Brief Communication
Clinical Microbiology

Ann Lab Med 2023;43:381-385
https://doi.org/10.3343/alm.2023.43.4.381
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Clinical Sensitivity of the (1–3)-β-D-glucan Test for Predicting Candidemia

Yun Woo Lee, M.D.[1], So Yun Lim, M.D.[1], Sol Jin, M.D.[2], Hye Jin Park, M.D.[3], Heungsup Sung, M.D., Ph.D.[4], Mi-Na Kim, M.D., Ph.D.[4], Seongman Bae, M.D., Ph.D.[1], Jiwon Jung, M.D., Ph.D.[1], Min Jae Kim, M.D., Ph.D.[1], Sung-Han Kim, M.D., Ph.D.[1], Sang-Oh Lee, M.D., Ph.D.[1], Sang-Ho Choi, M.D., Ph.D.[1], Yang Soo Kim, M.D., Ph.D.[1], and Yong Pil Chong, M.D., Ph.D.[1]

[1]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Department of Infectious Diseases, Kosin University Gospel Hospital, Busan, Korea; [3]Department of Infectious Diseases, Bumin Hospital, Seoul, Korea; [4]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

The sensitivity of the (1–3)-β-D-glucan (BDG) diagnostic test for candidemia varies in different clinical settings, and its usefulness in early diagnosis of candidemia is suboptimal. We evaluated the sensitivity of the test for early candidemia prediction. All adult patients with culture-proven candidemia who underwent a serum Goldstream Fungus (1–3)-β-D-Glucan Test within seven days prior to candidemia onset at a tertiary referral hospital between January 2017 and May 2021 were included. Any-positive BDG results within seven days prior to candidemia onset were obtained in 38 out of 93 (40.9%) patients. The positive rate increased when the test was performed near the day of candidemia onset (P=0.04) but reached only 52% on the day of candidemia onset. We observed no significant differences between BDG-positive and -negative groups in terms of underlying disease, risk factors for candidemia, clinical presentation, origin of candidemia, and 30-day mortality. *Candida albicans* was significantly associated with positive BDG results than with all-negative BDG results (P=0.04). The Goldstream BDG test is unreliable for candidemia prediction because of its low sensitivity. Negative BDG results in patients with a high risk of invasive candidiasis should be interpreted with caution.

Key Words: Candidemia, (1–3)-β-D-glucan, Sensitivity, *Candida albicans*, Early diagnosis, Systemic candidiasis

Received: September 16, 2022
Revision received: November 8, 2022
Accepted: December 28, 2022

Corresponding author:
Yong Pil Chong, M.D., Ph.D.
Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3306
Fax: +82-2-3010-6970
E-mail: drchong@amc.seoul.kr

Candidemia is a major cause of hospital-acquired infections and mortality [1-3]. The *Candida* cell wall polysaccharide (1–3)-β-D-glucan (BDG) is widely used as an antigenic marker for early diagnosis of invasive candidiasis, including candidemia [4, 5]. The BDG test is used to decide on the use of antifungal agents and discontinuation of empirical antifungal therapy in patients at risk of invasive candidiasis [6, 7]. However, the performance of the test varies substantially [4, 5, 8]. We analyzed the sensitivity of the Goldstream Fungus (1–3)-β-D-Glucan Test for predicting candidemia and evaluated the clinical and microbiological characteristics of patients with positive BDG results before or on the day of candidemia onset.

This retrospective study included 93 adult patients with candidemia who underwent a serum BDG test within seven days prior to the onset of candidemia at Asan Medical Center—a 2,700-bed tertiary referral hospital in Seoul, Korea—between January 2017 and May 2021. Patients were identified by cross-checking candidemia cases in a database of BDG test results. Data on age, sex, admission department, underlying disease, risk factors for candidemia, clinical presentation, origin of candidemia, *Candida* species, antifungal therapy, serum BDG, and outcome were collected, and the clinical characteristics and out-

comes of patients with any-positive BDG results versus all-negative BDG results were compared. The Institutional Review Board of Asan Medical Center approved this study (approval number 2022-0873). The requirement for obtaining informed consent from the patients was waived given the observational and retrospective nature of the study.

Candidemia was defined as the isolation of *Candida* species from blood in patients with signs and symptoms of infection. Candidemia onset was defined as the date of the first culture-positive blood sample. Any-positive BDG results were defined as at least one positive result in the performed BDG tests. Other definitions are provided in the Supplemental Data.

Blood was cultured in Bactec Plus Aerobic/F and Bactec Lytic/10 Anaerobic/F vials (Becton Dickinson DIS, Sparks, MD, USA), according to the manufacturer's instructions. Yeasts were identified using a Vitek 2 YST card (bioMérieux, Marcy l'Étoile, France) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonik, Bremen, Germany). The blood samples were subjected to the Goldstream Fungus (1–3)-β-D-Glucan Test (GKT-12M; Gold Mountain River Tech Development, Beijing, China). Values above the maximum detectable level (1,000 pg/mL) were recorded as >1,000 pg/mL. The cut-off value for a positive BDG result was 80.0 pg/mL, according to the manufacturer's instructions.

Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, and continuous variables using the Mann–Whitney *U*-test. $P<0.05$ was considered to indicate significance. Data were managed and analyzed using IBM SPSS Statistics for Windows version 21.0 (IBM, Armonk, NY, USA) or R version 4.0.4 (R Project for Statistical Computing, Vienna, Austria).

During the study period, 576 adults were diagnosed as having candidemia, 93 of whom underwent a serum BDG test within seven days prior to the onset of candidemia, yielding 149 BDG serum samples in total (median, 1.6 tests per patient). The median age of the 93 patients was 63 years (range, 24-87 years), and 64.5% (60/93) were males. In total, 38 (40.9%) patients gave any-positive BDG results. The median BDG value in the any-positive BDG group was 254.9 pg/mL (interquartile range [IQR], 146.6-792.8 pg/mL). Fig. 1 shows the proportions of positive BDG results at 0, 1, 2, 3-5, and 6-7 days before candidemia onset. The positive rate increased as the day of candidemia onset was approached ($P=0.04$) but still reached only 52% (38% at 0-2 days before candidemia). Of the 93 patients, 37 (39.8%) underwent a BDG test in the first two days after candidemia, 21 of whom gave any-positive results.

Table 1 compares the clinical and microbiological characteristics of the any-positive and all-negative BDG groups. There were no significant differences in terms of admission department, underlying disease, risk factors for candidemia, and clinical presentation. In the all-negative group, 17 (30.9%) patients received systemic antifungals within a month prior to candidemia onset, compared to 17 (44.7%) in the any-positive group ($P=0.17$). The *Candida* species detected are listed in Table 1. *Candida al-*

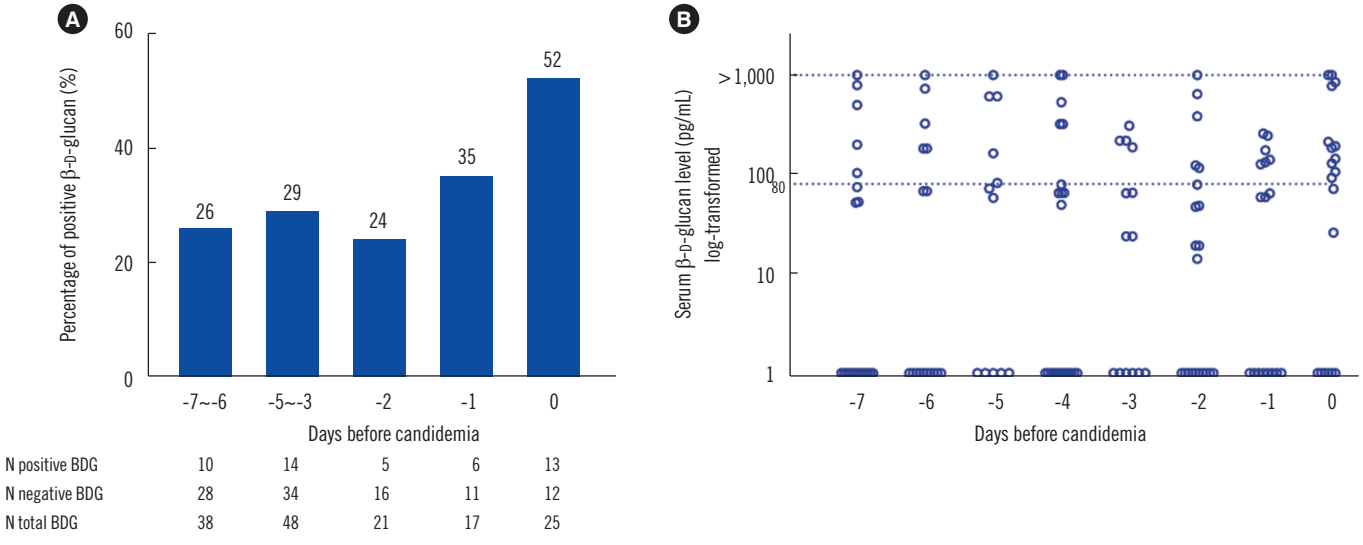

Fig. 1. Proportions and distributions of the BDG results. (A) Proportions of positive BDG results at different time points before candidemia onset. The proportion of positive BDG results increased over time ($P=0.04$ for trend). (B) Distribution of the BDG values. Values above the maximum detectable level (1,000 pg/mL) were recorded as >1,000 pg/mL. The cut-off value for a positive BDG test was 80.0 pg/mL.
Abbreviation: BDG, (1–3)-β-D-glucan.

https://doi.org/10.3343/alm.2023.43.4.381

Table 1. Demographic and microbiological characteristics and outcomes of patients with candidemia according to positive vs. negative test results within seven days prior to candidemia onset

Characteristic	Any-positive BDG results (N=38)	All-negative BDG results (N=55)	*P*
BDG value, median (IQR)	254.9 (146.6-792.8)	0 (0-49.3)	
Male	22 (57.9)	38 (69.1)	0.28
Age, yr, median (IQR)	62.5 (56.5-69.3)	64 (53-72)	0.26
Admission department			
Medical ward	20 (52.6)	24 (43.6)	0.39
Surgical ward	2 (5.3)	3 (5.5)	0.97
Medical ICU	13 (34.2)	21 (38.2)	0.70
Surgical ICU	3 (7.9)	5 (9.1)	0.84
Emergency room	0	2 (3.6)	0.24
Underlying disease*			
Cardiovascular disease	18 (47.4)	22 (40.0)	0.62
Hematologic malignancy	16 (42.1)	25 (45.5)	0.75
Solid cancer	10 (26.3)	19 (34.5)	0.54
Diabetes mellitus	9 (23.7)	18 (32.7)	0.48
Bone marrow transplant	7 (18.4)	3 (5.5)	0.10
Chronic liver disease	6 (15.8)	10 (18.2)	0.98
Solid organ transplant	6 (15.8)	10 (18.2)	0.98
Chronic kidney disease	5 (13.2)	4 (7.3)	0.56
Risk factors for candidemia			
Previous antibiotics†	38 (100)	52 (94.5)	0.14
Total parenteral nutrition	30 (78.9)	40 (72.7)	0.49
Previous antifungals†	17 (44.7)	17 (30.9)	0.17
Chemotherapy†	13 (34.2)	24 (43.6)	0.36
Candida colonization†	12 (31.6)	21 (38.2)	0.51
Antifungal use on the day of BDG test	11 (28.9)	15 (27.3)	0.86
Neutropenia	10 (26.3)	20 (36.4)	0.31
Surgery†	6 (15.8)	3 (5.5)	0.10
Clinical presentation			
Septic shock	16 (42.1)	23 (41.8)	0.98
Pitt score, median (IQR)	4 (0-7)	4 (1-6)	0.63
Pitt score ≥4	21 (55.3)	30 (54.5)	0.95
Origin of candidemia			
CVC-related	22 (57.9)	29 (52.7)	0.78
Primary	12 (31.6)	18 (32.7)	>0.99
Intraabdominal	2 (5.3)	5 (9.1)	0.77
Urinary tract	1 (2.6)	2 (3.6)	>0.99
Other‡	1 (2.6)	1 (1.8)	>0.99
Candida species			
Candida albicans	16 (42.1)	12 (21.8)	0.04
Candida glabrata	9 (23.7)	12 (21.8)	0.83
Candida tropicalis	7 (18.4)	18 (32.7)	0.13
Candida parapsilosis	2 (5.3)	5 (9.1)	0.49
Candida krusei	2 (5.3)	4 (7.3)	0.70
Candida lusitaniae	2 (5.3)	2 (3.6)	0.70
Candida guilliermondii	0	2 (3.6)	0.24
Antifungal therapy			
Echinocandin	29/38 (76.3)	45/53 (84.9)	0.52
Liposomal amphotericin B	5/38 (13.2)	5/53 (9.4)	0.53
Azole	4/38 (10.5)	3/53 (5.7)	0.36
Time to antifungal therapy, days, median (IQR)	1 (0-2)	1 (1-2)	0.38
Infection source control	24/26 (92.3)	25/34 (73.5)	0.06
Time to source control from initial candidemia date, days, median (IQR)	2 (1-4.75)	2 (1-4)	0.69
Persistent candidemia (≥5 days)	2/38 (5.3)	10/51 (19.6)	0.05
30-day mortality	23 (60.5)	26 (47.3)	0.21

Data represent N (%), unless indicated otherwise.
*Some patients had more than one underlying disease or condition; †Within the previous month; ‡Includes empyema (one patient) and mediastinitis (one patient).
Abbreviations: BDG, (1–3)-β-D-glucan; IQR, interquartile range; ICU, intensive care unit; CVC, central venous catheter.

bicans was significantly associated with any-positive BDG results than with all-negative BDG results (42.1% vs. 21.8%, *P*=0.04). Fig. 2 shows the distribution of BDG values according to *Candida* species. The highest median value for positive BDG results was observed for *Candida tropicalis* (median, 846 pg/mL; IQR, 231.9-1,000 pg/mL), followed by *C. albicans* (median, 328.2 pg/mL; IQR, 158.9–816.4 pg/mL). There were no significant differences in the BDG values among the different *Candida* species.

We found no difference in the use of antifungal therapy, including echinocandins, between the groups (29/38 [76.3%] vs. 45/53 [84.9%], *P*=0.52; Table 1), but patients with any-positive BDG results may have had more adequate source control (24/26 [92.3%] vs. 25/34 [73.5%], *P*=0.06) and less persistent candidemia (2/38 [5.3%] vs. 10/51 [19.6%], *P*=0.05). There was no significant difference in 30-day mortality (60.5% vs. 47.3%, *P*=0.21).

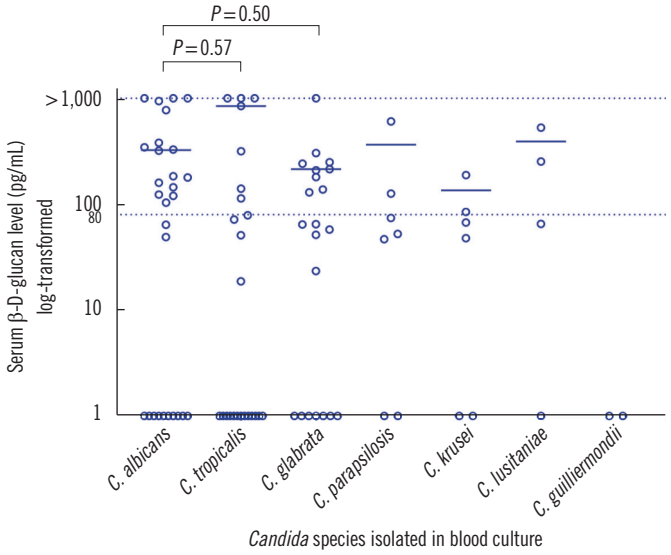

Fig. 2. Distribution of BDG values according to *Candida* species. Values above the maximum detectable level (1,000 pg/mL) were recorded as >1,000 pg/mL. The cut-off value for a positive BDG test was 80.0 pg/mL. Interspecies differences in BDG values were not statistically significant. The horizontal lines denote the median of positive BDG results.
Abbreviation: BDG, (1–3)-β-D-glucan.

More than half the patients with candidemia gave all-negative BDG results shortly before candidemia onset. Thus, the Goldstream BDG test for candidemia has low predictive value for candidemia. *C. albicans* was the only *Candida* species significantly associated with any-positive BDG results before candidemia onset, but its ability to predict candidemia was also low (57.1%).

Positive blood culture for *Candida* species is the mainstay of candidemia diagnosis, but the sensitivity of blood culture is suboptimal, and cultures may take several days to become positive [5]. Studies have evaluated the BDG test as an alternative diagnostic method; the sensitivities varied from 47% to 95%, perhaps due to differences in study design, patient population, or test method [4, 8, 9]. One study using the same kit as we used reported a sensitivity of 80% [10]. Overall, 59.1% of our patients with proven candidemia gave all-negative BDG results within seven days prior to candidemia onset, a substantially higher proportion than those reported in the previous studies. Given the low predictive value of the BDG test used in our study, negative BDG results should be interpreted with caution and should not be used to exclude the possibility of invasive candidiasis.

The BDG results may have been influenced by previous use of systemic antifungals or the level of systemic fungal burden [11, 12]. However, there was no difference in previous antifungal therapy between patients with any-positive BDG results and those with all-negative BDG results.

Predicting candidemia is especially important in critically ill patients who are at high risk of candidemia and have a high mortality rate. Therefore, it may be useful to use the *Candida* score or colonization index in combination with the BDG test [13, 14].

Different levels of association between *Candida* species and any-positive BDG results have been reported [15, 16], and our data support previous evidence [17] of a positive association between *C. albicans* and positive BDG results ($P=0.04$).

This study had some limitations. First, because it was a single center-based investigation, our findings may not apply to populations with other candidemia prevalence or other tests. The Goldstream Fungus kit, which we used, is less studied than the Fungitell test (Associates of Cape Cod, Falmouth, MA, USA) [9, 18]. Lastly, this was a retrospective study; the BDG tests were not performed at regular intervals, and test numbers varied among patients.

In conclusion, because of its limited sensitivity before candidemia onset, the Goldstream Fungus BDG test appears to be less reliable than anticipated from prior research. Hence, negative BDG values should be interpreted with caution in patients at high risk of invasive candidiasis.

ACKNOWLEDGEMENTS

None.

AUTHOR CONTRIBUTIONS

Conceptualization: Chong YP; Data curation: Lee YW, Chong YP; Formal analysis: Lee YW, Chong YP, Kim SH, Lee SO; Investigation: Lee YW, Lim SY, Jin S, Park HJ; Methodology: Lee YW, Chong YP, Sung HS, Kim MN; Project administration: Sung HS, Kim MN, Chong YP; Supervision: Bae SM, Jung JW, Kim MJ, Kim SH, Lee SO, Choi SH; Validation: Choi SH, Kim YS; Visualization: Lee YW, Lim SY, Chong YP; Writing—Original draft: Lee YW; Writing—Review and editing: Chong YP, Sung HS.

CONFLICTS OF INTEREST

None declared.

RESEARCH FUNDING

This research was supported by a grant of the Korea Health Tech-

nology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Korea (grant number HI22C2010).

ORCID

Yun Woo Lee	https://orcid.org/0000-0001-6452-4020
So Yun Lim	https://orcid.org/0000-0002-5647-3718
Sol Jin	https://orcid.org/0000-0002-8720-2005
Hye Jin Park	https://orcid.org/0000-0003-2262-3877
Heungsup Sung	https://orcid.org/0000-0002-6062-4451
Mi-Na Kim	https://orcid.org/0000-0002-4624-6925
Seongman Bae	https://orcid.org/0000-0001-6375-3657
Jiwon Jung	https://orcid.org/0000-0003-4333-3270
Min Jae Kim	https://orcid.org/0000-0002-5489-8608
Sung-Han Kim	https://orcid.org/0000-0002-6596-8253
Sang-Oh Lee	https://orcid.org/0000-0003-1381-8787
Sang-Ho Choi	https://orcid.org/0000-0002-4972-4531
Yang Soo Kim	https://orcid.org/0000-0002-6785-8824
Yong Pil Chong	https://orcid.org/0000-0003-1672-3185

REFERENCES

1. Falagas ME, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. Eur J Clin Microbiol Infect Dis 2006;25:419-25.
2. Tsay SV, Mu Y, Williams S, Epson E, Nadle J, Bamberg WM, et al. Burden of candidemia in the United States, 2017. Clin Infect Dis 2020;71:e449-53.
3. Colombo AL, Guimarães T, Sukienik T, Pasqualotto AC, Andreotti R, Queiroz-Telles F, et al. Prognostic factors and historical trends in the epidemiology of candidemia in critically ill patients: an analysis of five multicenter studies sequentially conducted over a 9-year period. Intensive Care Med 2014;40:1489-98.
4. Alam FF, Mustafa AS, Khan ZU. Comparative evaluation of (1, 3)-β-D-glucan, mannan and anti-mannan antibodies, and *Candida* species-specific snPCR in patients with candidemia. BMC Infect Dis 2007;7:103.
5. Clancy CJ and Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis 2013;56:1284-92.
6. Nucci M, Nouér SA, Esteves P, Guimarães T, Breda G, de Miranda BG, et al. Discontinuation of empirical antifungal therapy in ICU patients using 1,3-β-D-glucan. J Antimicrob Chemother 2016;71:2628-33.
7. Kritikos A, Poissy J, Croxatto A, Bochud PY, Pagani JL, Lamoth F. Impact of the beta-glucan test on management of intensive care unit patients at risk for invasive candidiasis. J Clin Microbiol 2020;58:e01996-19.
8. Martínez-Jiménez MC, Muñoz P, Valerio M, Alonso R, Martos C, Guinea J, et al. *Candida* biomarkers in patients with candidaemia and bacteraemia. J Antimicrob Chemother 2015;70:2354-61.
9. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. β-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis 2011;52:750-70.
10. Son HJ, Sung H, Park SY, Kim T, Lee HJ, Kim SM, et al. Diagnostic performance of the (1-3)-β-D-glucan assay in patients with *Pneumocystis jirovecii* compared with those with candidiasis, aspergillosis, mucormycosis, and tuberculosis, and healthy volunteers. PLoS One 2017;12:e0188860.
11. Guitard J, Isnard F, Tabone MD, Antignac M, Brissot E, Senghor Y, et al. Usefulness of β-D-glucan for diagnosis and follow-up of invasive candidiasis in onco-haematological patients. J Infect 2018;76:483-8.
12. Pfeiffer CD, Samsa GP, Schell WA, Reller LB, Perfect JR, Alexander BD. Quantitation of *Candida* CFU in initial positive blood cultures. J Clin Microbiol 2011;49:2879-83.
13. Posteraro B, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, et al. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index. Crit Care 2011;15:R249.
14. Kazancioglu S, Bastug A, Kayaaslan B, Mutlu NM, Calci E, Turhan T, et al. Diagnostic value of β-D-glucan alone or combined with Candida score, colonization index and C-reactive protein for candidemia. J Infect Dev Ctries 2022;16:362-8.
15. Mikulska M, Giacobbe DR, Furfaro E, Mesini A, Marchese A, Del Bono V, et al. Lower sensitivity of serum (1,3)-β-D-glucan for the diagnosis of candidaemia due to *Candida parapsilosis*. Clin Microbiol Infect 2016;22:646.e5-8.
16. Farooqi J, Niamatullah H, Irfan S, Zafar A, Malik F, Jabeen K. Comparison of β-D-glucan levels between *Candida auris* and other *Candida* species at the time of candidaemia: a retrospective study. Clin Microbiol Infect 2021;27:1519.e1-5.
17. Angebault C, Lanternier F, Dalle F, Schrimpf C, Roupie AL, Dupuis A, et al. Prospective evaluation of serum β-glucan testing in patients with probable or proven fungal diseases. Open Forum Infect Dis 2016;3:ofw128.
18. Theel ES and Doern CD. β-D-glucan testing is important for diagnosis of invasive fungal infections. J Clin Microbiol 2013;51:3478-83.