

Risk Factors Predicting Candida Infective Endocarditis in Patients with Candidemia

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REVISED ABSTRACT

Background: Candida infective endocarditis (CIE) is a rare but serious complication of *Candida* bloodstream infection (BSI). The risk factors contributing to the development of CIE is poorly defined from small cohorts. Identifying clinical predictors associated with this clinical entity may be associated with more judicious use of cardiac imaging.

Methods: We conducted a retrospective analysis of all hospitalized patients aged ≥18 years old diagnosed with *Candida* BSI at our institution. Data included demographics, comorbidities, vital signs, laboratory parameters, and microbiology data. Univariable and multivariable regression analyses were used to identify risk factors associated with CIE.

Results: Of 1,873 patients with *Candida* BSI, 47 (2.5%) were identified to have CIE. In multivariate logistic model, valvular disease was associated with a higher risk for CIE (odds ratios [OR], 7.7; 95% confidence interval [CI], 2.9-19.8). Conversely, isolation of *C. glabrata* (OR, 0.17; 95% CI, 0.040-0.69), hematological malignancy (OR, 0.09; 95% CI, 0.013-0.68), and use of total parenteral nutrition (TPN) (OR, 0.38; 95% CI, 0.16-0.91) were less likely to be associated with CIE. The final model had a c-statistic of 0.732 (95% CI, 0.678-0.786), suggested good discrimination. The crude 90-day mortality for CIE was 48.9%, similar to the overall non-CIE mortality of 41.9% ($p=0.338$).

Conclusions: In a population of patients with *Candida* BSI, valvular disease was the only factor associated with a greater risk of development of CIE. Patients with TPN use, hematological malignancy, and isolation of *C. glabrata* were less likely to develop CIE. These findings may reduce the need for expensive and invasive imaging study as a subset of patients may be at low enough risk for CIE not to warrant further testing.

BACKGROUND

- The incidence of *Candida* bloodstream infection (BSI) is increasing over the past few decades and has now emerged as a leading nosocomial BSI.¹
- Candida infective endocarditis (CIE) is a rare and serious complication of *Candida* BSI.
- Predisposing factors such as prosthetic valve, intravascular catheter, prior antimicrobial therapy, and an identifiable portal entry for nosocomial *Candida* BSI were established as potential risk factors for CIE.
- However, current literature is limited by small cohorts and confined to nosocomial *Candida* BSI as well as prosthetic valve endocarditis.²⁻³
- Given the complexity and rarity of CIE, our study aimed to create a risk predictive model for CIE in patients with *Candida* BSI.

METHODS

Collection:

- Data obtained from Barnes Jewish Hospital, a 1,315-bed tertiary care academic hospital.
- All hospitalized adults aged ≥18 years with an isolation of ≥ 1 *Candida spp.* from ≥ 1 blood culture were included.
- The Elixhauser comorbidity index was used to control for underlying health conditions.⁴
- Dates of death were extracted from the hospital consortium's Medical Informatics database and supplemented if necessarily with the information from the Social Security Death Index.
- Those without a date of death were censored at the date of the last outpatients visit or inpatient discharge.

Statistical Analysis:

- Statistical analysis was performed using SAS v9.4 Software (SAS Institute Inc. Cary, NC).
- For descriptive statistics, Chi-square or Fisher exact and Mann-Whitney U test tests were used for categorical and continuous data respectively, as appropriate for non-normally distributed variables.
- Univariate logistic regression was performed to evaluate the potential risk factors, comorbidities, medication use, and laboratory values. Risk factors with a $p < 0.2$ in univariable analysis were included in multivariable model.
- Multivariable logistic regression model was constructed in a parsimonious manner with the use of previous literature.
- We used the c-statistic to assess discrimination.
- All statistical tests were 2-tailed and significance was set at $p \leq 0.05$.

DEFINITIONS

- Route of acquisition of *Candida* BSI was categorized into:
 - Community-acquired if positive blood culture within 48 hours of hospitalization.
 - Nosocomial if positive blood culture in ≥ 48 hours of hospitalization.
- Persistent candidemia was defined as continued blood culture positivity for ≥ 72 hours while on appropriate antifungal treatment.
- All CIE cases were diagnosed by fulfilling 2 major criteria of modified Duke criteria 1994.⁵

RESULTS

Table 1: Baseline Characteristics

	CIE (n= 47)	Non-CIE (n=1,826)	p value ^a
Age, median (IQR)	56 (24)	59 (24)	0.820
Male	26 (55.3)	953 (52.2)	0.672
Comorbidities			
Diabetes mellitus, n (%)	6 (12.8)	433 (23.7)	0.080
Chronic kidney disease, n (%)	8 (17.0)	297 (16.3)	0.890
Chronic liver disease, n (%)	3 (6.4)	124 (6.8)	1
Chronic heart failure, n (%)	22 (46.8)	763 (41.8)	0.491
Hematological malignancy, n (%)	1 (2.1)	345 (18.9)	0.004
Solid organ tumors, n (%)	9 (19.1)	640 (35.0)	0.024
Other potential predisposing factors			
Structural heart disease, n (%)	17 (36.2)	394 (21.6)	0.017
TPN	6 (12.8)	489 (26.8)	0.032
Presence of CVC	17 (36.2)	482 (26.4)	0.135
Removal of CVC ≤72 hours, n (%)	14 (77.8)	471 (77.0)	0.935
Neutropenia, n (%)	0 (0)	137 (7.5)	0.045
Bone marrow transplant, n(%)	0 (0)	36 (2.0)	1
Cancer chemotherapy, n (%)	0 (0)	111 (6.1)	0.110
Exposure to corticosteroid within 90 days prior to Candida BSI, n (%)	6 (12.8)	523 (28.6)	0.002
Any in-patient GI procedure, n (%)	4 (8.5)	168 (9.2)	1
Laboratory values			
Absolute neutrophil counts, median (IQR)	6.3 (6.2)	5.7 (6.3)	0.261
Platelet, median (IQR)	157 (129)	143 (180)	0.063
Candida isolated			0.013
<i>C. albicans</i> , n (%)	28 (59.6)	889 (48.7)	
<i>C. glabrata</i> , n (%)	2 (4.2)	388 (21.3)	
<i>C. parapsilosis</i> , n (%)	7 (14.9)	297 (16.3)	
<i>C. tropicalis</i> , n (%)	6 (12.8)	133 (7.3)	
<i>C. krusei</i> , n (%)	0 (0)	59 (3.2)	
Others, n (%)	4 (8.5)	60 (3.3)	
Duration of candidemia, median (IQR)	3 (3.5)	3 (2)	0.052
Persistent candidemia (>72 hours), n (%)	27 (57.4)	711 (38.9)	0.010
Onset of candidemia			0.032
Community onset, n (%)	27 (57.4)	763 (41.8)	
Nosocomial, n (%)	20 (42.6)	1063 (58.2)	

Abbreviations: CIE, candida infective endocarditis; IQR, interquartile range; TPN, total parenteral nutrition; CVC, central venous catheter.
^ap values for continuous variable were calculated using Mann-Whitney U statistic tests, while p values for categorical variable were obtained using either Chi-square or Fisher exact tests.

Table 2: Selected Univariate Risk Factors for CIE

	Coefficient	Odds ratio (95% CI)	p value
Demographics			
Sex (reference= male)	-0.1259	0.88 (0.493, 1.578)	0.672
Race (reference= non-African american)	-0.0514	0.90 (0.479, 1.699)	0.750
Age	-0.0022	1.000 (0.981, 1.015)	0.797
BMI	-0.0395	0.961 (0.916, 1.008)	0.104
Selected Elixhauser comorbidities			
Valvular disease	1.0368	7.95 (3.159, 20.020)	<.0001
CHF	0.5065	2.75 (0.683, 11.896)	0.175
Chronic pulmonary disease	0.0293	1.06 (0.491, 2.292)	0.882
Renal failure	-0.0270	0.95 (0.439, 2.046)	0.891
Liver disease	0.0954	1.21 (0.507, 2.887)	0.667
Drug abuse	n/a ^a		
Obesity	-0.2269	0.64 (0.195, 2.067)	0.451
Selected potential predisposing factors			
Hematological malignancy	-1.1858	0.09 (0.013-0.679)	0.019
Solid organ tumors	-0.4117	0.44 (0.211-0.913)	0.028
TPN within 30 days prior to candidemia	-0.9158	0.40 (0.169, 0.948)	0.038
Presence of CVC	0.0350	1.07 (0.600, 1.916)	0.813
Removal of CVC (reference = <72 hours)	-0.0205	0.96 (0.311, 2.962)	0.943
Neutropenia	n/a ^a		
Bone marrow transplant	n/a ^a		
Cancer chemotherapy	n/a ^a		
Corticosteroid within 90 days prior to candidemia	-0.5043	0.37 (0.154- 0.864)	0.022
Any in-patient GI procedure	-0.0427	0.92 (0.326, 2.589)	0.872
Preceding bacterial infection	0.1132	1.25 (0.536, 2.936)	0.602
Candida isolated			
<i>C. albicans</i>	0.2202	1.55 (0.861, 2.801)	0.143
<i>C. glabrata</i>	-1.8032	0.17 (0.040, 0.682)	0.013
<i>C. parapsilosis</i>	-0.0522	0.90 (0.400, 2.030)	0.801
<i>C. tropicalis</i>	0.3111	1.86 (0.777, 4.468)	0.163
<i>C. krusei</i>	n/a ^a		
Duration of candidemia	0.0544	1.06 (0.988, 1.128)	0.106
Dichomatized duration of candidemia (Reference= No persistence candidemia or <72 hours)	0.1891	1.46 (0.797, 2.675)	0.221
Onset of candidemia (reference= nosocomial-acquired)	0.3158	1.88 (1.047, 3.378)	0.035
Vital Signs^b			
Temperature	-0.3868	0.68 (0.510, 0.904)	0.008
Heart rate	-0.0078	0.99 (0.979, 1.006)	0.259
Respiratory rate	-0.0509	0.95 (0.885, 1.021)	0.164
Laboratory Values			
Absolute neutrophil count	-0.0072	0.99 (0.962, 1.025)	0.655
Platelets	0.0013	1.00 (0.999, 1.003)	0.170
Creatinine	-0.0039	1.00 (0.820, 1.211)	0.969

Abbreviations: CIE, candida infective endocarditis; CI, confidence interval; BMI, body mass index; CHF, congestive heart failure; TPN, total parenteral nutrition; CVC, central venous catheter.
^aPatients with neutropenia, bone marrow transplant, and cancer chemotherapy, none had CIE.
^bThe most extreme vital signs (temperature, heart rate, respiratory rate) measured within 24 hours of preceding *Candida* bloodstream infection.

Table 3: Multivariate Logistic Regression of Significant Risk Factors for CIE

	Odd ratio (95% CI)	p value
Valvular disease ^a	7.7 (2.9-19.8)	<.0001
<i>C. glabrata</i>	0.17 (0.040-0.69)	0.013
Hematological malignancy	0.09 (0.013-0.68)	0.019
TPN	0.38 (0.16-0.91)	0.030

Abbreviations: CIE, candida infective endocarditis; BSI, bloodstream infection; CI, confidence interval; TPN, total parenteral nutrition.
^aValvular disease included ICD-9 codes for structural valve disorders, infective endocarditis, and history of heart valve replacement as described in Elixhauser comorbidity index.⁴

RESULTS

Cohort

- 1,873 hospitalized patients diagnosed with *Candida* BSI were eligible.
- Forty-seven patients (2.5%) had CIE.
- Echocardiography
 - Both TTE and TEE in 28 (59.6%)
 - TTE alone in 10 (21.3%)
 - TEE alone in 9 (19.1%)

Multivariate Logistic Regression Model

- The C-statistic was 0.732 (95% CI, 0.678-0.786).
- Hosmer and Lemeshow Goodness-of-Fit Test was 0.7426.

Mortality

- The 90-day crude mortality for CIE was 48.9%, similar to the non-CIE mortality of 41.9 ($p=0.338$).

CONCLUSIONS

- Our study provides important clarity on the risk factors for CIE among patient with *Candida* BSI.
- Valvular disease was the only factor associated with a greater risk of development of CIE.
- Patients with TPN use, hematological malignancy, and isolation of *C. glabrata* were less likely to develop CIE.
- Our findings may reduce the need for expensive and sometimes invasive diagnostic cardiac imaging such as TEE, as a subset of patents may have low enough risk for CIE not to warrant them. Prospective validation is required to determine if this model can be accurately used to predict CIE.

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