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Can Time to Blood Culture Positivity Influence the Treatment Strategy in Candidemia Management?

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ABSTRACT

Objective: The primary objective of this study was to investigate whether time to blood culture positivity (TTP) can reliably differentiate *Candida* species and to evaluate their antifungal susceptibility profiles to support more effective clinical decision-making.

Materials and Methods: This retrospective study was conducted at Sivas Numune Hospital between January 1, 2022 and February 28, 2025. Adult patients (>18 years) with positive blood cultures for *Candida* species were included.

Results: A total of 101 blood culture bottles from 70 patients were evaluated. *C. albicans* was the most common isolate (51.5%), followed by *C. glabrata* (21.5%). The shortest TTP was observed for *C. tropicalis* (19 hours), and the longest for *C. glabrata* (42 hours). When *C. albicans* and *C. tropicalis* were classified as early TTP species and *C. glabrata* and *C. parapsilosis* as late TTP species, the median TTP values were 21 and 35 hours, respectively. Receiver operating characteristic (ROC) analysis identified a TTP cut-off value of 28 hours as optimal for predicting the early TTP group (area under the curve: 0.751), indicating moderate discriminatory ability. Early TTP species were generally susceptible to fluconazole, whereas resistance was more frequent among late TTP species.

Conclusion: Blood culture positivity times differ among *Candida* species. Early TTP species, such as *C. albicans* and *C. tropicalis*, were more likely to be fluconazole-susceptible, suggesting that fluconazole may be an appropriate option for empirical therapy in such infections.

Keywords: Antifungal susceptibility, candidemia, empirical treatment, fluconazole, signal time.

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INTRODUCTION

Microorganisms of the genus *Candida* are the most common cause of fungal infections. *Candida* species reproduce by budding and may form true or pseudohyphae. They can cause invasive infections associated with high mortality rates despite antifungal therapy.[1] Because certain *Candida* species naturally colonize the skin and the genitourinary and gastrointestinal tracts, most invasive infections arise endogenously. According to the World Health Organization (WHO) fungal pathogens list (2022), *Candida auris* and *Candida albicans* are categorized as critical priority pathogens, whereas *Candida glabrata*, *Candida tropicalis*, and *Candida parapsilosis*

are classified as high-priority pathogens.[2,3] Since *Candida auris* was first identified in 2009 in the external ear canal of a patient, antifungal resistance rates in *C. auris* as well as in other *Candida* species have shown a steady and concerning increase, underscoring the growing challenges in managing infections caused by these opportunistic pathogens.[4–6] Given the rising resistance rates, it is essential for each medical center to determine its local resistance patterns to guide empirical antifungal therapy.

Early targeted treatment of fungal infections is of vital importance; however, delays in initiating therapy are frequently encountered.[7] One of the initial strategies to facilitate early treatment is the determination of blood culture time to positivity (TTP). A limited number of studies suggest that this parameter may aid in the identification of *Candida* species. Moreover, assessment of TTP may contribute to the development of additional strategies to assist in selecting appropriate antifungal therapy.[8]

This study aimed to investigate variations in blood culture positivity times among *Candida* species and to evaluate whether this parameter could serve as a diagnostic marker. Additionally, in light of increasing resistance rates, we sought to assess the antifungal susceptibility profiles of *Candida* spp. in our center. Through this approach, the study aims to contribute to optimizing antifungal therapy selection and improving early treatment strategies.

KEY MESSAGES

- Signal durations in fungal cultures differ significantly among *Candida* species. Species such as *C. albicans* and *C. tropicalis* exhibit early signals, whereas *C. glabrata* and *C. parapsilosis* tend to signal later.
- Early-signaling *Candida* spp. are susceptible to fluconazole, while fluconazole resistance is more frequently observed in later-signaling species.
- Signal duration of *Candida* spp. may help guide empirical antifungal treatment decisions. Fluconazole may be considered an appropriate option for species that signal early.

MATERIALS AND METHODS

Study Design and Data Collection

Prior to the initiation of this retrospective cohort study, formal ethical approval was obtained from Sivas Cumhuriyet University Health Sciences Research Ethics Committee (approval number: 2025-04/04, date: 24.04.2025), ensuring that all study procedures adhered to established ethical standards and guidelines. The study included all hospitalized patients aged over 18 years at Sivas Numune Hospital who had blood cultures positive for *Candida* spp. between January 1, 2022 and February 28, 2025. Blood culture bottles from patients under 18 years of age, those contaminated with skin flora, or those inoculated with non-blood specimens (e.g., pleural fluid or synovial fluid) were excluded. For each patient, the time to positivity of each individual blood culture bottle collected simultaneously was recorded separately. Antifungal susceptibility results, however, were documented as a single consolidated result per patient. Bottles inoculated with non-blood specimens (e.g., pleural fluid or synovial fluid) and patients under 18 years of age were excluded from the study. Patient demographic data (age and sex), the species and strain of the isolated pathogen, and the time to positivity (in hours) were retrieved from the hospital information system and recorded in Microsoft Excel (Microsoft Office Version 365, USA; URL: https://www.office.com/).

Laboratory Procedures

Blood samples were aseptically collected at the patient's bedside and inoculated into BACTEC Plus Aerobic Medium bottles (Becton Dickinson, USA). Following inoculation, the bottles were incubated for up to five days in an automated BACTEC blood culture system (Becton Dickinson, USA) to ensure optimal conditions for microbial growth and detection. Bottles signaling positive growth were subjected to Gram staining, and samples were subcultured onto blood agar and Sabouraud dextrose agar. Colonies grown on agar media were isolated and identified, and antifungal susceptibility testing was performed using a fully automated identification and susceptibility testing system. TTP was defined as the duration (in hours) between placement of the inoculated bottle into the automated culture system and detection of microbial growth, which triggered an alert.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 23 (IBM Corp., USA). The normality of continuous variables was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov tests. For descriptive statistics, normally distributed variables were expressed as mean±standard deviation (SD), whereas non-normally distributed variables were presented as median and interquartile range (IQR).

Comparisons between study groups were performed using parametric or non-parametric tests according to data distribution. Continuous variables with normal distribution were analyzed using the independent samples Student's t-test, while not meeting normality assumptions were evaluated using the Mann–Whitney U test. Categorical variables were summarized as absolute numbers and corresponding percentages. The discriminatory performance of selected

Table 1. Distribution of yeast isolates in blood cultures

Species	No. of Isolates (%)
C. albicans	36 (51.5)
C. glabrata	15 (21.5)
C. parapsilosis	8 (11.5)
C. tropicalis	6 (8.5)
C. melibiosica	2 (2.8)
C. kefyr	1 (1.4)
C. lipolytica	1 (1.4)
C. dubliniensis	1 (1.4)
Total	70 (100)

Table 2. Comparison of time to positivity (TTP) among *Candida* isolates

	Signal Time Median (hours, IQR)	p
C. albicans	21 (16-32)	**<0.001**
C. glabrata	42 (35-48)	
C. albicans	21 (16-32)	0.082
C. tropicalis	19 (8-22)	
C. albicans	21 (16-32)	0.116
C. parapsilosis	29 (21-44)	
C. glabrata	42 (35-48)	**<0.001**
C. tropicalis	19 (8-22)	
C. glabrata	42 (35-48)	0.068
C. parapsilosis	29 (21-44)	
C. tropicalis	19 (8-22)	**0.004**
C. parapsilosis	29 (21-44)	

IQR: Interquartile range.

laboratory and clinical parameters was further evaluated using receiver operating characteristic (ROC) curve analysis. Optimal threshold values were determined using the Youden index, which maximizes the combined sensitivity and specificity of a test. All analyses were conducted using two-tailed statistical tests, and statistical significance was defined as a p-value <0.05.

Given the retrospective nature of the study, no prospective sample size calculation was performed prior to data collection. However, a post hoc power analysis was conducted based on the observed intergroup differences in blood culture time to positivity among *Candida* species. Assuming an alpha level of 0.05, the resulting statistical power was estimated to be approximately 85%, indicating an adequate ability to detect clinically meaningful differences.

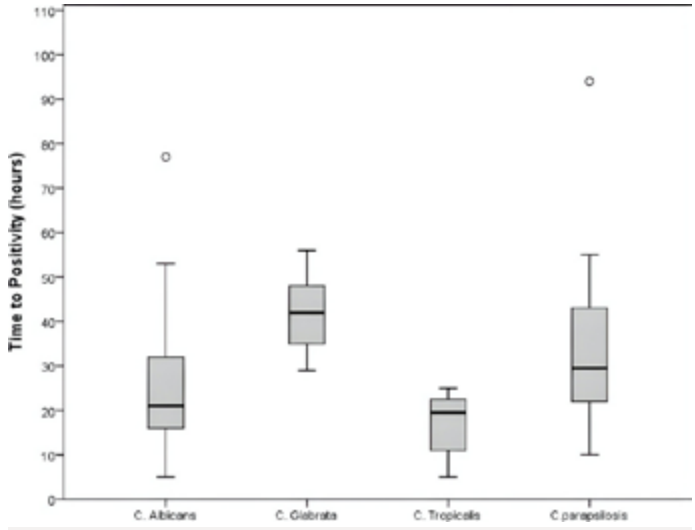

Figure 1. Time to blood culture positivity (TTP) among *Candida* isolates.

RESULTS

A total of 101 blood culture specimens obtained from 70 individual patients with *Candida* species growth were included in the analysis. The cohort consisted of 31 males and 39 females, with a mean age of 73.2±12.0 years (±SD). Antifungal susceptibility results were available for 48 of the 70 patients included in the study. Among the 70 patients, *C. albicans* was isolated in 36 cases, *C. glabrata* in 15 cases, *C. parapsilosis* in eight cases, *C. tropicalis* in six cases, and other *Candida* species in five cases (Table 1). Time to positivity data were available for 82 blood culture bottles. *C. glabrata* demonstrated a significantly longer TTP compared to both *C. albicans* and *C. tropicalis*. Although TTP was also longer compared to *C. parapsilosis*, this difference did not reach statistical significance (Table 2). Among all *Candida* species, *C. tropicalis* exhibited the shortest time to positivity; this difference was statistically significant when compared to *C. glabrata* and *C. parapsilosis* (Table 2). The distribution of TTP values for all *Candida* isolates is presented in Figure 1.

Antifungal susceptibility results were available for 48 patients included in the study. All *C. albicans* isolates were susceptible to fluconazole and amphotericin B, while susceptibility rates to voriconazole, anidulafungin, and micafungin exceeded 95%. *C. glabrata* isolates demonstrated 100% susceptibility to amphotericin B and anidulafungin, and 66% susceptibility to fluconazole. All *C. tropicalis* isolates included in the study exhibited complete susceptibility (100%) to all antifungal agents tested. Detailed antifungal susceptibility profiles of the *Candida* isolates are summarized in Table 3.

Table 3. Susceptibility of *Candida* isolates to antifungal agents

Susceptibility (n)	*C. albicans* (%)	*C. glabrata* (%)	*C. tropicalis* (%)	*C. parapsilosis* (%)
Fluconazole (48)	22 (100)	6 (50)	4 (100)	6 (85.7)
Voriconazole (38)	21 (95.4)	4 (80)	4 (100)	5 (71.4)
Amphotericin B (42)	22 (100)	11 (100)	2 (100)	7 (100)
Anidulafungin (43)	20 (95.2)	12 (100)	3 (100)	5 (71.4)
Micafungin (43)	21 (95.4)	10 (83.3)	2 (100)	7 (100)

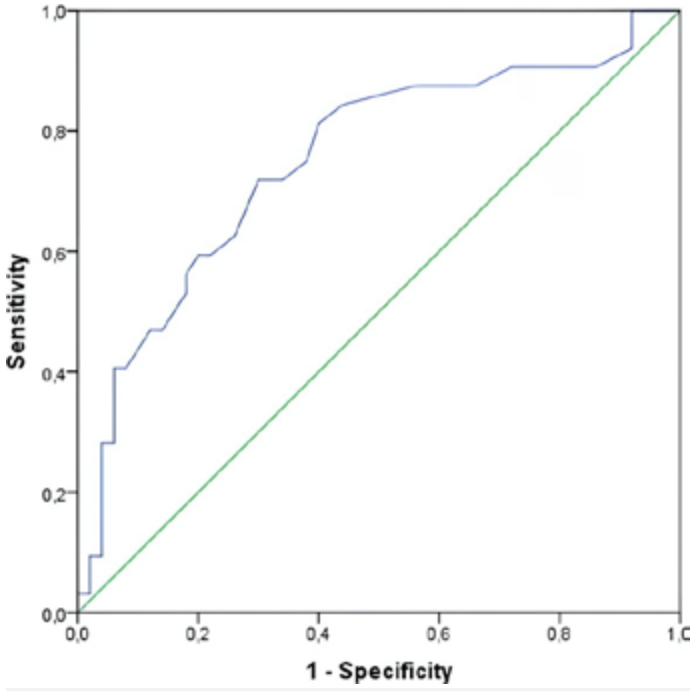

Figure 2. Receiver operating characteristic curve of time to blood culture positivity (TTP) for predicting the *C. albicans*–*C. tropicalis* group.

In our study, as all *C. albicans* and *C. tropicalis* isolates demonstrated complete susceptibility to fluconazole and their TTP values did not differ significantly, these two species were combined into a single group. In contrast, *C. glabrata* and *C. parapsilosis* were categorized into a separate group for TTP comparison. The median TTP for the *C. albicans*–*C. tropicalis* group was 21 hours (IQR: 16–30), whereas it was 35 hours (IQR: 23–47) for the *C. glabrata*–*C. parapsilosis* group; this difference was statistically significant ($p<0.001$). The discriminatory ability of TTP to identify the *C. albicans*–*C. tropicalis* group and the corresponding threshold values were evaluated using ROC analysis, enabling assessment of both sensitivity and specificity (Fig. 2). According to the ROC analysis, a cut-off value of 28 hours provided the optimal balance between sensitivity (72%) and specificity (70%) (area under the curve: 0.751; 95% confidence interval: 0.638–0.863).

DISCUSSION

Infections caused by *Candida* species may involve various organs, including the lungs (pneumonia), the heart (endocarditis), and the central nervous system, and are associated with high mortality rates. Established risk factors for infections caused by *Candida* spp. include the use of broad-spectrum antibiotics, receipt of blood transfusions, prior *Candida* colonization, and administration of total parenteral nutrition.[9,10] The World Health Organization classifies *Candida* species within the critical and high-priority fungal pathogen groups.[2] Given the clinical significance of these microorganisms, early and effective treatment is essential.

Although recent studies have highlighted the increasing prevalence of non-albicans *Candida* species in *Candida* infections,[11,12] *C. albicans* accounted for the majority of isolates in our study (51.5%) (Table 1). A total of eight distinct *Candida* species were identified among the isolates analyzed during the present investigation. Species identification was performed using the BD Phoenix 100 system, which has been reported to reliably and accurately identify the most commonly encountered *Candida* species, such as *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*, with an overall accuracy exceeding 95%, thereby providing a robust tool for clinical and laboratory diagnosis.[13] In our study, 92.8% of the isolates were common *Candida* species (Table 1). Based on these findings, the likelihood of species misidentification was considered to be low.

The study evaluated variations in TTP among different *Candida* isolates, including *C. albicans*, *C. parapsilosis*, *C. glabrata*, and *C. tropicalis*, using blood culture specimens. Consistent with the findings of Sachu et al.[8] and Yang et al.,[14] *C. tropicalis* demonstrated the shortest TTP among the species analyzed (Fig. 1). However, although *C. tropicalis* had the shortest median TTP, the difference compared with *C. albicans* did not reach statistical significance ($p=0.082$) (Table 2). This may be attributable to the limited number of blood culture samples positive for *C. tropicalis* in our study. In line with previous reports,[8,14] *C. glabrata* exhibited the longest TTP.

Candida species are conventionally classified as albicans and non-albicans groups.[11] However, in the present study, grouping

was based primarily on similarity in TTP values. *C. albicans* and *C. tropicalis* isolates exhibited similar growth kinetics, with no statistically significant difference in their TTP values. In contrast, *C. glabrata* and *C. parapsilosis* demonstrated longer TTP values. Therefore, grouping species with similar growth dynamics was considered appropriate for TTP-based analyses. When classified according to TTP, *C. tropicalis* and *C. albicans* constituted the early-detection group, whereas *C. glabrata* and *C. parapsilosis* comprised the late-detection group, with median TTPs of 21 hours and 35 hours, respectively ($p<0.001$). Based on ROC analysis, the optimal threshold value was determined to be 28 hours. When TTP was less than 28 hours, the sensitivity and specificity for identifying the *C. albicans*–*C. tropicalis* group were 72% and 70%, respectively, indicating that this threshold provides moderate discriminatory ability for correctly classifying these species in blood culture specimens (Fig. 2). While Sachu et al.[8] reported a cut-off value of 24 hours for *C. tropicalis*, Yang et al.[14] reported 25.5 hours. The higher cut-off value identified in our study (28 hours) may be attributable to the inclusion of *C. albicans* alongside *C. tropicalis*. In addition, another study reported a cut-off value of 33.1 hours for *C. tropicalis* and found that antifungal susceptibility was not associated with TTP.[15] Taken together, these findings suggest that TTP may serve as a useful indicator for species identification.

A total of 48 *Candida* isolates underwent antifungal susceptibility testing. Fluconazole susceptibility was observed in all *C. albicans* and *C. tropicalis* isolates. These findings suggest that empirical fluconazole therapy could be considered for early-detecting *Candida* species. A recent systematic review including 89 studies reported fluconazole susceptibility rates of 93.25% for *C. parapsilosis*, 91.6% for *C. albicans*, 79.4% for *C. glabrata*, 77.95% for *C. tropicalis*, 76% for C. guilliermondii, 50% for C. pelliculosa, and 0% for *C. auris*.[16] In another recent study evaluating antifungal susceptibility patterns of *Candida* species, *Candida albicans* isolates demonstrated 13.3% resistance to fluconazole, 2.2% resistance to amphotericin B, and no resistance to anidulafungin. *Candida glabrata* isolates showed 40% resistance and 60% intermediate susceptibility to fluconazole, while *Candida* parapsilosis isolates were 83% susceptible to fluconazole.[15] The lower fluconazole susceptibility rates observed for *C. glabrata* and *C. parapsilosis* in our study may be attributable to the relatively small number of isolates included in this investigation.

Given that all *C. albicans* and *C. tropicalis* isolates were susceptible to fluconazole, this agent may represent an appropriate option for empirical therapy in patients with early yeast detection. Additionally, all *Candida* isolates in our study were susceptible to amphotericin B, whereas echinocandin resistance was observed among the late-detecting species (*C. glabrata* and *C. parapsilosis*) (Table 3). Based on these findings, amphotericin B may be considered in cases of late yeast detection. Each center should determine the distribution of *Candida* species, antifungal resistance patterns, and TTP values using their own systems to guide the management of fungal infections, which are associated with substantial mortality and serious clinical complications.

Although it has been suggested that candidemia concentration may influence TTP, Yang et al.[14] demonstrated that TTP is independent of inoculum concentration by inoculating blood culture bottles with various concentrations and species of *Candida* isolates.

The relatively small sample size of our study, its single-center design, and its restriction to a single city limit our ability to establish definitive antifungal resistance rates and TTP thresholds. Moreover, the impact of TTP on mortality was not evaluated, which represents an additional limitation of our study.

CONCLUSION

In conclusion, although TTP alone may not definitively predict *Candida* species, it may serve as a useful supportive indicator. When combined with local antifungal resistance data, these findings may assist clinicians in selecting appropriate empirical therapy. As no previous studies from Türkiye have addressed this topic, this research aims to fill an existing knowledge gap and provide an original and valuable contribution to the scientific literature in Türkiye.

Ethics Committee Approval: Ethics committee approval was obtained from Sivas Cumhuriyet University Health Sciences Research Ethics Committee (date: 24.04.2025, number: 2025-04/04).

Informed Consent: Written consent was obtained from all participants (or their legal representatives/guardians). The consent form provided detailed information about the study's purpose, methodology, potential risks, expected benefits, and participant rights. Additionally, participants were informed about the confidentiality of their personal data and the protection of their anonymity.

Conflict of Interest: The authors have no conflicts of interest to declare.

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