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Original Article

Clinical Usefulness of Serum (1,3)-β-D-glucan to predict invasive candidiasis in patients with severe burn trauma

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KEYWORDS
(1,3)-β-D-glucan;
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Abstract *Background:* (1,3)-β-D-glucan (BD) assays were developed as a method to rapidly diagnose invasive candidiasis (IC). The incidence of fungal infections and the demands for BD assay are gradually increasing in patients with severe trauma and under intensive care. However, the ideal BD cut-off value to predict IC has not been clarified. In this study, we evaluate the predictability of the BD assay and investigate the optimal cut-off value in patients with severe burn injuries.
Methods: From July to December 2018, 134 samples from 86 patients with severe burns were analyzed. Serum BD levels were measured utilizing a Fungitell (Cape Cod Inc.) assay. A receiver operator characteristic (ROC) curve was generated, and the cumulative progression of IC was studied using a Cox proportional hazards model. Partial dependence plots (PDP) was applied to predict the risk of IC.
Results: Eleven patients were diagnosed with IC. BD over 120 pg/mL (HR = 8.68; $P = 0.001$) was found to be independent predictor of the occurrence of IC, when the multivariable Cox model was adjusted for age, total body surface area, inhalation injury, and antifungal agents. The area under the ROC curve was 0.658 (95% CI, 0.513–0.803), at an optimal cut-off value of 124.7 pg/mL. PDP analysis showed the higher predicted IC occurrence at a BD level of 120–150 pg/mL and TBSA over 60%.
Conclusion: Our findings suggest that BD is an independent predictor for IC, and that a BD level between 120 and 150 pg/mL could be utilized for IC prediction.

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Introduction

Invasive candidiasis (IC) is considered to be a major cause of mortality, with a higher risk of death than blood infections caused by other fungi.[1,2] The timely diagnosis of fungal infections has proven difficult as culture-based tests have a low sensitivity and specificity, and require a long time to establish the final diagnosis.[3,4] Therefore, the need for a more sensitive and rapid diagnosis has increased. This requirement led to the development of (1,3)-β-D-glucan (BD) assays.[5—9] BD is a major component of fungal cell walls and is known to be detected with relatively high sensitivity and accuracy during testing.[10,11] The revised European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria included BD testing for IC diagnosis and the revised European Society of Clinical Microbiology and Infectious Diseases criteria included BD assay results as diagnostic criteria for candidemia and invasive candidiasis.[12—14]

Burn patients have low immunity and are directly exposed to several infectious agents, making them a high-risk group for IC. Additionally, the incidence of bacterial infections in burn patients is decreasing globally, whereas the incidence of fungal infections is gradually increasing due to the suppression of normal flora and antibiotic-associated mucosal damage in the gastrointestinal tract.[15—17] Thus, an accurate diagnosis of IC is increasingly important for the early detection of the source of infection and the use of prophylactic antifungal agents.

Nevertheless, to date, the efficacy of the BD test in patients with severe burns and trauma under intensive care unit has not been clarified. In particular, studies on performance evaluation and the clinical efficacy of the BD assay have been performed intermittently in patients with hematologic malignancy and organ transplantation but have rarely been conducted in patients with severe burns and trauma.[16,18] Moreover, the ideal cut-off value for BD testing to predict IC, utilizing various statistical methods has not been studied. Therefore, this study aimed to analyze the predictive ability of the BD assay on IC progression in patients with severe burns.

Methods

Patients

The study was conducted with a study population of burn-injured adult patients who visited the burn intensive care unit (ICU) in Hangang Sacred Heart Hospital from July to December 2018. Patients who were referred from other hospitals during treatment or over a week after the burn injury were excluded from the study. For each of the patients, the duration of the study period began on the day of ICU admission and continued up till 60 days from the day of admission. Serum samples were collected to measure BD values on the first day of ICU admission, as well as Day 7 and Day 14.

We investigated patient medical records including demographic data, medical history such as medication, clinical course, comorbidities, and laboratory tests conducted at admission including complete blood count, routine chemistry, C-reactive protein (CRP) and procalcitonin for each patient. Additionally, the factors associated with burn severity including total body surface area (TBSA), inhalation injury and full-thickness burns were recorded. Fungal culture data was collected during the study period. The VITEK®2 Compact System YST ID card (Biomerieux, France) was used for fungus identification. Other possible factors associated with a false increase in the BD level including the use of intravenous immunoglobulin (IVIG), albumin and dialysis equipment were investigated. This study was approved by the Institutional Review Board (IRB) of Hangang Sacred Heart Hospital of Hallym University (IRB No. 2018—054), and all included patients provided informed consent.

Measurement of (1,3)-β-D-glucan (BD) levels

BD levels were measured using a Fungitell® Assay (Associates of Cape Cod, East Falmouth, Mass.) according to the manufacturer's instructions. Positive values were determined according to the reference values provided by the manufacturer (positive, $>$ 80 pg/mL; intermediate, 60—80 pg/mL; negative, $<$ 60 pg/mL).

Definition of invasive fungal infection

IC was defined according to revised diagnostic criteria from the EORTC/MSG.[14] In this study, two investigators reviewed the cases, and patients identified as 'IC-proven', 'IC-probable', and 'IC-possible' during the study period were classified as IC cases. The results of the BD assay have not been utilized previously for the diagnostic classification of IC. A patient without clinical evidence of IC was defined as a patient with 'No IC'. Blood culture examinations were conducted twice a week for all patients; fungus culture tests were conducted as the patients had clinical symptoms of fungal infection. The date of detection of fungus using the culture test was considered the date of IC.

Statistics

Descriptive statistics for the patient dataset included measures of central tendency for continuous variables and frequencies for categorical variables. Chi-square tests and Mann—Whitney *U* tests were utilized to compare demographics and laboratory findings, based on IC status. A ROC curve analysis and cumulative IC progression analysis were performed on a total of 134 samples. The ROC curve was used to evaluate the discriminatory ability of the BD test for IC, and to visualize the sensitivity (true-positive results) versus 1-specificity (false-positive results) at different cut-off values of BD. Sensitivity and specificity were analyzed using the samples tested. Cumulative IC progression-free survival (PFS) curves for the groups with low BD levels ($<$60 pg/mL), intermediate BD levels ($>$60, and $\leq$120 pg/mL), and high BD levels ($>$120 pg/mL) were calculated using the Kaplan—Meier method and compared using the log-rank test. The prognostic impact of BD on PFS was assessed using a Cox proportional hazards model. Age, TBSA, and inhalation injury, which are known as risk factors for burns, and the presence of antifungal agent affecting candidiasis, were adjusted for in the multivariable Cox analysis. BD was measured as a time-dependent variable

every week until the third week, and data on the other variables were obtained at admission as a fixed time point. If there were missing values for time-dependent BD levels at a given time, they were replaced by using the Last Observation Carried Forward method for the extended Cox analysis. None of the variables violated the proportional hazards assumption. One of the global interpretability techniques, partial dependence plot (PDP) analysis was applied to present the ability of BD values on the first day of ICU admission for IC prediction. Cox and proportional assumption analyses, and PDPs, were performed using the statistical R-project program, version 3.6.2.

Results

Characteristics of the patients and (1,3)-β-D-glucan levels

Between July and December 2018, 86 burn-injured adult patients were enrolled as study participants. Of the 86 patients, 29 patients and 19 patients had their BD levels measured on Day 7 and Day 14, respectively. During the study, 11 patients were diagnosed with IC, and 75 patients were determined to have no evidence of IC. The median age of all the patients was 51 years and the number of male and female patients was 76 and 10, respectively. According to the mode of burns, flame was the predominant cause of burns (75.6%), followed by electric (17.4%), scalding (5.8%) and chemical (1.2%) burns. There were no statistically significant differences in age, sex, and the mode of burn injury between the 'IC' and 'No IC' patient groups. The median percentage of TBSA in the IC patients was significantly higher than in those without IC (50 vs. 29%, $P < 0.001$). Critical laboratory data for burn patients at ICU admission, including white blood cell, absolute neutrophil count, CRP, procalcitonin, lactic acid, and lactate dehydronase, were investigated; there were no statistically significant differences observed between the two groups (Table 1). None of the patients in the study population had ever utilized IVIG, albumin, or dialysis equipment. The mean

Table 1 Comparison of patients at the time of admission.

Variable	All (N = 86)	Value by IC category	
		IC (N = 11)	No IC (N = 75)
Age (IQR)	51 (45–62)	59 (48–66)	51 (45–62)
Male:Female	76:10	8:3	68:7
(1,3)-β-D-glucan (pg/mL)			
Hospital day #1	55.5 (10.0–158.0)	157.2 (124.7–185.2) [a]	51.3 (10.0–125.0)
Hospital day #7	10.0 (10.0–52.7)	10.0 (10.0–197.7)	10.0 (10.0–51.8)
Hospital day #14	10.0 (10.0–83.8)	83.9 (10.0–1000.0)	10.0 (10.0–75.4)
Mode of Burn			
Flame/Chemical/Electric/Scalding	65/1/15/5	9/0/1/1	56/1/14/4
TBSA (IQR)	32 (20–40)	50 (35–74) [b]	29 (20–39)
Inhalation burn, no. (%)	38 (44.2)	6 (54.5)	32 (42.7)
Full thickness burn, no. (%)	68 (79.1)	10 (90.9)	58 (77.3)
Blood culture positivity, no (%)	25 (29.1)	7 (63.6) [a]	18 (24.0)
Death, no. (%)	12 (14.0)	2 (18.2)	10 (13.3)
Antifungal agents (%)	11 (12.8)	9 (81.8)	2 (2.7)
WBC (/10^3 x uL)	15.6 (10.6–21.3)	17.6 (11.8–27.8)	15.5 (10.3–20.6)
ANC (/10^3 x uL)	12.5 (7.9–18.7)	13.7 (9.2–23.8)	12.5 (7.1–18.1)
CRP (mg/L)	2.0 (0.8–14.6)	2.1 (0.9–43.9)	1.9 (0.6–10.3)
Procalcitonin (ng/mL)	1.1 (0.1–2.5)	1.6 (1.6–1.6)	0.6 (0.1–3.7)
Lactic acid (mmol/L)	2.8 (1.8–4.3)	4.1 (2.2–7.0)	2.8 (1.7–4.0)
LDH (IU/L)	348.5 (277.5–524.0)	365 (325.0–527.0)	330 (271.0–521.0)
Myoglobin (ng/mL)	181.8 (70.1–824.0)	358.9 (81.3–778.1)	161.4 (68.3–935.9)
CK (IU/L)	291.5 (167.0–895.0)	479.0 (209.8–1030.8)	284.0 (160.3–894.8)
Total bilirubin (mg/dL)	0.8 (0.5–1.0)	0.9 (0.6–1.5)	0.7 (0.5–1.0)
Direct bilirubin (mg/dL)	0.3 (0.2–0.4)	0.3 (0.2–0.6)	0.3 (0.2–0.4)
Source of IC, no. (%)			
Candida albicans	5	5	Not applicable
Candida tropicalis	2	2	
Candida parapsilosis	1	1	
Candida glabrata	2	2	
Candida species, not albicans	1	1	

[a] $P < 0.05$.
[b] $P < 0.005$.
Data are medians (IQRs, interquartile ranges) or frequencies.
Abbreviation: IC, invasive candidiasis; IQR, interquartile ranges; TBSA, total body surface area; WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein; LDH, lactate dehydronase; CK, Creatine kinase.

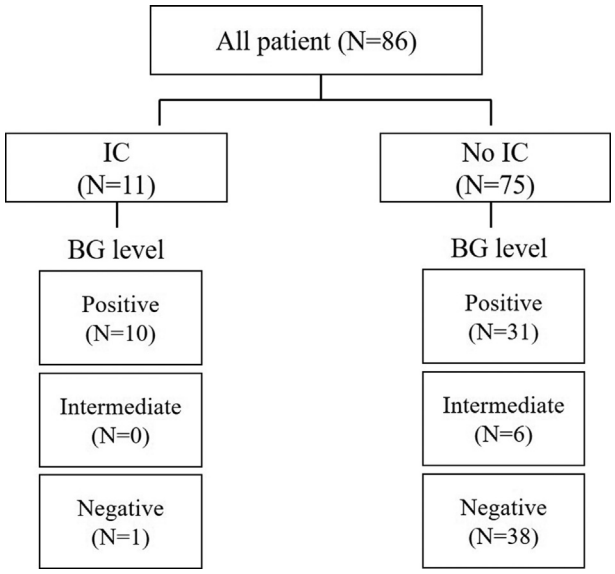

Fig. 1. Classification of enrolled patients by invasive candidiasis (IC) status and (1,3)-β-D-glucan (BD) levels measured on the first day of ICU admission.

period from the date of the BD test to IC diagnosis was 1.92 ± 3.06 days, which was shorter than the mean period required for a positive blood culture or clinical diagnosis of IC (21.27 ± 13.84).

According to the manufacturers' reference range, positive results (>80 pg/mL) were observed in 41 (47.7%) patients, intermediate (>60, and ≤80 pg/mL) in 6 (7.0%) patients, and negative (<60 pg/mL) in 39 (45.3%) patients (Fig. 1). The median BD level measured at ICU admission was 55.5 pg/mL (95% CI, 10.0—158.0 pg/ml; range, 10—1000 pg/ml), and the median BD level in IC patients was statistically significantly higher than in those without IC (157.2 vs. 51.3 pg/mL, $P = 0.014$; Table 1). The average duration between the date of the first measurement of BD to the date of IC was 22.4 days. Among the 11 patients with IC, five were confirmed to have IC by blood culture. The remaining six patients who were strongly suspected to have IC had fungal colonization in their urine and burn wounds. The most common causes of IC were *Candida albicans*, followed by *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

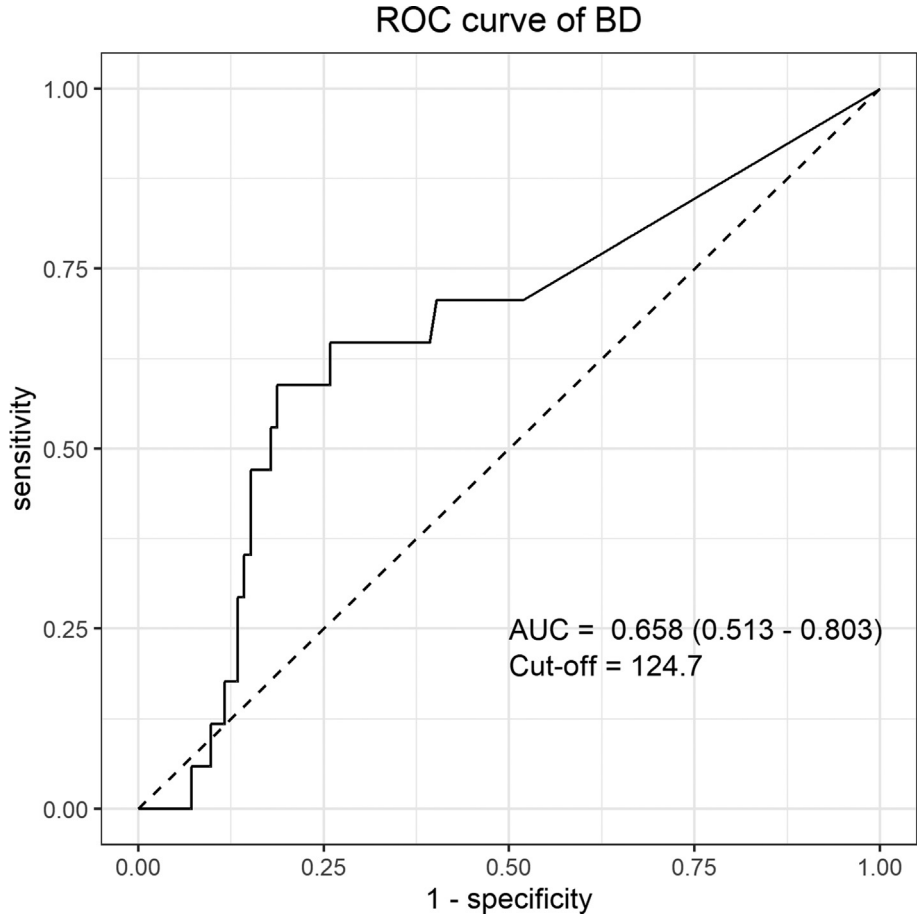

Fig. 2. Receiver operator characteristic (ROC) curve utilized to evaluate the (1,3)-β-D-glucan (BD) level for the diagnosis of invasive candidiasis (IC). The area under the ROC curve was 0.658 (95% CI, 0.513—0.803), and the cut-off value for best diagnostic accuracy was 124.7 pg/mL with a sensitivity of 58.8%, and a specificity of 81.2%.

Serum (1,3)-β-D-glucan levels for diagnosis and prediction of IC

The ROC analysis was performed to evaluate BD levels for the diagnosis of IC. The area under the ROC curve (AUC) was 0.658 (95% CI, 0.513–0.803), indicating a moderate discriminatory ability for detecting IC. The optimal cut-off value for the best diagnostic accuracy was 124.7 pg/mL with a sensitivity of 58.8%, and a specificity of 81.2% (Fig. 2).

The association of serum BD levels with PFS for IC was evaluated using a Cox univariable proportional hazards analysis. BD levels were subdivided into >60 and ≤60 pg/mL, and a higher BD level was found to be significantly associated with PFS (hazard ratio [HR] = 4.77; 95% CI, 1.31–17.37; $P = 0.018$). BD cut-off levels that were >80 pg/mL (HR = 5.84; 95% CI, 1.56–21.8; $P = 0.009$), >100 pg/mL (HR = 6.04; 95% CI, 1.90–19.2; $P = 0.002$), and >120 pg/mL (HR = 6.12; 95% CI, 1.92–19.5; $P = 0.002$) showed increased statistical significance with PFS. Clinical markers such as the percentage of TBSA (HR = 1.05; 95% CI, 1.03–1.08; $P < 0.001$) and lactic acid (HR = 1.24; 95% CI, 1.02–1.50; P = 0.028) and antifungal agent (HR = 45.06; 95% CI, 10.55–192.93; $P < 0.001$) were significantly associated with decreased PFS (Table 2A). The multivariable Cox model was adjusted for age, TBSA, inhalation injury, and antifungal agents, and showed that BD levels over 60 pg/mL (HR = 11.59; 95% CI, 3.83–35.11 $P < 0.001$), 80 pg/mL (HR = 12.16; 95% CI, 4.09–36.1; $P < 0.001$), 100 pg/mL (HR = 8.66; 95% CI, 2.37–31.6; $P = 0.001$), and 120 pg/mL (HR = 8.68; 95% CI, 2.39–31.5; $P = 0.001$) were independent predictors of IC occurrence (Table 2B). Patients with high BD levels (>120 pg/mL) had significantly lower PFS ($P = 0.002$, Fig. 3) than patients with low (<60 pg/mL) and intermediate (>60, and ≤120 pg/mL) BD levels. The survival probability of the patients with low BD levels was 0.946 (95% CI, 0.876–1.000), while that of the patients with intermediate BD levels was 0.889 (95% CI, 0.706–1.000) and that of the patients with high BD levels was 0.639 (95% CI, 0.431–0.945) at Day 30 (Fig. 3).

The PDPs showed that BD level until 60 pg/mL had the low probability for IC, and as BD level increased over 120 pg/mL, the probability for IC was rapidly increased until 150 pg/mL. TBSA between ~30 and 80% showed the linear relationship with IC probability (Fig. 4). When interactions between BD level and TBSA was analyzed, for

Table 2 Cox proportional hazards model for factors associated with invasive candidiasis.

(A) Crude univariable analysis			
Variables	HR (95% CI)	*P*	C-index (95% CI)
BD (>60 vs. ≤ 60 pg/mL)	4.772 (1.311–17.365)	0.018	0.720 (0.606–0.834)
BD (>80 vs. ≤ 80 pg/mL)	5.837 (1.564–21.777)	0.009	0.745 (0.630–0.860)
BD (>100 vs. ≤ 100 pg/mL)	6.040 (1.896–19.240)	0.002	0.730 (0.600–0.859)
BD (>120 vs. ≤ 120 pg/mL)	6.118 (1.915–19.541)	0.002	0.732 (0.601–0.863)
BD (>140 vs. ≤ 140 pg/mL)	3.673 (1.167–11.561)	0.026	0.645 (0.494–0.796)
Age (year)	1.028 (0.971–1.087)	0.344	0.546 (0.367–0.725)
TBSA (%)	1.050 (1.025–1.075)	<0.001	0.834 (0.722–0.947)
Inhalation burn	1.676 (0.518–5.421)	0.389	0.534 (0.372–0.696)
Antifungal agent	45.064 (10.526–192.929)	<0.001	0.865 (0.753–0.976)
WBC (/10^3 x uL)	1.033 (0.979–1.091)	0.235	0.635 (0.453–0.818)
ANC (/10^3 x uL)	1.035 (0.973–1.100)	0.274	0.653 (0.474–0.831)
CRP (mg/L)	1.001 (0.994–1.007)	0.804	0.503 (0.331–0.676)
Lactic acid (mmol/L)	1.237 (1.023–1.495)	0.028	0.713 (0.558–0.868)
LDH (IU/L)	0.999 (0.998–1.001)	0.443	0.438 (0.255–0.620)
Myoglobin (ng/mL)	1.000 (0.999–1.000)	0.785	0.409 (0.232–0.587)
(B) Multivariable analysis adjusted for age, TBSA, inhalation injury, and antifungal agent			
Variables	HR (95% CI)	*P*	C-index (95% CI)
BD (>60 vs. ≤ 60 pg/mL)	11.594 (3.829–35.109)	<0.001	0.953 (0.920–0.986)
BD (>80 vs. ≤ 80 pg/mL)	12.155 (4.093–36.095)	<0.001	0.955 (0.922–0.988)
BD (>100 vs. ≤ 100 pg/mL)	8.662 (2.373–31.618)	0.001	0.950 (0.915–0.985)
BD (>120 vs. ≤ 120 pg/mL)	8.680 (2.393–31.485)	0.001	0.950 (0.915–0.985)
BD (>140 vs. ≤ 140 pg/mL)	2.469 (0.409–14.908)	0.325	0.945 (0.908–0.981)
WBC (/10^3 x uL)	0.982 (0.876–1.102)	0.760	0.934 (0.898–0.969)
ANC (/10^3 x uL)	0.986 (0.886–1.102)	0.739	0.935 (0.899–0.972)
CRP (mg/L)	0.990 (0.978–1.002)	0.111	0.951 (0.920–0.983)
Lactic acid (mmol/L)	1.182 (0.872–1.603)	0.282	0.947 (0.912–0.982)
LDH (IU/L)	1.000 (0.999–1.002)	0.700	0.921 (0.836–1.006)
Myoglobin (ng/mL)	1.000 (0.999–1.001)	0.511	0.934 (0.890–0.979)

Abbreviation: OR, odd ratio; BD (1,3)-β-D-glucan; TBSA, total body surface area; WBC, white blood cells; ANC, absolute neutrophil count; CRP, C-reactive protein; LDH, lactate dehydrogenase.

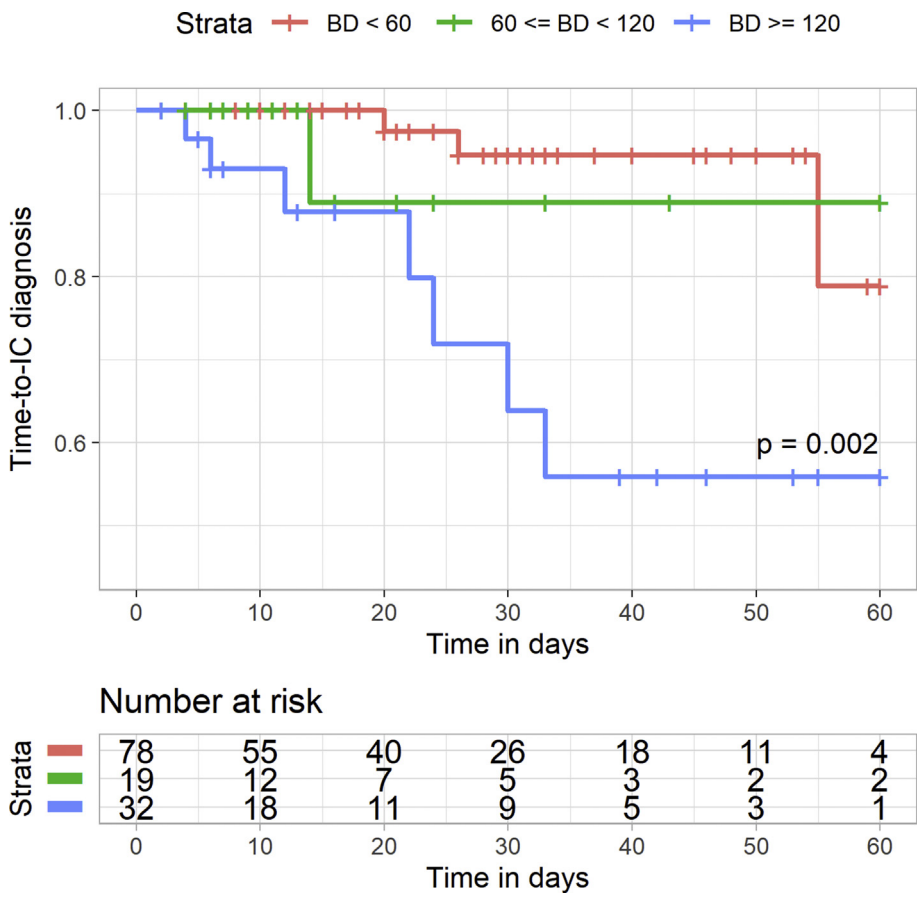

Fig. 3. Kaplan–Meier analysis of Time-to-IC diagnosis with <60, 60 and ≤ 120, >120 pg/mL (1,3)-β-D-glucan (BD) levels. Time-to-IC diagnosis was significantly shorter in patients with high BD levels than in those with low BD levels ($P = 0.002$).

TBSA over 60%, BD level among 120 pg/mL and 150 pg/mL had a higher predicted IC risk (Fig. 5).

Discussion

In this study, 86 patients with severe burn injuries were prospectively analyzed to evaluate the ideal cut-off value of the BD test on predict IC. The results showed that BD levels over 120 pg/mL in burn patients were significantly associated with reduced PFS for those with IC; ROC analysis also showed the ideal cut-off for IC detection as 124.7 pg/mL. Moreover, PDP analysis showed that BD between 120 and 150 pg/mL, could be optimal cutoff value for IC prediction.

Previously, the cut-off value of the BD assay is systemically reviewed by Song et al.[19] They performed a meta-analysis covering 28 individual studies, and identified 60 pg/mL of BD as the best cut-off value to distinguish patients with IC. Our study also showed the significant association with PFS in patients with BD levels over 60 pg/mL. Although Song et al. evaluated the effect of study design and reference standard,[19] the characteristics of study group has not been considered. Preceding studies on patients with severe burn insisted that BD false positives are common and about half of the burn patients showed enhanced baseline BD levels.[16,18] These results suggest that it is necessary to consider the cut-off level according to the characteristics and diagnosis of the patient group. Moreover, it is also necessary to consider the IC predictive power of BD values after adjusting clinical factors that may affect BD values for each patient group. The present study identified a significant association between TBSA and IC, but the BD level remained an independent predictor of IC occurrence even after the adjustment of the clinical factors.

In this study, we applied PDP analysis, a machine learning method for depicting functional relationship of variables and predictions. When PDPs were drawn after analyzing clinical variables on the first day of ICU admission including BD values into random forests, BD and TBSA were found to play an important role in IC prediction. This analysis showed a rapid increase in IC probability starting at 120 pg/mL of BD, suggesting once again that 120 pg/mL has clinical significance as a cut-off value. In addition, when analyzed through the PDP plot, the BD value increases linearly with the TBSA%, as shown in the previous study.[16,18] However, when the interaction between TBSA and BD values was additionally analyzed, IC probability could be further increased in patients with a BD value of 120–150 pg/mL, among patients with TBSA 60% or more.

Although the BD test has been identified as a useful early diagnostic marker for IC in patients with hematologic malignancy and transplantation,[20–22] there is a lack of relevant research conducted among patients with severe

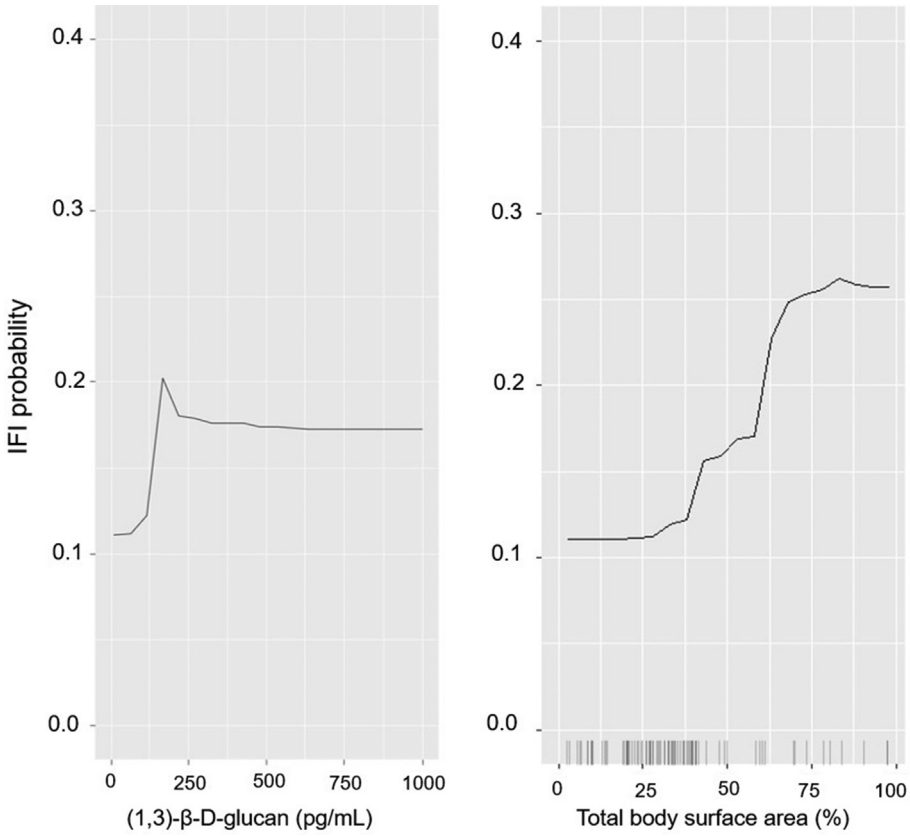

Fig. 4. Partial dependence plots (PDP) for the invasive candidiasis prediction model based on (1,3)-β-D-glucan (BD) levels and total body surface area (TBSA). For BD, the PDP showed that the probability was low until 60 pg/ml, and increased rapidly after 120 pg/mL. For TBSA, the larger burn areas showed the higher predicted IC risk.

trauma. IC in patients with major burns has been suggested to be an important emerging cause of late-onset morbidity and mortality.[17,23–25] Additionally, the frequency of fungal infections is increasing in critically ill patients receiving intensive care, and there is a risk of secondary IC in patients with severe bacterial infections such as sepsis.[26] Therefore, for the purpose of early detection and close monitoring of IC, the efficiency of the BD assay in patients with severe burns or trauma should be explored further. Our data suggested that BD levels in burn patients could be a prognostic prediction tool for IC, and a higher cut-off level than the reference values provided by the manufacturer would enhance the predictability of IC progression.

This study has some limitations, including the number of patients recruited for the serial test and the clinical categorization of IC. Considering the prospective study design and the measurement of BD levels every week, there are missing data in the follow-up tests. Moreover, the BD value was not measured for a sufficiently long period to analyze the relationship between the antifungal agent and outcome. Moreover, considering that other clinical data were collected on the day of admission, the serial BD test should be interpreted with caution. Further studies with more follow-up samples are necessary to assess the effect of BD levels on IC prognosis with anti-fungal agents. Additionally, in this study, patients with possible IC were included in the IC-positive group. This would result in lower accuracy of the IC diagnosis. In the case of burn trauma patients, clinical symptoms such as continuous fungal colonization in non-sterile areas coupled with fever, the lack of response to antibiotics without leukocytosis, and septic features without other infectious findings are strongly suggested in those with IC. In these patients, there were many cases where the fungal culture tested falsely negative in sterile samples. Moreover, in some patients, fungal colonization was followed by an invasion of microorganisms, giving rise to burn wound infections.[27,28] Therefore, we classified the patients who had suspected clinical symptoms for IC and fungal colonization as part of the IC-possible group.

In conclusion, we established that BD is an independent predictor of IC in patients with severe burns. As the number of critically ill patients and the significance of fungal infection in their mortality and prognosis in ICUs increases, the importance of BD testing is expected to be further emphasized in the future. In the present study, BD value is considered to have the capability to function for the prediction of IC, regardless of the level of TBSA. Although the performance including AUC of BD is not high enough, BD has clinical utility as one of the major factors affecting the occurrence of IC. Additionally, in the case of burn patients, it is recommended that the BD cut-off value 120 pg/mL could be utilized to predict IC occurrence.

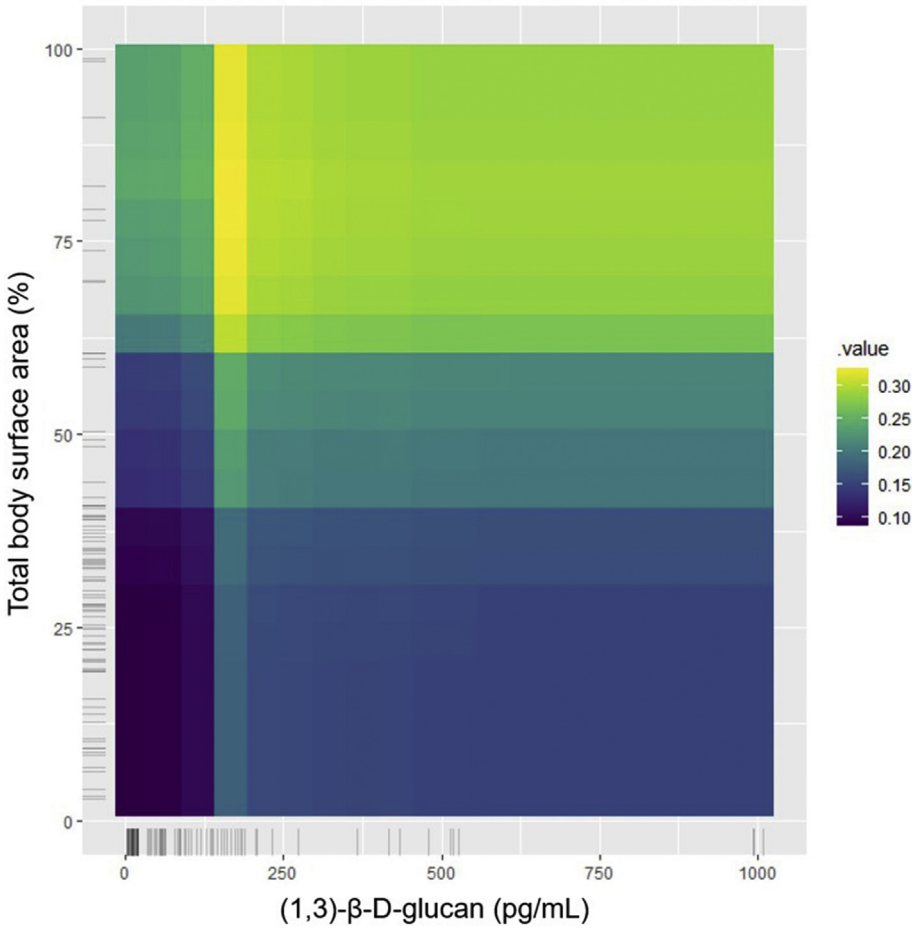

Fig. 5. Interaction of (1,3)-β-D-glucan (BD) levels and total body surface area (TBSA) for probability of invasive candidiasis (IC) using partial dependence plot. The yellow areas (BD 120—150 pg/mL, TBSA 60% and more) showed the higher predicted IC occurrence.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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