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Original Article

Diagnostic value of β-D-glucan alone or combined with *Candida* score, colonization index and C-reactive protein for candidemia

Sumeyye Kazancioglu[1], Aliye Bastug[2], Bircan Kayaaslan[3], Nevzat Mehmet Mutlu[4], Esin Calci[5], Turan Turhan[6], Ipek Mumcuoglu[7], Esragul Akinci[2], Hurrem Bodur[2]

[1] Department of Infectious Diseases and Clinical Microbiology, Ankara City Hospital, Ankara, Turkey
[2] Department of Infectious Diseases and Clinical Microbiology, Health Science University Turkey, Ankara City Hospital, Ankara, Turkey
[3] Department of Infectious Diseases and Clinical Microbiology, Yildirim Beyazit University, Ankara City Hospital, Ankara, Turkey
[4] Department of Anesthesiology, Ankara City Hospital, Ankara, Turkey
[5] Department of Clinical Biochemistry, Uşak Public Health laboratory, Uşak, Turkey
[6] Department of Clinical Biochemistry, Ankara City Hospital, Ankara, Turkey
[7] Department of Clinical Microbiology, Ankara City Hospital, Ankara, Turkey

Abstract

Introduction: Candidemia causes high mortality and is occuring at increasing rate in intensive care units (ICUs). (1,3)- β-D-glucan (BDG) testing is recommended in neutropenic patients. However the usefulness of BDG in ICUs is unclear.

Methodology: This study was conducted to compare the diagnostic value of *Candida* score (CS), colonization index (CI), serum BDG detection, and routine laboratory parameters in ICU patients. Characteristics and laboratory data of 83 patients (15 patients with candidemia and 68 patients without candidemia) were evaluated.

Results: Median serum BDG was significantly higher in the candidemia group (129 pg/mL vs. 36 pg/mL, $p < 0.001$). BDG assay with standard cut-off value ≥ of 80 pg/mL had 93.33% sensitivity and 64.18% specificity (Areas under the ROC curve (AUC): 0.788). This study concluded that the optimal cut-off value for BDG assay was 112 pg/mL with sensitivity of 86.67% and specificity of 82.09% (AUC: 0.844). C-reactive protein (CRP) with optimal cut-off value ≥ 85 mg/L and BDG ≥ 80 pg/mL had the highest AUC (0.862, 95% CI: 0.768 - 0.928) with sensitivity 93.33% and specificity 79.1%.

Conclusions: Predicting candidemia is essential in critically ill patients who are at high risk and have high mortality rates. The results of this study suggest that BDG testing is useful for predicting candidemia in ICU. However, BDG combined with CRP may be a stronger predictor for candidemia.

Key words: Candidemia; (1,3)-β-D-glucan; C-reactive protein; ICU.

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Introduction

Invasive fungal infections are common nosocomial infections [1]. Candidemia is a blood-stream infection observed at increasing rates in non-neutropenic patients admitted to intensive care units (ICUs) and causes high mortality [2,3]. Risk factors of candidemia such as total parenteral nutrition (TPN), central venous catheterization (CVC), immunosuppressive agents, and surgery are well described in ICUs [4-6]. However, diagnosis of candidemia is challenging because the standard methods (e.g. clinical signs and symptoms, host risk assessment, physical examination, radiography) are not specific [7]. Blood culture is the gold standard test for candidemia diagnosis. However, blood culture positivity rates are 40 - 60% for candidemia, and culture incubation for at least 3-4 days is required [8,9]. Therefore, clinical prediction rules or scoring systems for invasive candidiasis have been developed. Colonization index (CI) and *Candida* score (CS) ≥ 3 are used in clinical practice in ICUs [10,11].

Testing (1,3)-β-D-glucan (BDG), a polysaccharide in the fungal cell wall, becomes important in the diagnosis of candidemia. BDG testing appears to be useful for patients with hematological malignancies and BDG testing is recommended in neutropenic patients [12].

This study was conducted to compare the diagnostic value of CS, CI, serum BDG detection, and routine

laboratory parameters in a prospective cohort of ICU patients at risk for *Candida* bloodstream infection.

Methodology

Study design and participants

This study was approved by the ethics committee of Ankara Numune Training and Research Hospital (No: E-15-540). The study was conducted in a 26-bed adult ICU of a tertiary training and research hospital. All patients consecutively admitted to ICU for four months were eligible for enrollment in this study. Patients were enrolled if they stayed in the ICU for more than seven days, had not been diagnosed with and treated for invasive fungal infection (IFI) at baseline, and had neutrophil count ≥ of 500/mm^3. Age, gender, Acute Physiology and Chronic Health Evaluation (APACHE), systemic inflammatory response syndrome (SIRS) score, primary diagnosis, presence of various known risk factors for candidiasis (for example, an indwelling CVC, broad-spectrum antibiotic therapy, immunosuppression or malignancy, mechanical ventilation, hemodialysis, hospitalization time in ICU longer than ten days, coexisting bacteremia, TPN, abdominal surgery, fever conditions, existing bacterial infections, laboratory values (C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin level, platelet and white blood cell (WBC) counts, glomerular filtration rate, blood culture results, and outcome were recorded. Variables potentially influencing BDG test results such as β-lactam antibiotics, renal replacement therapy, bacteremia, and recent administration of albumin and immunoglobulin products were also recorded. For all patients, specimen from the *Candida* surveillance sites, such as the rectum, oropharynx, skin (axillary surface), urinary tract, and tracheal aspirate cultures were obtained on the day of admission to the ICU and once a week thereafter until discharge from the ICU or death. Corn Meal agar was used for *Candida* isolation and species definition. Specimen for cultures from other anatomical sites (such as a wound) were ordered as clinically indicated by the attending physician. BDG assay (from a peripheral venipuncture) and blood cultures (from a peripheral venipuncture and/or intravascular catheter) were obtained on the day of admission to the ICU and once a week thereafter until discharge from the ICU or death. Blood cultures were also obtained when the patient had fever and/or at the onset of sepsis. Blood cultures were processed using the automated BACTEC system (Becton Dickinson Diagnostic Instruments, Sparks, MD, USA).

Although blood and microbiological samples were taken prospectively, clinical follow-up and treatment status of the patients was not interfered with by the researchers. Patients receiving prophylactic or empirical antifungal agents were excluded from the study.

Candida score and Colonization index

CS and CI were calculated from the results of the patients' surveillance cultures that were available once a week. CS with a cut-off value of 3 was as follows: TPN × 1, plus surgery × 1, plus multifocal *Candida* colonization × 1, plus severe sepsis × 2. The colonization index was calculated as the ratio of the number of culture-positive surveillance sites to the total number of sites cultured. The cut-off points were taken as ≥ 3 for CS and ≥ 0.5 for CI [10,13]. Maximum values recorded for CS and colonization index in each patient at or before candidemia were used in the analysis. In the absence of candidemia, the maximum of all observed values was used.

BDG Assay

Samples were collected in serum separation tubes and centrifuged within 30 minutes of collection. Samples were separated into aliquots and were frozen at -20°C until they were assayed. BDG measurements were performed in batches, and samples had no more than two freeze-thaw cycles. BDG concentrations were measured using a commercially available Fungitell test kit following manufacturer's recommendation (Associates of Cape Cod Inc, East Falmouth, MA). Measurable ranges were 31, 25-500 pg/mL. BDG concentrations of < 60 pg/mL were interpreted as negative, ≥ 80 pg/mL as positive and 60-79 pg/mL as intermediate result. Hemolysis, lipemia, and apparent bilirubin interfered with the measurement and results. All samples were analyzed in triplicate and the mean value was used for further analysis.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA). Normally distributed continuous variables were reported as mean ± SD, and compared using Student's *t*-test. Medians with ranges were used to describe non-normally distributed continuous variables, and compared using the Mann-Whitney U-test. Comparisons for categorical variables were executed using the Pearson Chi-square test or Fisher's exact test. The receiver operation characteristic (ROC) curve analysis was used to determine the efficacy of BDG, CS, and CI for

discriminating the patients with candidemia. Statistical significance was defined as $p < 0.05$.

Results

Of the 137 patients admitted to ICU during the study period, 83 met the inclusion criteria specified above, and were enrolled in the study. Characteristics of the 83 patients (15 in the candidemia group and 68 in the group without candidemia) are shown in Table 1. Mean age of the patients was 68.3 ± 17.0 years. 56.6% of the patients were male. Age and gender were not significantly different between candidemia and non-candidemia groups. Candidemia patients stayed longer in the ICU (43.5 ± 31.7 vs. 16.3 ± 8.6 days, $p = 0.05$). There were no differences in comorbidities between the groups. All candidemia patients had CVC and broad-to-spectrum antibiotics. The overall mortality rate was 45.8%. There was no significant association between gender and mortality ($p = 0.830$, 44.4% (n=16) in female vs 46.8% (n = 22) in male). Twelve (80%) of the patients with candidemia died. Mortality rate was significantly higher in patients with candidemia ($p = 0.003$).

Candidemia was detected in 15 (18%) of the patients. Non-albicans *Candida* species were more common (10 of 15 patients, *Candida parapsilosis;* n = 5, *Candida krusei*; n = 3, *Candida glabrata*; n = 1, *Candida famata*; n = 1). Candidemia often occurred in the last days of hospitalization (29.2 ± 25.2 days). Six patients did not receive appropriate antifungal therapy (Table 1, 2).

As shown in Table 1, the percentages of patients with sepsis and Gram-positive bacteremia were significantly higher in patients with candidemia ($p < 0.05$). Nine patients (60%) had sepsis in the candidemia group. In the non-candidemia group, the presence of sepsis was found in eighteen patients (26.5%) due to the coexistence of Gram-negative and Gram-positive bacteremia in two patients (in 20 bacteremia cases).

Table 1. Clinical characteristics of patients with or without candidemia.

	Total (n = 83)	**Candidemia (n = 15)**	**Non-candidemia (n = 68)**	***p*-value**
Age, median years	68.3 ± 17.0	71.8 ± 14.8	67.6 ± 17.5	0.67
Male (%)	47 (56.6)	8 (53.3)	39 (57.3)	0.78
APACHE score	23.7 ± 7.9	25 ± 5.5	23.4 ± 8.4	0.48
ICU stay, median	21.2 ± 18.6	43.5 ± 31.7	16.3 ± 8.6	0.05*
Underlying diseases (n, %)				
Diabetes mellitus	20 (24.1)	6 (40)	20 (29.4)	0.540
Hypertension	45 54.2)	10 (66.7)	35 (51.5)	0.290
Immunosupression/malignancy	15 (18.1)	3 (20)	12 (17.6)	1.000
COPD	18 (21.7)	3 (20)	15 (22.1)	1.000
Chronic renal failure	10 (12)	1 (6.7)	9 (13.2)	0.680
Coronary arterial disease	32 (38.6)	7 (46.7)	25 (13.2)	0.480
Cerebrovasculer disease	29 (34.9)	4 (26.7)	25 (13.2)	0.460
Surgery	18 (21.7)	4 (26.7)	14 (20.6)	0.730
Risk factors (n, %)				
Broad to spectrum antibiotics	79 (94.0)	15 (100)	64 (94.1)	1.000
Central venous catheter	68 (81.9)	15 (100)	53 (77.9)	0.060
Total parenteral nutrition	55 (66.3)	12 (80)	43 (63.2)	0.210
Abdominal surgery	4 (4.8)	1 (6.7)	3 (4.4)	0.560
Mechanical ventilation	70 (84.3)	14 (93.3)	56 (82.4)	0.450
Hemodialysis	26 (31.3)	7 (46.7)	19 (27.9)	0.220
ICU stay > 10 days	66 (79.5)	14 (93.3)	52 (76.5)	0.290
Clinical conditions				
Fever	64 (77.1)	15 (100)	49 (72.1)	0.020*
Sepsis	27 (32.5)	9 (60)	18 (26.5)**	0.020*
Pneumonia	31 (37.3)	7 (46.7)	24 (35.3)	0.410
Gram-positive bloodstream infection	14 (16.9)	6 (40)	8 (11.8)	0.020*
Gram-negative bloodstream infection	15 (18.1)	3 (20)	12 (17.6)	1.000
Positive BDG results	41 (49.4)	14 (93.3)	27 (39.7)	0.010*
Colonization score value ≥ 3	25 (30.1)	10 (66.7)	15 (22.1)	0.001*
Colonization index ≥ 0.5	11 (13.3)	6 (40)	5 (7.4)	0.025*
ICU mortality	38 (45.8)	12 (80)	26 (38.2)	0.003*

Data are mean ± SD or n (%). *p*-values comparing candidemia patients and non-candidemia patients. APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease; BDG: (1,3)- β-D-glucan. * Statistical significance was defined as $p < 0.05$. ** The coexistence of Gram-negative and positive bacteremia in two patients.

Table 2. Characteristics of fifteen patients with candidemia.

Patient No	Underlying Conditions	Age	Admission Diagnosis	CI	CS	BDG level	Treatment	Treatment time	*Candida* species	Hospital stay	The day of candidemia	Outcome
70	Diabetes, hypertension, orthopedic surgery	89	Wound infection	0.4	4	37	fluconazole	0	*C. parapsilosis*	10	10	dead
59	Malignancy, abdominal surgery	68	Mediastinitis, pneumonia	0.4	4	523	-	0	*C. parapsilosis*	44	41	dead
132	Malignancy	50	Pneumonia	0.4	4	417	-	0	*C. krusei*	18	13	dead
49	Diabetes, hypertension	76	Cerebrovasculer event	0.2	3	523	-	0	*C. krusei*	102	98	dead
48	Hypertension	73	Encephalitis	0.2	1	115	anidulafungine	4	*C. albicans*	24	16	alive
41	Hypertension, orthopedic surgery	89	Respiratory failure	0.8	4	165	-	0	*C. parapsilosis*	21	16	dead
33	Coronary artery disease	83	Respiratory failure	0.2	1	82	fluconazole	2	*C. krusei*	14	8	dead
32	Diabetes, hypertension,	84	Respiratory failure	0.6	3	523	fluconazole	1	*C. albicans*	16	11	dead
19	Coronary artery disease	49	Acute coronary syndrome	0.2	1	523	fluconazole	7	*C. glabrata*	58	6	alive
9	Diabetes, hypertension,	81	Subaracnoid hemorrhage	0.8	4	523	-	0	*C. famata*	27	24	dead
6	Diabetes, hypertension, dementia	76	Pneumonia	0.8	3	236	fluconazole	2	*C. albicans*	45	28	dead
104	Diabetes, hypertension,	63	*Listeria* menengitis	0.2	0	369	fluconazole	4	*C. parapsilosis*	50	40	alive
99	Diabetes, hypertension,	69	Pneumonia	0.4	3	461	anidulafungine	1	*C. albicans*	106	20	dead
21	Dementia, hypertension, trauma	84	Respiratory failure	0.8	4	523	-	0	*C. albicans*	62	59	dead
66	Chronic renal failure, quadriplegic	43	Pneumonia	0.4	2	144	caspofungine	4	*C. parapsilosis*	73	51	dead

CI: Colonization index; CS: *Candida* score; BDG: (1,3)-β-D-glucan.

Table 3. Laboratory parameters of patients with and without candidemia.

	Total (n = 83)	Candidemia (n = 15)	No-candidemia (n = 68)	*p*-value
Leucocytes	11200 (3200-37900)	15300 (3200-31000)	11050 (4400-37900)	0.290
Neutrophils	8900 (100-33200)	11800 (300-28700)	8850 (100-33200)	0.520
Lymphocytes	1100 (200-7200)	1500 (200-7200)	1100 (200-3500)	0.210
Platelets	195000 (8800-588000)	173000 (24000-461000)	205000 (8800-588000)	0.500
Hemoglobin	9.9 (6.7-13.4)	9.5 (7.3-13.0)	10.0 (6.7-13.4)	0.540
ALT	26 (3-712)	19 (4-712)	26.5 (3-325)	0.990
AST	32 (1-1118)	60 (17-365)	29.5 (1-1118)	0.820
GFR	41.3 (7-60)	32 (20-60)	49.5 (7-60)	0.680
CRP	122.4 (2-356)	124 (86-317)	90 (2-356)	0.020*
NLR	8.2 (0.08-133)	7.6 (0.08-94)	8.8 (0.11-133)	0.670
BDG level	68 (0-523)	129 (8-523)	36 (0-523)	< 0.001*

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GFR: Glomerular filtration rate, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocytes ratio, BDG: (1,3)-β-D-glucan. * Statistical significance was defined as $p < 0.05$.

Fever was also significantly higher in the group with candidemia ($p = 0.020$). There was no difference in underlying diseases between the two groups. There were only two patients in the non-candidemia group who were treated with corticosteroids. Therefore, the relationship between corticosteroids and candidemia could not be analyzed.

Routine laboratory parameters are shown in Table 3. Significantly higher CRP, leucocytes, neutrophils, and lower platelets were found in the candidemia group.

Several surveillance specimens from the 83 patients were screened for the presence of *Candida* species. *Candida* species colonized in at least one anatomical site in all patients in the candidemia group with colonization index ≥ 0.5, and was found in 9% (6/68) of non-candidemia patients and 33.3% (5/15) of patients with candidemia ($p = 0.025$). CS ≥ 3 was found in 22.1% (15/68) of non-candidemia patients and in 66.7% (10/15) of patients with candidemia ($p = 0.001$).

BDG positivity was higher in the candidemia group than in the non-candidemia group. BDG positivity was found in all but one of the candidemia patients. Among the patients who had no candidemia, 27 of 68 patients tested were BDG-positive. But 23 of these 27 patients had ≥ 2 false-positive factors. The median serum BDG was significantly higher in the candidemia group (129 pg/mL vs. 36 pg/mL, $p < 0.001$) (Figure 1).

Diagnostic test indices for candidemia are presented in Table 4. BDG assay with a standard cut-off value ≥ of 80 pg/mL had 93.33% sensitivity and 64.18% specificity (Area under the curve (AUC): 0.788). This study demonstrated that the optimal cut-off value for BDG assay was 112 pg/mL with sensitivity of 86.67% and specificity of 82.09% (AUC: 0.844).

Figure 1. (1,3)-β-D-glucan levels in patients with candidemia and without candidemia.

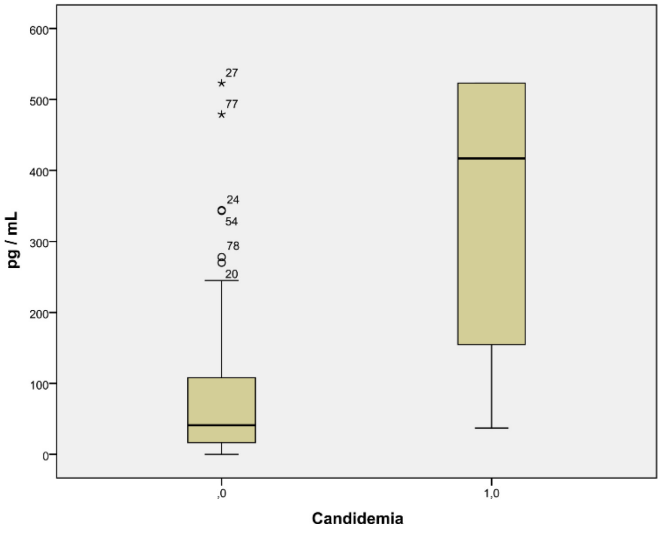

Figure 2. ROC analysis of (1,3)-β-D-glucan alone, (1,3)-β-D-glucan + C-reactive protein, and (1,3)-β-D-glucan + Candida score ≥ 3 for the diagnosis of candidemia.

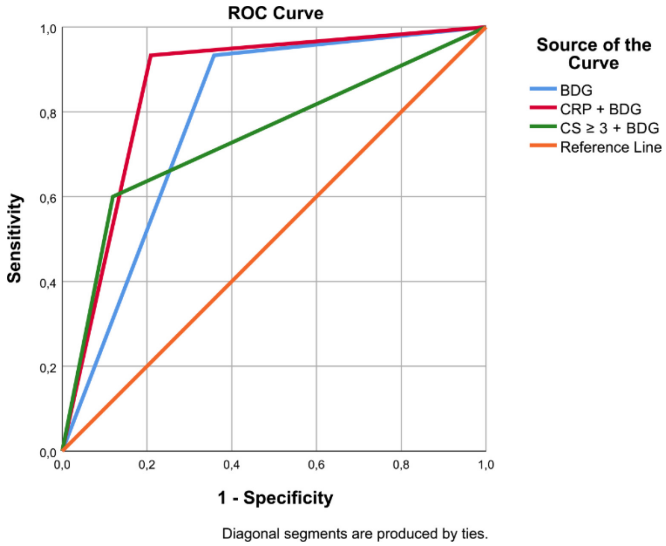

Table 4. ROC analysis for the diagnosis of candidemia.

	Sensitivity	Specificity	+ LR	- LR	+ PV	- PV	AUC	95% CI	*p*-value
BDG ≥ 80 pg/mL	93.33	64.18	2.61	0.1	36.8	97.7	0.788	0.683-0.870	< 0.0001*
BDG ≥ 112 pg/mL	86.67	82.09	4.84	0.16	52	96.5	0.844	0.747-0.915	< 0.0001*
CI ≥ 0.5	33.33	91.04	3.72	0.73	45.5	85.9	0.622	0.508-0.727	0.062
CS ≥ 3	66.67	77.94	3.02	0.43	40	91.4	0.723	0.614-0.816	0.001*
CRP ≥ 85 g/dL	100	48.53	1.94	0	30	100	0.743	0.635-0.832	< 0.0001*
Sepsis	60	66.04	1.77	0.61	33.3	85.4	0.630	0.504-0.744	0.076
CRP ≥ 85 g/dL + BDG ≥ 80 pg/mL	93.33	79.1	4.47	0.084	50	98.1	0.862	0.768-0.928	< 0.0001*
CRP ≥ 85 g/dL + BDG ≥ 112 pg/mL	86.67	82.09	4.84	0.16	52	96.5	0.844	0.747-0.915	< 0.0001*
CI ≥ 0.5 + ≥ 80 pg/mL	33.33	92.54	4.47	0.72	50	86.1	0.629	0.516-0.733	0.047*
CI ≥ 0.5 + ≥ 112 pg/mL	33.33	94.03	5.58	0.71	55.6	86.3	0.637	0.523-0.740	0.034*
CS ≥ 3 + BDG ≥ 80 pg/mL	53.33	91.04	5.96	0.51	57.1	89.7	0.722	0.612-0.815	0.001*
CS ≥ 3 + BDG ≥ 112 pg/mL	60	88.06	5.02	0.45	52.9	90.8	0.740	0.632-0.831	0.000*
Sepsis + BDG ≥ 80 pg/mL	53.33	82.69	3.08	0.56	47.1	86	0.680	0.555-0.789	0.012*
Sepsis + BDG ≥ 112 pg/mL	46.67	84.62	3.03	0.63	46.7	84.6	0.656	0.530-0.768	0.028*

BDG: (1,3)-β-D-glucan; CI: Colonization index; CS: *Candida* score; CRP: C-reactive protein. * Statistical significance was defined as $p < 0.05$.

CRP with optimal cut-off value ≥ 85 mg/L (based on this study) + BDG ≥ 80 pg/mL had the highest AUC (0.862, 95% CI: 0.768 - 0.928) with sensitivity 93.33% and specificity 79.1%. CS ≥ 3 was found to be associated with a diagnosis of candidemia whereas CI ≥ 0.5 was not significantly associated. While sepsis alone was not a significant association in the diagnosis of candidemia, sepsis and BDG positivity were significantly associated with the diagnosis. The specificity increased when the BDG assay was evaluated with CI and CS instead of BDG assay on its own. The AUCs for BDG, CS, CI, and CRP were presented in Table 4 and Figure 2.

Discussion

Using CI, CS and BDG levels of patients ın ICU were evaluated in this study. The patients included 15 with candidemia and 68 with no candidemia. In this study, the optimal cut-off value for BG level ≥ 112 pg/mL was found to have sensitivity of 86.67% and specificity of 82.09% for the diagnosis of candidemia. CRP ≥ 85 mg/L + BDG ≥ 80 pg/mL had the highest AUC with high sensitivity and specificity. Additionally, it was observed that specificity for candidemia increased when the BDG assay was evaluated along with CI or CS.

According to a meta-analysis, sensitivity 81.3% (95% CI; 75.3% to 86.0%) and specificity 64.1% (95% CI; 55.6% to 71.8%) were estimated for BDG with standard cut-off value ≥ 80 for candidemia [7]. Similarly, in this study BDG, with standard cut-off value ≥ of 80 pg/mL, sensitivity of 93.33% and 64.18% specificity. Higher negative predictive value (NPV) of BDG (97.7%) was found in this study, similar to previous reports in the literature; therefore BDG testing can also be useful for excluding candidemia [8]. However, CRP (optimal cut-off value 85 mg/L) + BG ≥ 80 pg/mL had the highest AUC with sensitivity of 93.33% and specificity of 79.1%. The major uncertainty for BDG testing, particularly in high-risk populations in ICUs is poor specificity and positive predictive value (PPV). Similarly, in this study, BDG testing alone (with a cut-off of 80 pg/mL) had low specificity 64.18% and low PPV 36.8%. Therefore, when evaluated together with the increased optimal cut-off value (112 pg/mL) and CRP; specificity and PPV were found to be more diagnostic. Previously, Guo *et al*. reported that BDG combined with hsCRP increased diagnostic value for candidemia [14]. CRP is a traditional inflammatory marker that can be useful for the diagnosis of candidemia. Miglietta *et al.* found CRP (cut-off value: 76.2 mg/L) had sensitivity of 77.2% and specificity of 63.6% for distinguishing candidemia from bacterial sepsis [15]. Therefore it was concluded that assessment of CRP and BDG together may be more useful to predict candidemia.

Candida colonization is a predictor of candidemia in ICUs. CI ≥ 0.5 was more common in the candidemia group in this study. *Candida* colonization in combination with other risk factors such as TPN, surgery, and sepsis in ICU patients is more predictive for candidemia. Leon *et al*. showed that the AUC for CS ≥ 3 was 0.774 (95% CI 0.715 – 0.832) with sensitivity 77.6%, specificity 66.2%) compared with 0.633 (95% CI 0.557 – 0.709) for CI [10]. In this study, the AUC for CS ≥ 3 was 0.723 (95% CI 0.614 – 0.816) with sensitivity 77.94%, specificity 66.67%) compared with 0.622 (95% CI 0.508 – 0.727) for CI. It was suggested that BDG testing can be combined with other markers of candidemia (eg Candida score, *Candida albicans* germ tub antibody (CAGTA)) in ICUs [16]. The concerns over low positive predictive value (PPV) restrict use of BDG for the diagnosis of fungal infection in ICUs. A review article suggested that a combination of CS (two times a week) and non-culture microbiological tools for predicting candidemia in ICUs [17]. In this study, CS combined with BDG were found to be associated with improved specificity and PPV.

Conclusions

ICU patients represent a critical population to predict the diagnosis of candidemia due to high mortality rates. Blood culture is the gold standard test for candidemia diagnosis but the identification of a *Candida* species takes a long time. Our results suggest that BDG testing is useful for predicting candidemia. However, BDG combined with CRP (with an optimal cut-off value ≥ 85 mg/L) could be more predictive with higher sensitivity and specificity.

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Authors' Contributions

SK and BK contributed to the conception, design, and data collection. SK contributed to the statistical analysis, literature research, drafting and revision of the manuscript. AB helped in drafting and revising of the manuscript. NMM participated in data collection from patients and analysis. AC, TT, and IM

contributed to the collection of microbiological and biochemical data, statistical analysis, and interpretation of the results. HB and EA contributed to data interpretation, drafting the manuscript, critical revision of the manuscript, and supervision. All authors have read and approved the final manuscript.

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Corresponding author

Sumeyye Kazancioglu, MD.
Department of Infectious Diseases and Clinical Microbiology, Sağlık Bakanlığı Ankara City Hospital, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya/ ANKARA Postal Code: 06800
Phone: +90 505 375 03 36
Fax: +90 312 552 60 00
E-mail: sumeyye_yildiz@hotmail.com

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