An association of SOFA scores with Candida tropicalis septic shock: A Retrospective Analysis in a Thai Referral Center

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Research Article

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Abstract

Background

Candida tropicalis is a leading cause of candidemia in Thailand, with septic shock significantly increasing mortality risk. Although biofilm formation has been associated with worse outcomes in candidemia, its role in predicting septic shock remains unclear. This study aimed to investigate the clinical factors and biofilm formation associated with the development of septic shock in *C. tropicalis* bloodstream infections.

Methods

This retrospective study analyzed the medical records of 198 patients diagnosed with *C. tropicalis* candidemia at Siriraj Hospital, Thailand, from 2015 to 2019. Patients were categorized into septic shock and non-septic shock groups. Biofilm formation was measured using the XTT reduction assay. Statistical analyses, including Chi-square or Fisher's exact tests, univariable and multivariable regressions, were conducted to identify predictors of septic shock.

Results

Septic shock occurred in 35.9% of patients. The most significant predictors of septic shock included mechanical ventilation (87.3% vs. 47.2%, $p < 0.001$), ICU admission (70.4% vs. 39.4%, $p < 0.001$), and higher SOFA scores. However, the biofilm formation was not the significant predictor. Multivariable analysis revealed that respiratory SOFA (OR 2.70, 95% CI 1.25–5.83) and cardiovascular SOFA (OR 4.33, 95% CI 2.44–7.69) scores were independent risk factors for septic shock development.

Conclusions

These findings highlight the importance of early identification and targeted management strategies to mitigate the risk of septic shock in patients with *C. tropicalis* bloodstream infections.

1 Background

Over a million people die from invasive candidiasis annually, and approximately 40% of these cases are caused by *Candida* bloodstream infections [1]. While *C. albicans* has traditionally been the leading cause of candidemia, the prevalence of non-albicans species, including *C. tropicalis*, has risen significantly in recent decades [2]. In the Asia-Pacific region, *C. tropicalis* is now the second most common cause of candidemia and has become the predominant species in Thailand and the Philippines [3–5].

Septic shock has been identified as a significant risk factor contributing to the high mortality rates observed in candidemia patients [6–8]. Limited research has focused on determining the specific characteristics of patients with *Candida* bloodstream infections at increased risk for septic shock [9–11]. Identifying these high-risk patients is crucial. Studies have suggested the establishment of strategies for the early detection of candidemia could improve clinical outcomes [10, 11]. This approach is especially critical in high-mortality regions like Thailand, where over two-thirds of patients die after a candidemia diagnosis [4].

Given the elevated mortality rate, it is imperative to assess tools such as the Sequential Organ Failure Assessment (SOFA) score. The SOFA score quantifies the extent of organ dysfunction by integrating clinical observations, laboratory parameters, and therapeutic interventions, offering a standardized approach to predict patient outcomes [12]. While previous studies have demonstrated that higher SOFA scores are associated with greater mortality risk, its utility for risk stratification in patients with candidemia remains unclear, largely due to insufficient research specifically targeting this population [7, 8, 13].

Biofilm formation has been recognized as a virulence factor and a predictor of mortality in *Candida* bloodstream infections [14–16]. Although direct evidence linking biofilm formation to the development of septic shock is lacking, this may be attributed to variability among patient populations, including differences in ethnicity, distribution of *Candida* species, and mortality rates [4, 10].

Despite its predominance in Thailand, clinical predictors specific to *Candida tropicalis* bloodstream infections have not yet been investigated. Therefore, we aimed to study the correlation between clinical characteristics, including SOFA scores, and biofilm formation associated with septic shock development in *C. tropicalis* bloodstream infection patients.

2 Methods

2.1 Study setting and design

The medical records of patients with *C. tropicalis* bloodstream infection were collected from January 2015 to December 2019 at Siriraj Hospital, a large referral center in Bangkok, Thailand. All *C. tropicalis* blood isolates were identified at the species level by MALDI-TOF MS using a Microflex LT mass spectrometer (Bruker Daltonics, Bremen, Germany), as previously described [17]. Medical records with patients younger than 18 years at the time of diagnosis, as well as those with unavailable data, were excluded. The study design was approved by the Siriraj Institutional Review Board (certificate of approval: Si 802/2019).

2.2 Definitions and data collection

An episode of *C. tropicalis* (CT-) candidemia was identified as the first hemoculture-positive *C. tropicalis* isolate in patients within the study period. Charlson's Comorbidity Index (CCI) was used to evaluate underlying diseases [18]. Predisposing factors involved in septic shock development at the onset of CT-candidemia were assessed, including a history of chemotherapy, antibiotics, or corticosteroids within 30 days, mechanical ventilation, neutropenia (absolute neutrophil count < 500 cells/mm^3), and the presence of central venous catheter. The source of bloodstream infections was collected according to the Infectious Diseases Society of America guidelines [19]. The total SOFA score was calculated by combining scores from the six organ systems: respiration, coagulation, liver, cardiovascular, central nervous system, and renal system [12, 20]. For any unavailable component of the SOFA score, a normal value was assumed and a score of 0 was assigned. [21].

After assessing the SOFA score, this study categorized the patients into septic and non-septic shock groups using The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [12]. Septic shock was defined as the dysregulated host response to the infection, characterized by an inability to maintain a mean arterial pressure greater than 65 mmHg, serum lactate level > 2 mmol/L, and the need for vasopressors [12].

2.3 Biofilm formation assay

An XTT [2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide] reduction assay was used to measure the biofilm formation of *C. tropicalis* isolates [22]. *C. tropicalis* isolates were cultured in yeast extract peptone dextrose (YPD) broth, shaking at 200 rpm, 30°C for 16-18 hours. Yeast cells were collected and washed with phosphate-buffered saline (pH 7.4). The cells were resuspended and adjusted to 0.5 McFarland standard in RPMI 1640 medium before being seeded with 200 µl in each flat-bottomed well of a 96 well-plate and incubated at 37°C for 48 hours. The medium was aspirated, and gently washed the wells three times with phosphate-buffered saline to remove planktonic cells. Then, the XTT reagent was added and incubated at 37°C for 3 hours in the dark.

The biofilm formation assay was performed in triplicates and measured by optical density (OD) at 490 nm. After the assay, the isolates were categorized based on their biofilm production into low, intermediate, and high biofilm producers [15, 23]. Isolates with biofilm formation below the 1st quartile (Q1) were classified as having low biofilm formation (LBF). Strains with metabolic activity above the 3rd quartile (Q3) were categorized as having high biofilm formation (HBF), while those falling between these two quartiles were designated as having intermediate biofilm formation (IBF, Q2) [15, 23].

2.4 Statistical analysis

The minimum sample size for a reliable prediction model was 137 isolates [24]. Categorical variables were presented as numbers and frequencies. Continuous variables were expressed as the mean and standard deviation (SD) or the median and interquartile range (IQR). Chi-square or Fisher's exact tests

were used to compare categorical variables. Continuous variables were analyzed using the Student's t-test and the Mann-Whitney U test. The association between septic shock and risk factors was assessed through univariable and multivariable regression analyses and reported as odds ratios (OR) and 95% confidence intervals (CIs). Variables with p <0.2 based on the categorical analysis were included in the univariable analysis. The backward stepwise approach was employed in the multivariable analysis to identify the best-fit model explaining the data. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 29.0; IBM Corp., Armonk, NY, USA).

3 Results

A total of 237 episodes of *C. tropicalis* bloodstream infection were reported during the study period. Thirty-nine episodes were excluded: 21 due to patients being under 18 years of age at the time of diagnosis and 18 due to lack of significant clinical data. Therefore, our study included 198 isolates for further analyses and septic shock was identified in 71 patients (35.9%). The selection process is detailed in Figure 1. Of these, the biofilm formation assay was retrospectively performed on 146 episodes.

3.1 Clinical characteristics of the study population

Comparisons of baseline clinical characteristics are shown in Table 1. The median age was 64 years, and 96 episodes occurred in male patients (48.5%). CT-candidemia developed in the intensive care unit (ICU) in 100 episodes (50.5%), and the median length of stay before CT-candidemia detection was 16.5 days. ICU admission rates were higher among septic shock patients (70.4% vs. 39.4%; p <0.001). The most common comorbidities were diabetes mellitus (27.8%), followed by lymphoma (21.2%) and solid tumor (16.7%). Leukemia occurred less frequently among septic shock patients (1.4% vs. 15.0%; p =0.002). The median Charlson comorbidity index score was 5 and was similar for both groups.

Both groups had similar histories of antimicrobial use, antifungal use, and chemotherapy use, as well as parenteral nutrition, surgery, and transplantation. The source of *C. tropicalis* bloodstream infection remained unknown in 57.1% of cases, followed by catheter-related bloodstream infection (CRBSI) at 40.4%. CRBSI was more frequent in the septic shock group (57.7% vs. 30.7%; p <0.001).

The septic shock group demonstrated worse clinical status compared to the non-septic shock group, including higher rates of mechanical ventilation (87.3% vs. 47.2%; p <0.001), central venous catheter use (69.0% vs. 50.4%; p =0.011), lower respiratory tract colonization (23.9% vs. 11.0%; p =0.016), and a higher mean SOFA score (13.7 vs. 6.5; p <0.001) (Table 2). Neutropenia was less frequently observed in the septic shock group (14.1% vs. 27.6%; p =0.030).

3.2 Factors associated with septic shock development

A multivariable analysis (Table 3) revealed that independent risk factors associated with septic shock development were the respiratory SOFA score (OR, 2.70; 95% CI, 1.25–5.83; p =0.011) and the cardiovascular SOFA score (OR, 4.33; 95% CI, 2.44–7.69; p <0.001).

4 Discussion

In our study, 35.9% of patients with *Candida tropicalis* bloodstream infections presented with septic shock. The respiratory SOFA and cardiovascular SOFA scores were identified as independent risk factors associated with septic shock development. Consistent with prior findings, the incidence of septic shock using the Sepsis-3 definition aligned with previous reports, which ranged from 21.9 to 39.2% [7, 10, 25, 26]. The ICU admission rate was 2-2.5 times higher than that reported in previous studies [10, 11]. This suggests that the patients in this cohort exhibited more critical and vulnerable conditions compared to previous studies [10, 11]. These differences were particularly evident in ICU admissions and CCI scores, which underscores the greater severity of their illness. Hematologic malignancies (leukemia and lymphoma) were present in almost one-third of this cohort, consistent with Fernández-Ruiz's study on CT-candidemia, while only 6.3% was observed in Bassetti's study [10, 27]. This contrast highlights differing patient populations and their varying risk of developing septic shock. Moreover, septic shock was significantly less frequent in leukemia and neutropenic patients. According to the previous study, no septic shock occurred in acute leukemia patients with candidemia [28]. The presence of hematologic malignancies may have reduced the incidence of septic shock while contributing to the overall severity of illness in these patients.

Although predisposing factors were not considerably different between the two groups, the clinical conditions at the onset of CT-candidemia were more severe in the septic shock group. This included higher rates of mechanical ventilation use (87.3% vs 47.2%), central venous catheter (CVC) placement (69.0% vs 50.4%), and a higher mean SOFA score (13.7 vs 6.5). These findings highlight the direct need for ICU admission, a risk factor that was similarly reported in Bassetti's study [10]. Furthermore, the SOFA score has proven its ability to predict mortality and organ failure, especially in critically ill patients, as was seen in our study [13]. The cardiovascular score, which included the need for vasopressors to maintain blood pressure, directly contributed to diagnosing septic shock [12]. The respiratory SOFA required the assessment of respiratory support, including mechanical ventilation [12]. Therefore, the cardiovascular and respiratory SOFA scores had a significant role in sepsis assessment and were identified as independent risk factors for septic shock development.

Similar to the previous CT-candidemia study, the most commonly identified source of *C. tropicalis* bloodstream infection was CRBSI, followed by abdominal infection (1.5%) [27]. Although HBF strains have been reported as a predictor of candidemia mortality, no significant difference in HBF strains was observed in our study [14–16]. *C. tropicalis* is well known for its ability to produce more biofilms than other *Candida* species [29]. Despite this association, the role of biofilm formation in the pathogenesis of septic shock remains unclear. A study using a human whole-blood infection model revealed that each *Candida* species exhibited independent strategies in response to the host environment, including

adhesion ability, which was not upregulated in *C. tropicalis* [30]. Therefore, host factors might play a more significant role in septic shock development than the organism's virulence factors. Given the prominence of septic shock and the difficulty in early detection, strategies like T2MR technology may provide valuable diagnostic benefits in high-risk patients [10, 31].

The strength of this study lies in its comprehensive evaluation of predisposing factors, the severity of patients, SOFA score components, and biofilm formation as a virulence factor. Nevertheless, this retrospective study has limitations, such as the inability to retrieve significant data for some patients, which could lead to observational bias. Furthermore, the SOFA score calculation may have been underestimated due to the lack of routine monitoring of the Glasgow Coma Scale (GCS) score and limited investigations, particularly arterial blood gas measurements to assess PaO_2.

5 Conclusion

The respiratory and cardiovascular SOFA scores were valuable tools for predicting septic shock development in *C. tropicalis* bloodstream infection patients. Early diagnostic strategies are needed for high-risk candidemia patients to prevent and promptly detect candidemia-induced septic shock.

Abbreviations

CCI
Charlson’s comorbidity index
CI
Confidence intervals
CRBSI
Catheter-related bloodstream infection
CT
Candida tropicalis
GCS
Glasgow coma scale
HBF
High biofilm formation
IBF
Intermediate biofilm formation
IQR
median and interquartile range
LBF
Low biofilm formation
OD
Optical density
OR

Odds ratios
SD
Standard deviation
SOFA
Sequential organ failure assessment
YPD
Yeast extract peptone dextrose

Declarations

Ethics approval and consent to participate

The study design was approved by the Siriraj Institutional Review Board (certificate of approval: Si 802/2019).

Clinical Trial

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analyzed during the current study were not publicly available due to the Thailand Personal Data Protection Act but were available from the corresponding author upon reasonable request.

Competing interests

The authors declared that they have no competing interests.

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Authors' contributions

Conceptualization, TL, and PN; methodology, TL, and OT; validation, TL, and OT; formal analysis, TL; investigation, TL, OT and AM; resources, TL and OT; data curation, TL; writing—original draft preparation,

TL, and OT; writing—review and editing, PN.; visualization, OT; supervision, PN; project administration, OT; funding acquisition, TL.

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Tables

Table 1. Comparison of the clinical characteristics and biofilm formation of *Candida tropicalis* candidemia patients

Variables	All episodes *N* = 198, *n* (%)	Septic shock *n* = 71, *n* (%)	Non-septic shock *n* = 127, *n* (%)	*p*-value
Demographics				
Age, year ± SD	63.0±18.5	66.5±18.3	61.1±18.4	0.050
Male, sex	96 (48.5)	37 (52.1)	59 (46.5)	0.445
Intensive care unit admission	100 (50.5)	50 (70.4)	50 (39.4)	<0.001
The median length of stay before the onset of candidemia, (IQR)	16.5 (9-29)	14 (8-25)	17 (9.5-30.5)	0.672
Comorbidities				
Ischemic heart disease	27 (13.6)	14 (19.7)	13 (10.2)	0.062
Chronic liver disease	28 (14.1)	12 (16.9)	16 (12.6)	0.405
Diabetes mellitus	55 (27.8)	18 (25.4)	37 (29.1)	0.569
Chronic kidney disease	26 (13.1)	11 (15.5)	15 (11.8)	0.462
Solid tumor	33 (16.7)	13 (18.3)	20 (15.7)	0.643
Leukemia	20 (10.1)	1 (1.4)	19 (15.0)	0.002
Lymphoma	42 (21.2)	14 (19.7)	28 (22.0)	0.701
CCI, mean ± SD	4.9±2.6	5.0±2.4	4.8±2.7	0.985
Predisposing factors[a]				
Chemotherapy administration	49 (24.7)	13 (18.3)	36 (28.3)	0.117
Corticosteroid administration	50 (25.3)	16 (22.5)	34 (26.8)	0.551
Parenteral nutrition	92 (46.5)	34 (47.9)	58 (45.7)	0.764
Transplantation	6 (3.0)	1 (1.4)	5 (3.9)	0.423
Antibacterial administration	195 (98.5)	71 (100.0)	124 (97.6)	0.554
Antifungal administration	45 (22.7)	13 (18.3)	32 (25.2)	0.267
Clinical features at onset of candidemia				
Neutropenia	45 (22.7)	10 (14.1)	35 (27.6)	0.030
Mechanical ventilation use	122 (61.6)	62 (87.3)	60 (47.2)	<0.001
CVC in place	113 (57.1)	49 (69.0)	64 (50.4)	0.011

Lower respiratory tract colonization	31 (15.7)	17 (23.9)	14 (11.0)	0.016
Polymicrobial bacteremia/fungemia	32 (16.2)	16 (22.5)	16 (12.6)	0.068
Source				
Primary (Unknown)	113 (57.1)	28 (39.4)	85 (66.9)	<0.001
CRBSI	80 (40.4)	41 (57.7)	39 (30.7)	<0.001
Abdomen	3 (1.5)	1 (1.4)	2 (1.6)	1.000
Virulence factor[b]				
High biofilm formation	37/146 (25.3)	18/54 (33.3)	19/92 (20.7)	0.095

[a]within the previous 30 days, [b]retrospective performed in 146 episodes, Abbreviations: CCI, Charlson Comorbidity Index; SOFA score, Sequential Organ Failure Assessment score; CVC, central venous catheter; CRBSI, Catheter-related bloodstream infection.

Table 2. The SOFA score for six organ systems in *Candida tropicalis* candidemia patients

Variables	All episodes *N* = 198, *n* (%)	Septic shock *n* = 71, *n* (%)	Non-septic shock *n* = 121, *n* (%)	*p*-value
Respiration SOFA score	1.5±1.7	2.3±1.2	1.0±1.1	<0.001
Coagulation SOFA score	2.1±1.4	2.4±1.3	2.0±1.5	0.067
Liver SOFA score	1.1±1.4	1.7±1.5	0.8±1.3	<0.001
Cardiovascular SOFA score	1.5±1.4	3.2±0.6	0.6±1.3	<0.001
Central nervous system SOFA score	0.8±1.4	1.2±1.6	0.6±1.1	0.005
Renal SOFA score	2.0±1.7	3.0±1.3	1.5±1.6	<0.001
Total SOFA score	9.1±5.3	13.7±3.9	6.5±4.1	<0.001

Table 3. Factors associated with septic shock development using univariable and multivariable analyses

Factors	Univariable analysis			Multivariable analysis		
	Crude OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Age	1.02	1.00-1.03	0.052			
Intensive care unit admission	3.67	1.97-6.83	<0.001			
Ischemic heart disease	2.15	0.95-4.89	0.066	2.92	0.60-14.28	0.187
Leukemia	0.08	0.01-0.62	0.005	0.11	0.01-1.55	0.101
Chemotherapy administration	0.57	0.28-1.16	0.119			
Neutropenia	0.43	0.20-0.93	0.013			
Mechanical ventilation use	7.69	3.52-16.80	<0.001	7.66	0.78-75.15	0.081
CVC in place	2.19	1.19-4.04	0.012	2.37	0.51-10.89	0.269
Lower respiratory tract colonization	2.54	1.17-5.53	0.019			
Polymicrobial bacteremia/fungemia	2.02	0.94-4.34	0.072			
Primary source (Unknown)	0.32	0.18-0.59	<0.001			
CRBSI	3.08	1.69-5.63	<0.001			
Respiratory SOFA score	2.32	1.76-3.07	<0.001	2.70	1.25-5.83	0.011
Coagulation SOFA score	1.22	0.99-1.50	0.068			
Liver SOFA score	1.51	1.22-1.86	<0.001			
Cardiovascular SOFA score	4.31	2.92-6.37	<0.001	4.33	2.44-7.69	<0.001
Central nervous system SOFA score	1.39	1.13-1.72	0.002			
Renal SOFA score	1.83	1.49-2.25	<0.001	1.275	0.85-1.93	0.247

Biofilm formation	1.71	1.05-2.78	0.032	1.42	0.57-3.54	0.448

Abbreviations: OR, odds ratio; SOFA score, Sequential Organ Failure Assessment; CVC, central venous catheter; CRBSI, Catheter-related bloodstream infection.

Figures

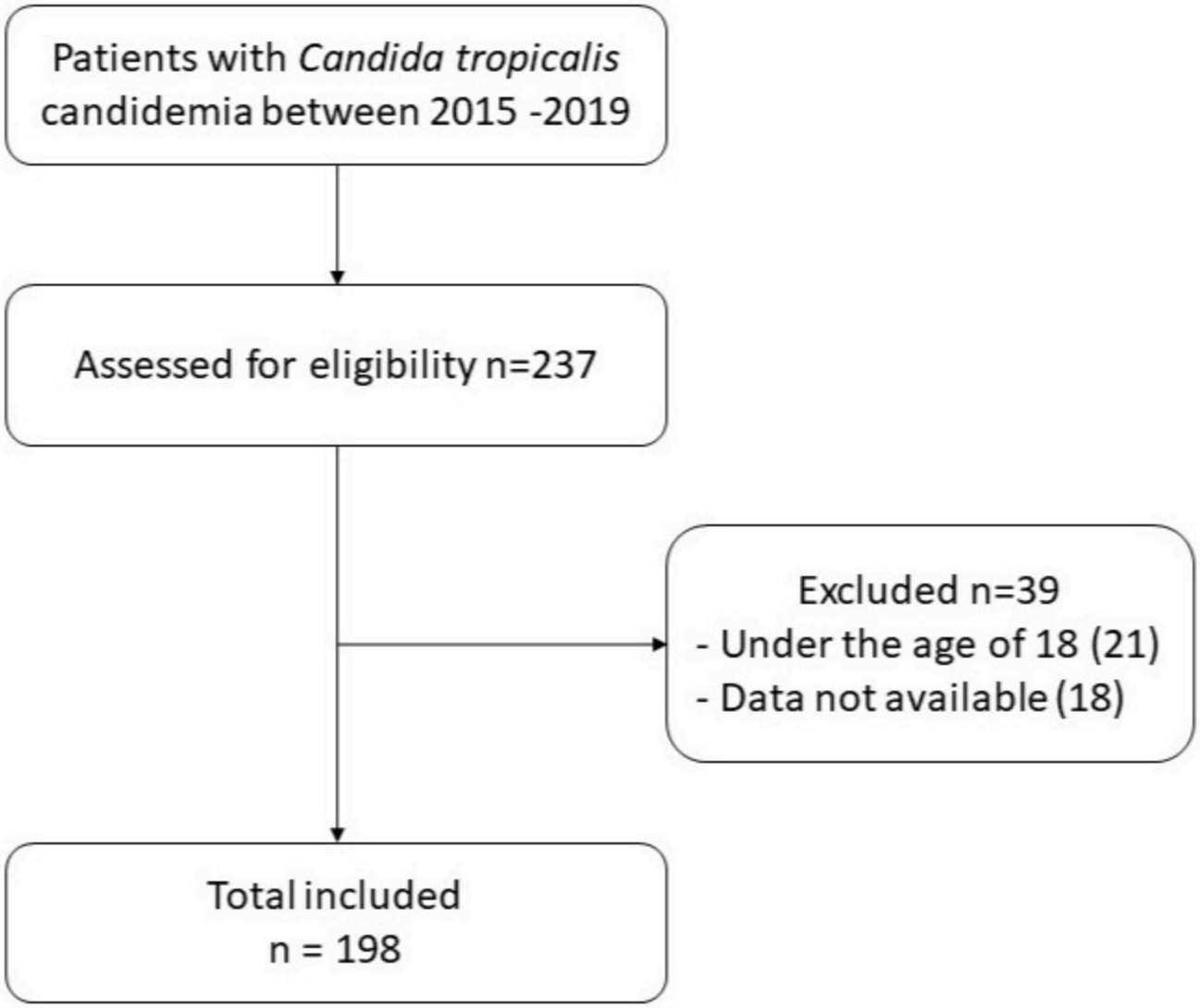

Figure 1

Flowchart of patients included in the study