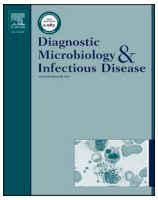
Diagnostic Microbiology & Infectious Disease 108 (2024) 116118

Contents lists available at ScienceDirect

Diagnostic Microbiology & Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio



Evaluation of the Performance of the Dynamiker Fungus (1-3)-β-D-Glucan and Fungitell Assay for Diagnosis of Candidemia: Need for New Cut-off Development and Test Validation

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ARTICLE INFO

Keywords:
(1-3)- β-D-glucan
Diagnosis
Candidemia
Fungal infection

ABSTRACT

(1-3)-Beta-D Glucan (BDG) detection has shown to be a highly effective tool to diagnose invasive fungal infections. Therefore, this study aimed to compare clinical characteristics of the Fungitell (FA) and Dynamiker Fungus (1-3)-β-D-Glucan assay (DFA) for the diagnosis of candidemia.

Using DFA and FA, the BDG levels of 57 serum samples from case and control groups were determined. The kappa coefficient (κ) and Spearman's rank correlation (r_s) were used to examine the consistency of assays on a quantitative and qualitative level, respectively.

The sensitivity, specificity, and accuracy were 94.6 %, 65.0 %, and 87.7% for DFA, and 94.6 %, 75.0 %, and 89.4 % for FA, respectively. The performance of the DFA for the diagnosis of candidemia was highly consistent with that of the FA, both quantitatively (r_s: 0.9) and qualitatively (kappa = 0.78).

Collectively, the DFA assay performed excellently in comparison to the FA for the diagnosis of candidemia.

1. Introduction

The diagnosis of invasive fungal infections (IFIs) is a challenging issue, as it is crucial for managing these potentially fatal diseases. Prompt and accurate diagnosis plays a vital role in determining an appropriate therapeutic procedure, leading to desired clinical outcomes and reduced mortality rates in patients with IFIs [1]. Guidelines for diagnosis of IFIs have introduced the culture method as the reference procedure for diagnosis of invasive candidiasis [2]. However, the diagnosis of candidemia, which is the most common type of invasive candidiasis, poses difficulties due to the low sensitivity and lengthy processing time of blood cultures. Typically, it takes 2-3 days for the cultures to yield positive results, but in some cases, this can extend to 8 days [3].

The detection of fungal antigens in easily obtained specimens such as serum has been advised due to the rising incidence of *Candida* bloodstream infections in immunocompromised or critically ill patients [4]. Beta-D-glucan (BDG) is one such antigens that can be measured in sera of high-risk patients suspicious of invasive fungal infections including candidiasis, aspergillosis, and pneumocystosis [5,6]. BDG is a polysaccharide component of the cell wall of most fungi that are released into body fluids during the fungal infections, with the exception of Zygomycetes and *Cryptococcus*. BDG can be measured with turbidimetric or colorimetric assays through the activation of factor G extracted from amebocytes of horseshoe crab species during a coagulation cascade [7,8]. Measurement of BDG in at least two consecutive serum samples is validated as a criterion for diagnosis of invasive candidiasis and pneumocystosis in terms of its capacity to identify IFIs [2,9].

There are now just a few commercial BDG diagnostic tests available for the detection of fungal infections. According to a recent systematic review evaluating the diagnostic performance of currently available BDG kits in immunocompromised or critically ill patients, there are significant differences in the sensitivity, specificity, and accuracy of the various kits [10]. Fungitell assay (FA; Associates of Cape Cod, MA, USA) is the first FDA-approved test that quantitatively measures BDG levels. Fungitell assay is widely used in the USA and European countries; therefore, numerous studies have reported its useful performance in clinical settings to diagnose such fungal infections as aspergillosis, candidemia, and Pneumocystis jirovecii pneumonia [8,11,12]. Also, diagnostic performance of FA has been evaluated among specific populations including patients with hematologic malignancies or solid organ tumors, and ICU patients [13–15]. The Dynamiker® Fungus BDG assay (DFA; Dynamiker Biotechnology; Tianjin; China) is another available kit that measures the level of BDG based on colorimetric assay

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https://doi.org/10.1016/j.diagmicrobio.2023.116118
Received 8 September 2023; Received in revised form 19 October 2023; Accepted 20 October 2023
Available online 27 October 2023

in a similar way to FA. A few studies have previously evaluated the performance of DFA in the diagnosis of fungal infections such as aspergillosis [16], invasive candidiasis, and Pneumocystis pneumonia [17]. However, there is not sufficient data to compare the performance of DFA to FA for diagnosis of candidemia. Thus, this work aimed to evaluate the performance of DFA for diagnosis of candidemia, and to compare its performance to FA assay.

2. Methods

2.1. Group definition and sample collection

In this case/control study, a total of 57 serum samples were collected for the quantitative measurement of BDG level. In his regard, serum samples from 37 adult patients with proven candidemia were considered as the case group. The diagnosis of candidemia was approved according to the European Organization for Research and Treatment of Cancer /Mycoses Study Group (EORTC/MSG) definition. So, the occurrence of candidemia had been confirmed by positive blood culture for *Candida* species in all patients of the case group.

Additionally, serum samples were collected from a control group consisting of 20 individuals who had negative blood cultures (for both yeasts and bacteria) and showed no clinical manifestation of fungal infection or evidence of fungal colonization. Also, potential causes of false positives for serum BDG including patients who underwent hemodialysis or abdominal surgery, who received blood or its derivatives or beta-lactam antibiotics were considered in control group. All samples were collected under aseptic and glucan-free conditions. To achieve this, endotoxin-free tubes were used to collect the specimens, and the samples were stored at –70°C. Some criteria were used to exclude patients with false-positive results including those who had undergone open abdominal surgery, hemodialysis, septicemia with gram-negative bacteria, and also receiving treatment with beta-lactam antibiotics.

This study was approved by the ethics committee of the Shiraz University of Medical Sciences (Code: IR.SUMS.REC.1398.1171). All methods were carried out in accordance with relevant guidelines and regulations, and informed consent was obtained from all subjects and/or their legal guardians.

2.2. Serum BDG measurement

To evaluate the BDG level, all archived samples were thawed at room temperature. After a short-time vortex of the serums, measurement of the BDG level was performed by DFA and FA assays according to the manufacturer's instructions. All samples were tested using both assays in duplicate by the same researcher, and the mean value obtained from two independent measurements was calculated as the final concentration of BDG for each sample.

2.2.1. Fungitell assay

Briefly, 5 µl of serum was treated with 20 µl of pretreatment reagent in wells of a 96-well plate. After 10 minutes incubation at 37°C, 100 µl of reagent was added to the pretreated serum samples. Quantitative absorbance measurements were performed at 405 nm (with 490 nm background subtraction) every 60s for 40 min at 37°C using a microplate reader (FLUOstar Omega Microplate Reader - BMG Labtech)

2.2.2. Dynamiker assay

DFA was performed using 20 µl of serum according to manufacturer's instructions. The absorbance is measured at 405 nm kinetically every 60 s for 40 min at 37°C.

A kinetic calibration curve was established using standard solutions provided in kits. Samples with a BDG concentration$>$ 95 pg/ml, and $\geq$ 80 pg/ml were considered positive for DFA and FA, respectively.

2.3. Statistical analysis

Sensitivity, specificity, positive/negative predictive values, positive/negative likelihood ratios, and accuracy of results obtained from both BDG assays were calculated using MedCalc statistical software. Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of each BDG assay to distinguish between case and control groups. Moreover, an optimal cut-off value for each BDG assay was determined from ROC curves.

The cut-off values for determining antigenemia positivity were assessed according to cut-offs provided by the manufacturers (FA: $\geq$ 80 pg/ml; DFA: > 95 pg/ml). Since BDG detection using FA kit is recommended by EORTC to diagnose the invasive candidiasis, a new cutoff value for DFA was calculated regarding the positivity for FA ($\geq$80 pg/mL) as a reference assay. The diagnostic performance of DFA assay was recalculated using the cutoff of $\geq$80 pg/ml recommended by FA. Also, the diagnostic performance of both assays was calculated based on the highest Youden index that determines a new cut-off value using a combination of the highest sensitivity and specificity, considering blood culture results as the gold standard method for diagnosis of candidemia.

The two BDG assays were compared quantitatively and qualitatively. For the quantitative analysis, the results of the assays were analyzed with paired Student's t-test or Wilcoxon matched-pairs signed rank test, depending on the validity of the normality assumption. The Spearman's rank correlation coefficient (r_s) was calculated, and linear regression analysis was conducted to determine whether the slope of the regression line differs significantly from zero. The Chi-square (χ^2) was used to evaluate whether there was a significant association between the results of the two assays, while the strength of agreement was assessed by calculating the kappa coefficient (κ).

3. Results

The mean BDG concentrations for the control group were 91.50 ± 51.07 pg/ml measured by DFA, and 135.50 ± 23.41pg/ml measured by FA. For patients in the case group, the mean BDG concentrations were 607.02 pg/ml and 686.92 pg/ml for DFA and FA assays, respectively. According to obtained results by both assays, BDG concentration was significantly higher in the patients with proven candidemia in comparison with the control group (P-value: <0.001). Considering the cut-off values defined for each assay, the BDG positivity among the case group was 35 (94%) and 36 (97 %) by DFA and FA, respectively.

According to manufacturer's recommended cut-offs, the sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of DFA were 94.6 %, 65.0 %, 2.70, and 0.08, respectively. For FA and based on its recommended cut-off value, sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were 94.6 %, 75.0 %, 3.78, and 0.07, respectively. Moreover, the diagnostic accuracy of DFA and FA assays for diagnosis of candidemia was determined 87.7 % and 89.4 %, respectively.

In addition, several false positive results were found, with 35% (7 out of 20) and 25% (5 out of 20) for DFA and FA, respectively. Among them, 5 patients had BDG levels above the defined cut-off points for both assays.

Afterward, new cutoff values for both assays were calculated with the highest Youden index. In this regard, a new cut off value of 93 pg/ml and 147 pg/ml for FA and DFA were determined, respectively. Moreover, a modified cut off value of 112 pg/ml was determined for DFA regarding the highest sensitivity and specificity of FA to detect candidemia (Table 1).

ROC curves of both DFA (AUC:0.94, 95% CI: 0.846 to 0.987), and FA (AUC: 0.92, 95%CI:0.826 to 0.979) assays showed significant similarity between the two areas under curves (p- value: <0.001) (Fig. 1).

The correlation between the BDG concentrations determined by the two assays showed a linear relationship between the concentrations reported by DFA and FA (r^2 0.67) (Fig. 2). Moreover, according to

Table 1
Diagnostic performance of Fungitell (FA) and Dynamiker (DFA) assays considering different cutoff values.

	Fungitell (FA)	Dynamiker (DFA)
Recommended cutoff by manufacturer	80	95
% Sensitivity (95% CI)	94.6 (81.8-99.2)	94.6 (81.8-99.3)
% Specificity (95 % CI)	75.0 (50.9-91.2)	65.0 (40.8-84.6)
PLR (95 % CI)	3.7 (1.8-8.1)	2.7 (1.5-4.9)
NLR (95 % CI)	0.07(0.02-0.3)	0.08 (0.02-0.3)
PPV	87.5	83.3
NPV	88.2	86.7
% Accuracy (95% CI)	89.4 (78.48-96.04)	87.7 (76.32-94.92)
Modified cutoffs with the highest Youden index	93	147
% Sensitivity (95% CI)	91.89 (78.09-98.3)	86.49 (71.2-95.5)
% Specificity (95% CI)	85 (62.11-96.79)	95 (75.1 - 99.9)
PLR (95% CI)	6.13 (2.15-17.5)	17.3 (2.5-11.74)
NLR (95% CI)	0.095 (0.03-0.3)	0.14 (0.06-0.3)
PPV	91.9	97.0
NPV	85	79.2
Modified Dynamiker cutoff to get a highest sensitivity and specificity achieved with a Fungitell cutoff of ≥ 80 pg/ml	80	112
% Sensitivity (95% CI)	94.6 (81.8-99.2)	90.24 (76.9 - 97.3)
% Specificity (95% CI)	75 (50.9-91.2)	93.75 (69.8 - 99.8)
PLR (95% CI)	3.78 (1.8-8.1)	14.44 (2.2-96.6)
NLR (95% CI)	0.07 (0.02-0.3)	0.1 (0.04-0.3)
PPV	87.5	97.4
NPV	88.2	78.9

PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence Interval.

Spearman's correlation coefficient, a significant correlation was observed between the BDG concentrations measured by the two assays (r_s: 0. 91, p- value: < 0.001). Also, a significant qualitative consistency was found between the two assays with an excellent agreement (κ= 0.78, p- value: < 0.001).

4. Discussion

Beta-D-glucan (BDG), a major cell wall component of the most important pathogenic fungi, has been considered as a biomarker to diagnose invasive fungal infections. According to results of some previous Meta-Analysis studies, pooled sensitivity and specificity of BDG for diagnosis of IFIs have been reported 76.8- 80% and 81- 85.3%, respectively [18–20]. These results indicate better performance of BDG measurement for diagnosis of IFIs compared to conventional methods with sensitivity ranging 20-70 %. In this regard, the assessment of BDG level has been recommended by most clinical guidelines for the diagnosis of IFIs. The current study was performed to evaluate and compare the

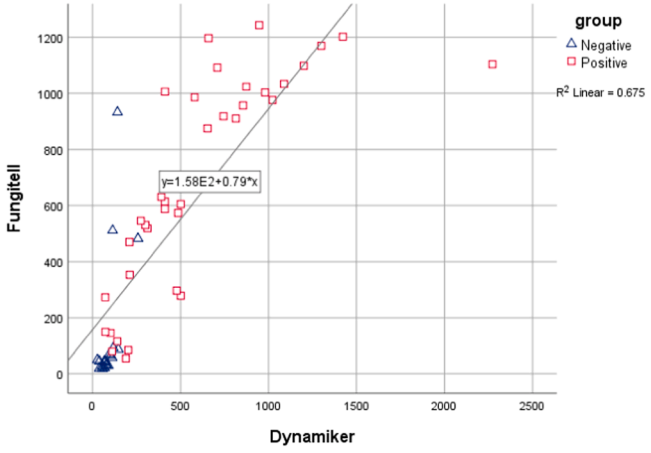

Fig. 2. Correlation between the BDG concentration measured by Dynamiker (DFA) and Fungitell (FA) assays.

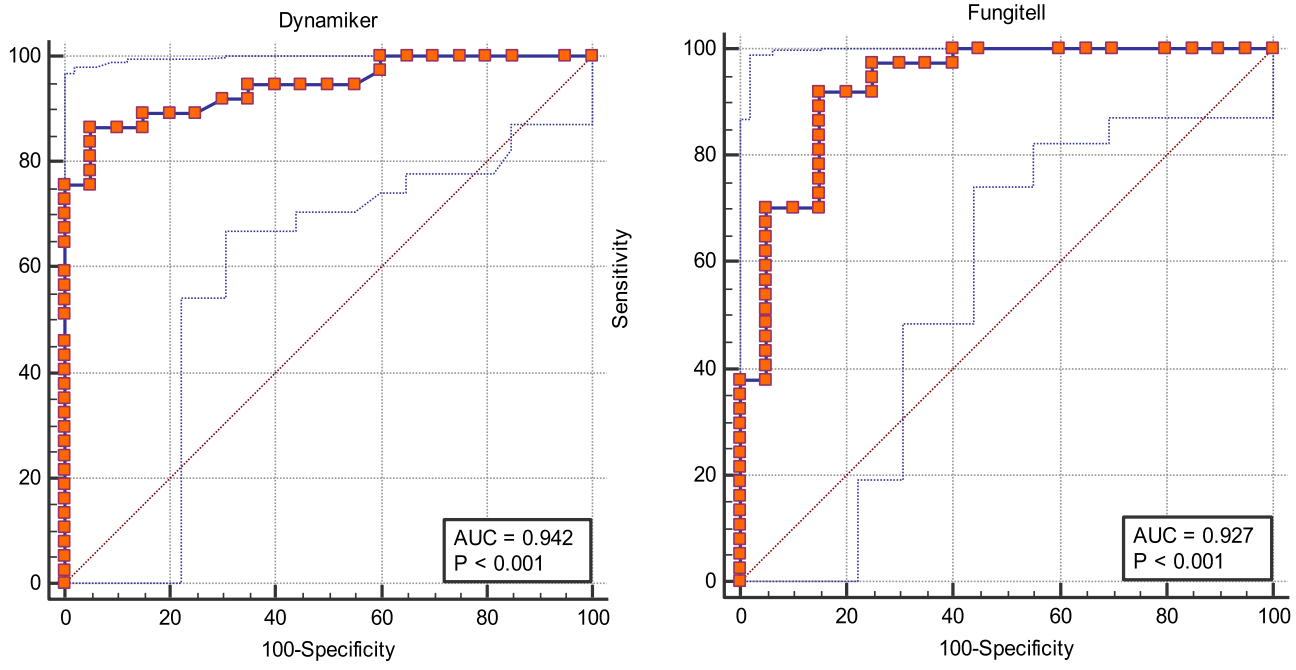

Fig. 1. Receiver Operating Characteristic (ROC) curves of the Dynamiker (DFA) and Fungitell (FA) assays in the diagnosis of candidemia.

performance of both DFA and FA to diagnose candidemia. The most important finding of this investigation was that the overall performance of the two assays for diagnosis of candidemia as evaluated by the area under the ROC curves was highly consistent based on the recommended cut-off points. In this regards, two assays were highly in agreement both quantitatively (Spearman rs: 0.91) and qualitatively (Kappa =0.78). These results are in agreement with previous reports that have declared good agreement and significant correlation of DFA and FA for diagnosis of IFIs [21–23]. In total, the performance of DFA for detection of candidemia is highly consistent with that of FA assay.

The Dynamiker® Fungus (1-3)-β-D-Glucan Assay (DFA) has recently become available to determine BDG level by protease zymogen-based colorimetric assay. Some earlier studies have investigated the diagnostic performance of DFA to show the potential of this assay to assist in diagnosis of invasive fungal infections. Our findings about the diagnostic performance of DFA are consistent with an earlier study that has declared a sensitivity of 81.4%, specificity of 78.1%, and AUC of 0.819 in order to diagnose proven/probable candidiasis, aspergillosis, and pneumocystosis in high-risk patients. In addition, the highest sensitivity and the best overall performance of DFA has been reported for the diagnosis of invasive candidiasis compared to invasive aspergillosis and pneumocystosis [22].

Compared to DFA assay, more information is available about FA assay regarding its earlier introduction to the market and widely used in USA and Europe. Based on findings revealed by White et al, FA has a sensitivity of 27% -100%, and a specificity of 0%-100% in immunocompromised and critically ill patients for detection of BDG level [10]. To diagnose candidemia, our results are in agreement with previous investigations that have reported sensitivity of 86.7% - 97 % and specificity of 65 %- 85 % for FA assay, respectively [12,24]. Altogether, both DFA and FA assay have remarkable performance to diagnose candidemia.

Furthermore, we determined a modified cutoff for DFA at which FA was considered as reference assay for detection of candidemia (at a cutoff of ≥80 pg/ml for positivity). At new cut-off of 112 pg/ml for DFA, both assays had a similar sensitivity, but DFA had a significantly higher specificity and PLR. So, it could be stated that candidemia could rule out with more reliability after changing the DFA cut-off.

The optimal cut-off value for BDG may differ depending on factors such as the tested population, prevalence of fungal infections in a region, and assay performance [18]. For example, higher serum BDG levels in healthy children compared to healthy adults or impact of neutropenia on BDG level have been reported, previously [25,26]. Thus, performing labs should conduct their analysis to determine a new optimal cutoff value that aligns with their patient population and testing accuracy . It could be remembered that changing the cut-off values should be considered cautiously, because these alterations lead to false results and inappropriate clinical management. To overcome this controversial issue, guidelines propose repeated sampling to assist the interpretation of data and rule out false positive results [2]. In view of these considerations, ROC curves were used to determine the optimal threshold by combining the highest sensitivity and specificity. In line with this, the best cut off values were determined for both assays considering highest Youden index. In most studies, optimal cut-off values to improve the diagnostic performance of assays is higher than cut off recommended by manufacturer that resulted in decreased sensitivity and increased specificity [24,27-29]. However, the optimal thresholds may be lower than those recommended by manufacturers, as it should take into account the modality of studies, the type of fungal infections, and the population being considered in order to achieve the best overall performance in various clinical settings [22].

In practical terms due to cost considerations, DFA can be used to test a small number of samples using the strips of the wells in DFA instead of 96-well plate in FA. Therefore, laboratory technicians will benefit from technical versatility and affordability of DFA as they process fewer samples in a cost-effective manner, especially in developing countries. consequently, the DFA is an alternative option for patients suspected of having candidemia providing highly consistent results with FA for laboratories with limited sample numbers.

Our study does, however, have some limitations. First, this study included only a small number of samples from patients with proven candidemia. To confirm the clinical validity and establish the clinical utility, a large scale and prospective evaluation is needed. Further studies are expected to evaluate the consistency of different BDG assays for diagnosis of candidemia. Additionally, it would be desirable to consider the clinical characteristics, underlying diseases, and also the sensitivity of assays to detect candidemia caused by different *Candida* species in future studies.

In conclusion, 1,3-β-D-glucan (BDG), a well-known fungal biomarker has valuable potential to diagnose of candidemia for proper antifungal therapy. According to our findings, BDG detection in serum has good performance for diagnosis of candidemia. Additionally, our evaluation of the two methods used to measure BDG levels demonstrated that the DFA has exhibited comparable performance to the FA in order to diagnose candidemia.

Funding

This study was supported by the Deputy of Research and Technology of Shiraz University of Medical Sciences, Shiraz, Iran [Grant number 18492].

CRediT authorship contribution statement

Somayeh Yazdanpanah: Formal analysis, Writing – original draft. **Maryam Rahbarmah:** Investigation. **Marjan Motamedi:** Data curation. **Hossein Khodadadi:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was extracted from a master thesis submitted by Maryam Rahbarmah. The authors acknowledge the staff of Emrafar Co. (Tehran, Iran) for their help and support.

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