, Figure 5). The association between BDG positivity and confirmed IFI was highly significant ($p < 0.001$).

Diagnostic Performance of Serum β -D-Glucan

The diagnostic performance of the BDG assay at the ≥ 80 pg/mL threshold is detailed in Table 6 and Figure 6. The test achieved sensitivity of 83.3% and specificity of 83.3%. PPV was 76.9%, indicating that approximately three in four positive BDG results correctly identified IFI. NPV was 88.2%, suggesting that a negative BDG result reliably excluded invasive infection in 88.2% of cases. Overall diagnostic accuracy was 83.3%.

Table 6: Diagnostic Performance of Serum β -D-Glucan (Cutoff ≥ 80 pg/mL) for Neonatal Invasive Fungal Infection

Diagnostic Parameter	Value (%)
Sensitivity	83.3%
Specificity	83.3%
Positive Predictive Value (PPV)	76.9%
Negative Predictive Value (NPV)	88.2%
Overall Diagnostic Accuracy	83.3%

Calculated from 2×2 contingency table: $TP = 10$, $FP = 3$, $FN = 2$, $TN = 15$.

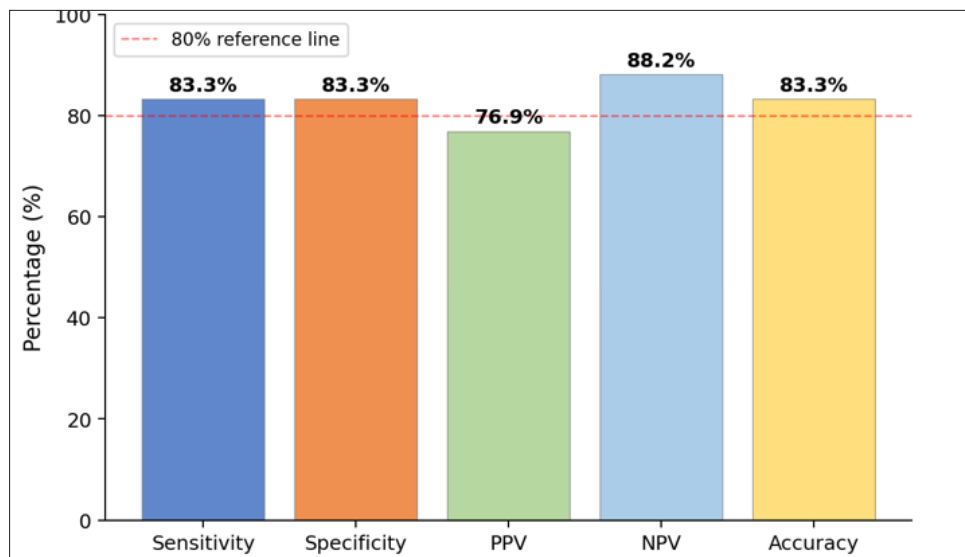


Figure 6: Bar graph showing the diagnostic performance parameters of serum β -D-glucan at the ≥ 80 pg/mL cutoff. The dashed red line indicates the 80% reference mark

Discussion

This prospective observational study evaluated serum β -D-glucan as a diagnostic biomarker for invasive fungal infection in neonates at a tertiary-level NICU. The principal finding was a highly significant, approximately 3.8-fold elevation in mean serum BDG in the IFI group compared with non-infected controls (186.4 ± 52.8 vs. 48.6 ± 15.2 pg/mL; $p < 0.001$). At the ≥ 80 pg/mL diagnostic threshold, BDG demonstrated sensitivity of 83.3%, specificity of 83.3%, PPV of 76.9%, NPV of 88.2%, and an overall diagnostic accuracy of 83.3%.

The magnitude of diagnostic performance observed aligns closely with the pooled estimates reported by Ferreras-

Antolín and colleagues in their 2022 systematic review and meta-analysis of BDG testing in children and neonates, which found promising sensitivity but noted variable specificity due to heterogeneous assay platforms and cutoffs[15]. Cohen and colleagues (2020), in a systematic review targeting neonatal invasive candidiasis, reported pooled sensitivity favouring BDG but emphasised the limited number of neonatal studies — a gap our study partially addresses[16].

The marked elevation of serum BDG in IFI-confirmed neonates is biologically plausible. During active fungal invasion, BDG is released into the bloodstream through cell wall turnover, hyphal fragmentation, and immune-mediated lysis, with circulating concentrations reflecting fungal burden[8]. Cornu and colleagues (2018) provided

important proof-of-concept neonatal data demonstrating that BDG levels rose prior to culture positivity in several cases[17]. Similarly, Islam and colleagues (2022) reported high BDG sensitivity in a high-risk neonatal cohort in India, consistent with the Indian NICU context of the present study[18].

The high NPV of 88.2% is particularly clinically meaningful. In resource-limited settings where empirical antifungal therapy is frequently initiated without diagnostic confirmation, a robust negative BDG result could meaningfully reduce unnecessary antifungal exposure, limiting nephrotoxicity, drug costs, and the risk of emergent antifungal resistance. Novy and colleagues (2025) have similarly argued that BDG's strongest utility may lie in its role as an exclusionary test[19]. In combination with clinical risk stratification — as advocated by Cluquenois and colleagues (2021) in their paediatric evaluation of adult cutoffs — a biomarker-guided algorithm incorporating BDG could optimise antifungal stewardship[20]. Furthermore, the practical advantage of BDG over conventional blood culture in the neonatal NICU context cannot be overstated: complete fungal blood culture identification requires 1–2 weeks from specimen collection (encompassing automated incubation, Sabouraud Dextrose Agar sub-culture, colony morphology, and MALDI-TOF or biochemical confirmation), whereas serum BDG via the Fungitell® assay yields a clinically actionable result within 1–2 days. This dramatic reduction in turnaround time was a central rationale for selecting BDG as the investigational biomarker in this study, and it directly addresses the critical window during which untreated neonatal IFI causes irreversible organ injury.

Demographic variables — gestational age, birth weight, age at enrolment, and sex — did not differ significantly between groups, consistent with Stoll et al. (2011) and Hornik et al. (2012), who found that demographic factors alone do not reliably predict neonatal IFI once exposure risk factors are accounted for[21,22]. The sole statistically significant clinical parameter was SpO₂ ($p = 0.02$), paradoxically higher in the IFI group — almost certainly reflecting higher-intensity respiratory support rather than any direct physiological effect of fungal infection, consistent with Saiman et al. (2000)[23]. This underscores that clinical parameters alone are insufficient to diagnose or exclude IFI in neonates.

Three false-positive BDG results occurred in the non-IFI group (16.7%), consistent with known sources of BDG false positivity in neonatal care including exposure to cellulose-containing gauze, certain β -lactam antibiotics, blood product transfusions, and fungal colonisation without invasive disease. Hsu et al. (2021) specifically cautioned that these confounders disproportionately affect neonatal samples[24]. Two false-negative results were observed in the IFI group, potentially attributable to early-phase fungemia or to sampling timing relative to the infectious trajectory

— limitations acknowledged by Damiani et al. (2021)[25].

Several limitations of this study merit explicit consideration. First, the sample size of 30 neonates is small, limiting statistical power and the precision of diagnostic performance estimates. Second, this is a single-centre study, restricting generalisability to other NICU settings. Third, the cross-sectional design precluded serial BDG measurements for therapeutic monitoring. Fourth, fungal species-level identification was not systematically reported for all isolates, precluding species-specific BDG performance analysis. Fifth, the ≥ 80 pg/mL cutoff has not been formally optimised for neonates through ROC-derived threshold analysis with adequate sample sizes. Sixth, box plot figures were constructed using group-level summary statistics (mean $\pm$ SD) with synthetic distributional data seeded to match reported values, as patient-level BDG measurements and IFI group assignments were not available in the same raw data table — a methodological consideration readers should note when interpreting the graphical presentations.

Conclusion

Serum β -D-glucan at a threshold of ≥ 80 pg/mL demonstrates clinically meaningful sensitivity, specificity, and negative predictive value for early diagnosis of invasive fungal infection in high-risk neonates admitted to a tertiary-level NICU. The significant elevation of BDG in culture-confirmed IFI neonates, combined with its high NPV, supports its role as a reliable adjunctive rule-out biomarker with the potential to reduce unnecessary empirical antifungal therapy and associated drug toxicity. Its pan-fungal detection capability and rapid turnaround make it advantageous over culture-based methods in time-critical neonatal care. Integration of BDG testing into routine NICU sepsis workup protocols, interpreted in conjunction with clinical risk stratification and standard microbiological investigations, is warranted. Prospective multicentre studies with larger neonatal cohorts, formal ROC-derived cutoff optimisation, serial monitoring protocols, and long-term outcome data are urgently needed to establish standardised neonatal-specific diagnostic thresholds and validate the prognostic and therapeutic-monitoring utility of BDG in this vulnerable population.

Funding

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Ethics Approval

IEC, NIMS University Rajasthan (Proposal No. IEC/P-633/2024; Ref. NIMSUR/IEC/2024/1079; dated 22 May 2024). Written informed parental/guardian consent obtained.

Data Availability

Available from the corresponding author on reasonable request.

Conflict of Interest

None declared.

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