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ORIGINAL RESEARCH

Time to Positivity Facilitates an Early Differential Diagnosis of *Candida tropicalis* from Other *Candida* species

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Background: Candidemia caused by *Candida tropicalis* has more serious adverse consequences and an even higher mortality. Time to positivity (TTP) has been widely used to identify microbial species, resistant microorganisms and distinguish real pathogens and pollutants. However, few studies have demonstrated TTP as a presumptive diagnosis of *C. tropicalis* in patients with candidemia.

Patients and Methods: A retrospective study of 136 episodes of candidemia and simulated blood cultures with 314 episodes of confirmed *Candida* strains were applied to explore the role of TTPs in diagnosing *C. tropicalis*. TTPs were recorded as the shorter one if both aerobic and anaerobic vials were positive. Lastly, relationships were tested between TTPs and resistance and initial inocula concentration.

Results: For the retrospective study, the mean of TTPs for *C. tropicalis* from 136 patients with candidemia was significantly shorter than other *Candida* species. The area under the receiver operating characteristics (ROC) curve was 0.8896 ± 0.030 with a sensitivity of 92.86% and a specificity of 77.87%, respectively, indicating TTPs with a cut-off value of <25.50 h had a strong diagnostic power for *C. tropicalis* in patients with candidemia. Moreover, TTPs from 314 simulated blood cultures showed similar results as the retrospective study, demonstrating TTP is a powerful diagnostic tool in early diagnosing *C. tropicalis* in patients with candidemia. Additionally, our results showed no statistical significance between TTPs and initial inocula concentration and resistance of *Candida* species, suggesting initial inocula concentration does not impact TTPs, and TTPs may not be promising in predicting the resistance of all *Candida* species.

Conclusion: TTP can be employed to early distinguish *C. tropicalis* from other *Candida* species in patients with candidemia, which is extremely helpful to initiate empiric antifungal treatments to improve clinical outcomes.

Keywords: time to positivity, *C. tropicalis*, presumptive diagnosis, *Candida* species, candidemia

Introduction

C. albicans, C. glabrata, C. tropicalis and *C. parapsilosis* are four major pathogens causing candidemia worldwide.[1,2] Invasive infections caused by these species have been increasingly seen in patients with immunodeficiency, organ transplantation, cancer patients with chemotherapies, and long-term antibiotics or glucocorticoid treatments.[3] Although *C. albicans* remains the most common pathogen in candidemia, non-*C. albicans* species are remarkably increasing as well, accounting for more than 50% of invasive candidiasis in multiple regions.[4–6] *C. tropicalis* is one of the invasive candidiasis notably increasing in recent years and has a sharp spike, especially in Latin America and part of Asian Pacific countries including India and China.[4,7] In addition, the resistance of *C. tropicalis* to azoles has deteriorated year by year as well.[8,9] It is reported from a Chinese five-year surveillance on invasive candidiasis that the resistance rate of *C. tropicalis* to fluconazole has increased the prominence from less than 8% in 2010 to over 22% in 2014.[10] It is

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noteworthy that invasive infection of *C. tropicalis* has more serious adverse consequences and relatively higher mortality compared with other *Candida* species,[11,12] and its clinical outcomes largely rely on early effective interventions including susceptible antifungal treatments.[5,13] However, identification of *C. tropicalis* takes a long time. Therefore, it is extremely important to identify potential pathogens and initiate immediate empiric therapy in patients with candidemia.[14]

Time to positivity (TTP) provided by automatic blood culture machines can be used as powerful evidence to determine microbial species,[15] resistance,[16] distinguish real pathogens and pollutants,[17] predict sources and prognosis of bacteremia.[18] Some studies have previously reported that TTP of *C. glabrata* is longer compared with other *Candida* species in patients with candidiasis in BacT/Alert[19] and BACTEC 9240 systems.[20] Mounting evidence has shown that *C. glabrata* tend to grow in anaerobic blood culture vials particularly,[19,20] and an exclusive or an earlier growth in anaerobic vials is useful to predict *C. glabrata*.[21] However, whether TTP can be applied as a presumptive diagnosis for *C. tropicalis* is rarely reported.

The purpose of this study was to investigate the diagnostic value of TPP in making an early differential diagnosis of *C. tropicalis* in patients with candidemia.

Materials and Methods

Retrospective Clinical Study

All patients with bloodstream infections were recorded in the clinical system from the Department of Microbiology Laboratory, the First Affiliated Hospital of Chengdu Medical College from January 1, 2015 to December 31, 2020. After exclusion of bacteremia, polymicrobial, filamentous fungemia, *Cryptococcus*, no recordings of TTPs, and duplicated strains, only patients with monomicrobial candidemia were enrolled in this retrospective study. Both their demographic information and TTPs were collected for further analysis. The blood culture vials used in the retrospective clinical study were Fastidious Antimicrobial Neutralization Media Aerobic & Fastidious Antimicrobial Neutralization Media Anaerobic (bioMérieux, France, containing activated carbon adsorbent). Around 8 mL −10 mL of blood was inoculated into each vial according to the manufacturer's instruction, but the exact amount was not recorded for each patient. All blood cultures were performed by BacT/Alert 3D120 system (bioMérieux, France). TTPs were recorded as time intervals between the beginning to an automatic alert signal appeared (indicating growth of organism) during the blood cultures. The shorter one was deemed as the TTP if both aerobic and anaerobic vials were positive. If a patient had persistent candidemia with multiple positive blood cultures, TTPs were recorded only for the first round.

Simulated Blood Cultures

Multiple impactors can affect TTP, including inoculation volume and transportation time. In order to test the accuracy of data obtained from the retrospective analysis, another 314 confirmed *Candida* spp. strains were applied for simulated blood cultures as an internal control. All these strains were isolated from the Department of Microbiology Laboratory of the First Affiliated Hospital of Chengdu Medical College during the fourth quarter of 2021 (Table S1). Those *Candida* spp. strains isolated from various clinical specimens, such as blood, urine, abscess, ascites, etc. They were inoculated into blood culture vials with an aerobic and anaerobic environment, respectively. The names of the vials were Fastidious Antimicrobial Neutralization Media PLUS Aerobic/Anaerobic (bioMérieux, France) containing adsorbent of resin. All the performances were followed according to a protocol from Yarbrough et al.[22] Briefly, 1000 colony-forming unit (CFU) was used as a final inoculation dose for each vial. Vials for blood cultures were incubated in BacT/Alert 3D120 system. Cultures were stopped until positive growths were detected. The maximum culture time was 120 hours. TTPs were recorded as the same method before. Vials with positive results were consequently sub-cultured to a chocolate agar plate and a sabouraud agar plate, respectively, for further validation of *Candida* colonies by identification of the pure growth and expected colony morphologies. The recovered growth colonies in the sub-cultures were confirmed by matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry (bioMérieux, France).

Antifungal Susceptibility Testing

Susceptibility tests of *Candida* spp. to antifungal antibiotics were performed on ATB ™ Fungus 3 stripe (bioMérieux, France). Minimum inhibitory concentrations (MICs) for all antifungal drugs were recorded after 24 hours of incubation. The MIC breakpoints for *Candida* spp. were referred to the Clinical and Laboratory Standards Institute (CLSI).[23,24] *C. albicans* ATCC 24433 and *C. parapsilosis* ATCC 22019 were used for quality controls. All results were tested within determined ranges.

Statistical Analysis

All data analyses were performed by GraphPad Prism 5. TTPs between *C. tropicalis* and other *Candida* species were compared by Student's *t*-test. Proportions were compared by X^2 or Fisher's exact test. The diagnostic values and cut-off values of TTPs for *C. tropicalis* were evaluated by the receiver operating characteristic (ROC) curve. $p<0.05$ was considered to be statistically significant.

Results

Demographic Features of 136 Patients with Candidemia in the Retrospective Study

A total of 5031 episodes of bloodstream infection were selected at the beginning of the retrospective study. After excluding bacteremia, polymicrobial, filamentous fungemia, *Cryptococcus*, no recordings of TTPs, and duplicated strains, a total of 136 episodes of monomicrobial candidemia were finally enrolled in this study (Figure 1). It was shown that *C. albicans* (n = 45; 33.09%), *C. parapsilosis* (n = 32; 23.53%), *C. glabrata* (n = 32; 23.53%), and *C. tropicalis* (n = 14; 10.29%) were four major pathogens in patients with monomicrobial candidemia.

The demographic features of 136 episodes of monomicrobial candidemia are listed in Table 1. Patients with urinary tract infection, renal insufficiency, and antibiotic use were significantly different in proportion of *C. albicans, C. glabrata, C. tropicalis* and *C. parapsilosis* bloodstream infection ($p < 0.05$). The results demonstrated that *C. glabrata* bloodstream infection was more likely to occur in patients with urinary tract infection (73.33%) or renal insufficiency (80.00%). Compared with other *Candida* species, patients with candidemia caused by *C. albicans* were less treated with broad-spectrum antibiotics (29.55%).

Diagnostic Value of TTP for *C. tropicalis*

As shown in Table 2, the mean TTP of *C. tropicalis* was 21.26 ± 3.20 h, which was the shortest among *Candida* species (*C. albicans*: 34.82 ± 15.55 h, *C. glabrata*: 66.84 ± 30.87 h, *C. parapsilosis*: 33.44 ± 8.32 h, *C. guilliermondii*: 31.00 ± 7.65 h, *C. sake*: 59.75 ± 19.55, and *C. krusei*: 30.75 ± 7.76 h). TTPs were statistically different between each type of *Candida* species (shown in Figure 2A, ** $p<0.01$, *** $p<0.001$).

The diagnostic value of TTP for *C. tropicalis* in candidemia and its optimal cut-off values were determined by the receiver operating characteristic (ROC) curve (Figure 2B). Area under the ROC curve (AUC) demonstrated that TTP had a strong diagnostic value to identify *C. tropicalis* from other *Candida* species (AUC 0.8896 ± 0.030; 95% confidence interval 0.831–0.949). Based on the results of AUC and ROC curve, TTP < 25.50 h was the best optimal cut-off value to

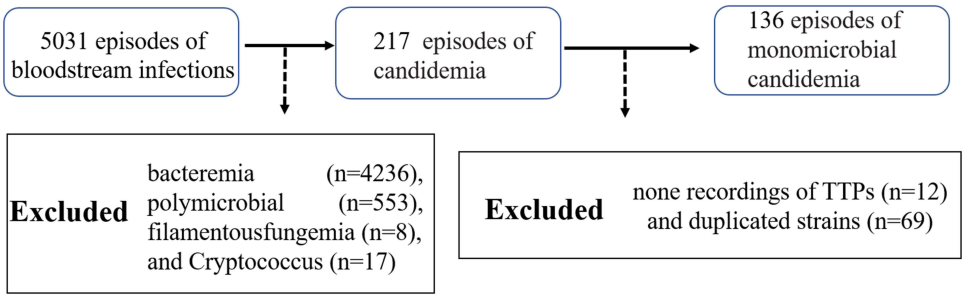

Figure 1 Flow chart showing the monomicrobial candidemia selection process.
Abbreviation: TTP, time to positivity.

Table 1 Demographic Features of 136 Patients with Candidemia

Variables	*C. albicans* (n=44)	*C. parapsilosis* (n=32)	*C. glabrata* (n=30)	*C. tropicalis* (n=14)	Other Species (n=16)	*p* value
Age, mean ± SD	67.5±13.4	65.3±11.3	63.2±14.1	66.8±8.94	62.6±16.8	0.88
Gender (male/female)	24/20	19/13	14/16	7/7	10/6	0.94
Acquisition of infection, n (%)						0.51
Community	4 (9.09%)	3 (9.38%)	1 (3.33%)	0 (0)	2 (12.50%)	
Hospital	40 (90.91%)	29 (90.62%)	29 (96.67%)	14 (100%)	14 (87.50%)	
Underlying diseases, n (%)						
Diabetes	21 (47.73%)	13 (40.63%)	14 (46.67%)	7 (50.00%)	9 (56.25%)	0.91
Urinary tract infection	9 (20.45%)	11 (34.38%)	22 (73.33%)	4 (28.57%)	4 (25.00%)	<0.001**
HIV infection	4 (9.09%)	3 (9.38%)	1 (3.33%)	0 (0%)	4 (25.00%)	0.51
Renal insufficiency	22 (50.00%)	22 (68.75%)	24 (80.00%)	6 (42.86%)	3 (18.75%)	0.02*
Solid organ malignancies	10 (22.73%)	8 (25.00%)	6 (20.00%)	2 (14.29%)	6 (37.50%)	0.86
Neutropenia	19 (43.18%)	12 (37.50%)	16 (53.33%)	6 (42.86%)	10 (62.50%)	0.65
Hematological malignancies	3 (6.82%)	4 (12.50%)	2 (6.67%)	2 (14.29%)	1 (6.25%)	0.71
Clinical symptoms, n (%)						
Fever	40 (90.91%)	28 (87.50%)	25 (83.33%)	10 (71.43%)	12 (75.00%)	0.31
Septic shock	3 (6.82%)	2 (6.25%)	2 (6.67%)	1 (7.14%)	3 (18.75%)	0.99
Risk factors, n (%)						
Corticosteroids	7 (15.91%)	3 (9.38%)	4 (13.33%)	4 (28.57%)	3 (18.75%)	0.41
Organ transplantation	7 (15.91%)	4 (12.50%)	3 (10.00%)	0 (0%)	1 (6.25%)	0.44
Catheter	27 (61.36%)	21 (65.63%)	20 (66.67%)	9 (64.29%)	5 (31.25%)	0.97
Dialysis	15 (34.09%)	16 (50.00%)	17 (56.67%)	3 (21.43%)	2 (12.50%)	0.07
Antibiotic usage	13 (29.55%)	21 (65.63%)	19 (63.33%)	10 (71.43%)	11 (68.75%)	0.02*
Intensive care unit	19 (43.18%)	20 (62.50%)	14 (46.67%)	5 (35.71%)	12 (75.00%)	0.27

Notes: *Statistically significant, **Statistically highly significant.

Table 2 TTPs of Different *Candida* species Included in the Retrospective Study

Species	No (%) of Positivity	Mean (SD) of TTP	Median (IQR) of TTP
C. albicans	45 (33.09)	34.82 (15.55)	31 (24.00–41.00)
C. glabrata	32 (23.53)	66.84 (30.87)	72 (45.50–85.00)
C. parapsilosis	32 (23.53)	33.44 (8.32)	33 (29.00–39.75)
C. guilliermondii	5 (3.68)	31.00 (7.65)	32 (24.00–37.50)
C. sake	4 (2.94)	59.75 (19.55)	54 (545.50–79.75)
C. krusei	4 (2.94)	30.75 (7.76)	29.5 (24.00–38.75)
C. tropicalis	14 (10.29)	21.26 (3.20)	20.38 (18.61–23.91)

Abbreviations: TTP, Time to positivity; SD, standard deviation; IQR, Interquartile Range.

identify *C. tropicalis* from other *Candida* species in candidemia. Accordingly, when predicting *C. tropicalis* with a TTP of <25.50 h, the sensitivity and specificity were 92.86% and 77.87%, respectively; the positive and negative predictive values were 34.15% and 98.96%, respectively.

To verify the accuracy of the retrospective data, another 314 *Candida* strains were applied as an internal control to exclude other impactors, such as inoculation volume, transportation time, etc. The information regarding the age, gender, sample source, and susceptibility to antifungal agents were shown in Table S1. Strains collected for simulated blood cultures comprised 161 *C. albicans* (51.3%), 53 *C. glabrata* (16.9%), 33 *C. parapsilosis* (10.5%), 51 *C. tropicalis* (16.2%), and 16 other *Candida* species. All the results were consistent with the data obtained from our retrospective study (Table S2 and Figure S1). The mean of TTP for *C. tropicalis* was the shortest compared with other *Candida* species (18.32 ± 1.70 versus 27.35 ± 6.34, $p < 0.0001$). The AUC was 0.933 ±0.015, suggesting that TTP had a strong diagnostic

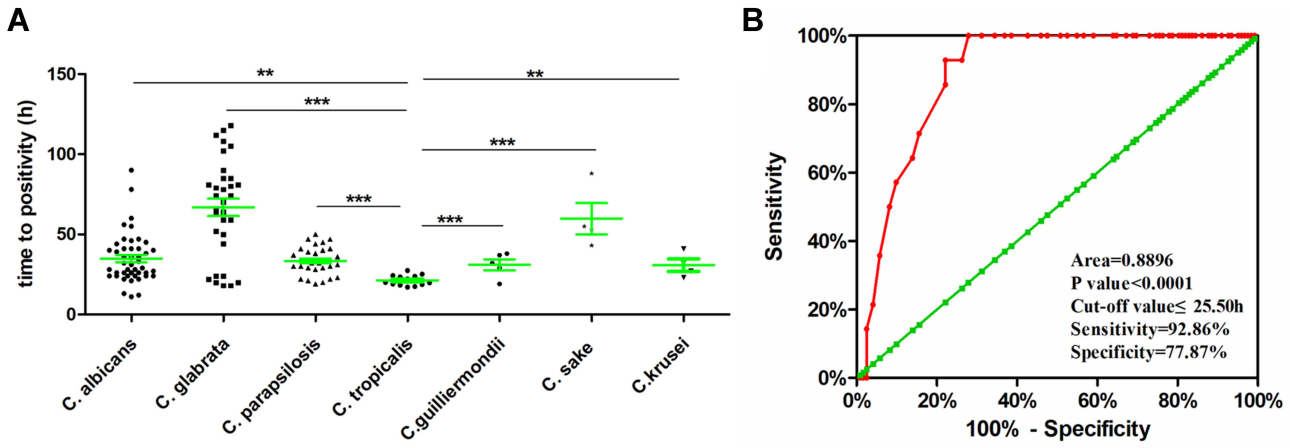

Figure 2 (**A**) Scatter plot of time to positivity (TTP) sorted by different *Candida* species, $^{**}p < 0.01$, $^{***}p < 0.001$. (**B**) Receiver operating characteristic curves of time to positivity as a diagnostic test for *C. tropicalis* in patients with candidemia.

value for *C. tropicalis* ($p<0.0001$) in simulated blood cultures. According to characteristics of ROC and AUC, the recommended cut-off value of *C. tropicalis* was <19.99 h, which generated sensitivity and specificity of 92.16% and 92.02%, respectively; the positive and negative predictive values were 69.12% and 98.37%, respectively.

Even though TTPs have been widely used for diagnosing *Candida* species, there are still some controversial issues. One current controversy is whether different concentrations of *Candida* species in the blood may have effects on TTP. Thus, we determined the effect of concentration of initial inocula of *Candida* species on TTP. Twenty *Candida* strains (selected from the above 314 strains randomly, including 8 *C. albicans*, 5 *C. glabrata*, 4 *C. tropicalis* and 3 *C. parapsilosis*) were inoculated with different concentrations (1000 CFU/vial, 5000 CFU/vial and 25000 CFU/vial) into vials (including anaerobic and aerobic vials), then the vials were incubated in BacT/Alert 3D120 system. It was found that TTPs tended to be shorter in vials with a higher concentration of initial inocula compared with lower one, but no statistical difference was found in each *Candida* species by comparisons among three different concentrations ($0.06 \leq p \leq 0.72$, Table S3).

Finally, the relationships were further tested between TTPs and susceptibility of *Candida* species to common antifungal drugs (amphotericin B, fluconazole, 5-fluorocytosine, and voriconazole). The results showed TTPs were not significantly different between resistant and susceptible strains to those four different antifungal agents ($p > 0.05$), suggesting that TTPs may not be potential to predict the susceptibility or resistance of each *Candida* species to amphotericin B, 5-fluorocytosine, fluconazole and voriconazole (shown in Table S4).

Discussion

Candidemia is an extremely dangerous clinical condition and carries a high mortality.[25,26] Timely clinical interventions will prominently save patients' lives. Therefore, an early and rapid diagnosis of potential pathogens is particularly important. Besides of blood cultures, several other methods can also be employed for the identification of candidemia.[27,28] Mannan antigen and its antibody can be used for diagnosing candidemia, it has a specificity of 90%, but its sensitivity is around 60%.[29] Moreover, mannan antigen and its antibody are cleared quickly in the blood and cannot be used to diagnose specific *Candida* species.[30] 1-3-β-D-glucan, a component of the cell wall of many pathogenic fungi, can be employed as an important auxiliary diagnosis of candidemia. However, since it has an extensive expression on various fungi, it has a high sensitivity but a low specificity to diagnose the specific species of *Candida* in candidemia.[30] Therefore, blood culture to isolation then to identification is still a widely accepted and commonly used method for diagnosis of specific *Candida* species in candidemia. However, since cultures of *Candida* species take a long time, it is challenging to make a prompt diagnosis of the exact species. As different *Candida* species have different susceptibilities to antifungal drugs, reasonable prediction of *Candida* species and choosing proper antifungal therapeutics can be extremely important and prominently reduce the mortality of candidemia.[31] In this study, data from a retrospective clinical study were firstly used to investigate relationships between

TTPs and *Candida* species in patients with candidemia. It was found that different *Candida* species had different TTPs. *C. glabrata* had the longest TTPs, with a mean of 66.84 ± 30.87 h. While *C. tropicalis* had the shortest TTP, with a mean of 21.26 ± 3.20 h, which was consistent with the previous study.[32] In their report, TTPs of *C. glabrata* and *C. tropicalis* were 62.68 h and 22.14 h, respectively. However, another study,[33] in which TTPs were slightly different from ours, reported that TTPs of *C. glabrata* and *C. tropicalis* were 53.4 h (the longest) and 28.3 h (the second shortest), respectively, and *C. krusei* had the shortest TTP (23.3 h). The major reason for these differences might be due to a small sample size of *C. krusei* enrolled in both their and our studies (both were only four strains of *C. krusei* included).

TTPs might be affected by inoculation volume (volume of blood drawn into vials) and transportation time (from ward to microbiology laboratory) as well. To exclude these effects, another 314 confirmed *Candida* strains were performed for simulated blood cultures, TTPs were recorded and analyzed accordingly. TTPs of *C. glabrata, C. parapsilosis, C. krusei, C. sake, C. albicans*, and *C. tropicalis* were 32.57 ± 5.77h, 28.59 ± 6.13 h, 27.52 ± 5.62 h, 25.91 ± 3.47 h, 25.41 ± 5.66 h, and 18.32 ± 1.70 h, respectively. These TTPs were consistent with but significantly shorter compared to the results obtained from our retrospective study. We speculated many factors could contribute to these differences, such as concentrations of *Candida* spp. (colony-forming units) in patients' blood, inoculation volume of blood, transportation time (from ward to microbiological laboratory), and different vials (vials used for our retrospective study were Fastidious Antimicrobial Neutralization Media containing activated charcoal, and vials for simulated blood cultures were Fastidious Antimicrobial Neutralization Media PLUS with adsorbent of resin). All in all, TTP of *C. tropicalis* was the shortest in both clinical retrospective study and simulated blood cultures.

The major current debate on TTP in patients with candidemia are impactors like the natural growth rate among different *Candida* species and the number of pathogens in the blood.[32,34,35] The number of pathogens in the blood is closely associated with clinical features (eg, the source or the severity of infection).[36] To answer this important question, we systematically evaluated the relationships between TTPs and the concentration of initial inocula. Our results demonstrated that the concentration of initial inocula had no significant effect on TTPs. Therefore, we believed that TTPs were mainly associated with the natural growth rate in *Candida* species, but not number of pathogens in blood. In addition, we also analyzed the relationships between TTPs and resistance of *Candida* species. We found no significant correlations between TTPs and resistance of each *Candida* species.

Secondly, the ROC curve was used to determine the diagnostic value of TTP for *C. tropicalis* in both retrospective clinical data and simulated blood cultures. In the retrospective study, AUC was 0.8896 ± 0.030 with a 95% confidence interval of 0.831–0.949, which was higher than other reports for making a diagnosis of *C. glabrata* by TTPs,[19,27,28] suggesting that TTP is a powerful tool to identify *C. tropicalis* from other *Candida* species. When TTP < 25.50 h was used as a cut-off value, the sensitivity and specificity of TTP for diagnosing *C. tropicalis* were 92.86% and 77.87%, and the positive and negative predictive values were 34.15% and 98.96%, respectively. Both specificity and sensitivity were prominently higher than previous reports on diagnosing *C. glabrata* by TTPs.[27,28] Consistent with our retrospective clinical data, TTPs in simulated blood cultures had a high diagnostic value for *C. tropicalis*, the AUC was 0.933 ± 0.015 with a 95% confidence interval of 0.904–0.962, the optimal cut-off value was TTP < 19.99 h. Those data suggest that TTP has a higher diagnostic value for *C. tropicalis* compared with *C. glabrata*.

There are some limitations in this study as well. Firstly, TTPs might be affected by multiple factors, including blood inoculation volume, culture conditions, time intervals between sample inoculation to reception time in the lab, prior antifungal treatments, and pathogen numbers in patients' blood, etc. However, our simulated blood cultures confirmed that these factors had little effect on the diagnostic value of TTP for *C. tropicalis*. Secondly, durations of candidemia were not recorded before blood specimens were collected and cultured, which may also have an impact on TTPs. Finally, this study was a single-center research with limited clinical samples, the results generated in our study might be different from other clinical centers due to different brands of vials and testing machines. Thus, multi-center studies with a large number of samples are required to further validate our results in the future.

Conclusion

In conclusion, our study shows that TTP is an ideal diagnostic tool to facilitate early identification of *C. tropicalis* from other *Candida* species in patients with candidemia, which can aid clinicians in timely treating patients with empirical antifungal therapies before final identification of the specific *Candida* species.

Ethics Approval and Consent to Participate

Protocols of human tests (clinical samples) and microbiological research were approved by the Scientific Research Ethics Committee of the Institutional Review Board (IRB) of Clinical Medical College and the First Affiliated Hospital of Chengdu Medical College. We have confirmed that all methods were performed in accordance with the relevant guidelines and regulations. For the collection of clinical isolates, written informed consent was conducted in accordance with the Declaration of Helsinki, and sufficient time was provided for questions and answers before signing written informed consent.

Author Contributions

All authors made a significant contribution to the manuscript, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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