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Risk factors predicting *Candida* infective endocarditis in patients with candidemia

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Abstract

Candida infective endocarditis (CIE) is a rare but serious complication of candidemia. Incidence and risk factors associated with CIE among candidemic patients are poorly defined from small cohorts. Identification of clinical predictors associated with this entity may guide more judicious use of cardiac imaging. We conducted a retrospective analysis of all inpatients aged ≥18 years diagnosed with candidemia at our institution. CIE was diagnosed by fulfilling two of the major Duke criteria: specifically a vegetation(s) on echocardiogram and positive blood cultures for *Candida* spp. We used univariable and multivariable regression analyses to identify risk factors associated with CIE. Of 1,873 patients with candidemia, 47 (2.5%) were identified to have CIE. In our multivariable logistic model, existing valvular heart disease was associated with a higher risk for CIE (adjusted odds ratio [aOR], 7.66; 95% confidence interval [CI], 2.95–19.84). Predictors that demonstrated a decreased risk of CIE included infection with *C. glabrata* (aOR, 0.17; 95% CI, 0.04–0.69), hematologic malignancy (aOR, 0.09; 95% CI, 0.01–0.68), and receipt of total parenteral nutrition (aOR, 0.38; 95% CI, 0.16–0.91). The 90-day crude mortality for CIE was 48.9%, similar to the overall non-CIE mortality of 41.9% ($P = .338$). We identified a set of clinical factors that can predict the presence of CIE among patient with candidemia. These findings may reduce the need for unnecessary expensive and invasive imaging studies in a subset of patients with a lower risk profile for endocarditis and alternative infection source.

Key words: *Candida* infective endocarditis, *Candida* bloodstream infection, candidemia.

Introduction

The incidence of *Candida* bloodstream infection (BSI) has increased over the past few decades and has now emerged as the leading nosocomial BSI in intensive care unit settings with an associated higher mortality, longer hospital stays, and increased hospital costs compared to bacterial BSI.[1–9]

Candida infective endocarditis (CIE) is a rare but serious complication of candidemia.[3,10–12] Prosthetic valves and an unidentifiable portal of entry for nosocomial candidemia have been implicated as potential risk factors for CIE development in the setting of candidemia.[11,12] However, these studies were small and limited to patients with nosocomial candidemia and prosthetic valve endocarditis.[11,12] The risk factors contributing to the development of CIE among candidemic patients have not been fully explored.

Early diagnosis and treatment of CIE are important to improve patient outcomes, due to the need for specialized management, including multidisciplinary care with antifungal

therapy and surgical evaluation.[2,13,14] The necessity of diagnostic echocardiography in patients with candidemia remains unclear and there is a lack of consensus among different professional organizations.[2,15] Infectious Diseases Society of America (IDSA) consensus guidelines recommend echocardiography in high-risk candidemic patients such as persistent candidemia despite an appropriate antifungal treatment.[2] In contrast, European guidelines recommend echocardiography in all patients with candidemia irrespective of CIE risk profile.[15] The level of evidence for this recommendation is low, indicating a need for more rigorous evaluation of these existing recommendations.

To address this clinical question, we performed a retrospective cohort analysis aimed at identifying risk factors that could predict the presence of CIE in the setting of candidemia. Understanding this can help risk stratify patients with CIE and decrease the unnecessary use of echocardiography.

Methods

Setting

We conducted a retrospective cohort analysis at Barnes-Jewish Hospital, a 1315-bed tertiary care hospital in St. Louis, Missouri, USA, from January 2002 to January 2015. This study was approved by the Human Research Protection Office at Washington University in St. Louis with a waiver of consent.

Cohort construction

All hospitalized adults aged 18 years and older with an isolation of *Candida* spp. from at least one blood culture were included in this study. The first blood culture positive for *Candida* spp. during the study timeframe was defined as the index blood culture. Patients were excluded if there was a previous episode of *Candida* BSI within 90 days of the index blood culture in order to limit the analysis to first occurrence. The data were extracted electronically from Barnes-Jewish Hospital Medical Informatics and chart review by the authors as previously described.[16]

Data collected included demographics, species of *Candida* isolated, duration of candidemia, the extremes of vital signs (highest temperature, respiratory rate, and heart rate), and laboratory parameters (absolute neutrophil count, platelets, and creatinine). Predisposing factors for CIE were explored and selected carefully (Table 1; Supplementary Table 1) based on available literature.[3,5,10–12] We defined the extremes of vital signs as highest temperature (°C), respiratory rate (breaths per minute), and heart rate (beats per minute) 48 hours prior to or 24 hours after a positive blood culture was collected. We defined neutropenia as an absolute neutrophil count less than 1500 cells/mm^3. Comorbidities from hospitalization within the study timeframe and those documented within 365 days prior to the index admission were determined using International Classification of Diseases 9th Revision, Clinical Modification (ICD-9 CM) diagnosis codes and Elixhauser comorbidity index.[17] ICD-9 CM codes for valvular heart disease were excluded to avoid misclassification bias. Other variables specific to risk factors associated with candidemia were computed, as previously published.[16,18]

Cases were classified into community- or nosocomial-acquired based on isolation of *Candida* spp. from blood cultures at < 48 hours and ≥ 48 hours after hospitalization, respectively.[19] Persistent candidemia was defined as the presence of positive blood cultures for *Candida* spp. for ≥ 3 days while on antifungal therapy. All CIE was diagnosed by fulfilling two major criteria of the modified Duke criteria 1994.[20]

Outcomes

We used the presence of CIE as the primary outcome in both univariable and multivariable analyses. We assessed 90-day all-cause mortality, as mortality beyond 90 days was considered less likely to be related to candidemia and attributable mortality is difficult to assess retrospectively. Dates of death were extracted from the hospital consortium's Medical Informatics database and supplemented, if necessary, with information from the Social Security Death Index (SSDI). Patients without a confirmed death were censored at the date of last follow-up.

Statistical analysis

Statistical analysis was performed using SAS v9.4 Software (SAS Institute Inc. Cary, NC, USA). For descriptive statistics, we used χ^2 or Fisher exact tests for categorical variables and Mann-Whitney *U* test for continuous variables, as appropriate for non-normally distributed variables.

We performed univariable logistic regression to evaluate the association of the predisposing factors, Elixhauser comorbidity index, extreme vital signs, and laboratory values with the presence of CIE. Collinearity between factors were assessed using bivariate correlation with a threshold of 0.8 and with careful inspection of the coefficients through different iterations of the model. However, we were unable to assess interactions due to the lack of power. Variables with $P < .20$ were considered for the multivariable models. Multivariable models were subsequently constructed from significant univariable comparisons in a parsimonious manner, with careful selection of candidate variables. Independent variables were added sequentially and were retained in the final model if they were found to be significant ($P < .05$). Those variables that were no longer found to be significant were sequentially removed from the model. We generated a *c*-statistic and receiver operating characteristic (ROC) curve using a final set of predictor variable. A Hosmer-Lemeshow

Table 1. Comparison of characteristics, comorbidities, and risk factors between patients with *Candida* infective endocarditis and those without *Candida* infective endocarditis.

Variable	CIE ($n = 47$)	Non-CIE ($n = 1826$)	*P* value[a]	Total ($n = 1873$)
Age in years, median (IQR)	56 (44–68)	59 (46–70)	.820	59 (46–70)
Sex	…	…	.672	…
Male, *n* (%)	26 (55.3)	953 (52.2)	…	979 (52.3)
Female, *n* (%)	21 (44.7)	873 (47.8)	…	894 (47.7)
Comorbidities	…	…	…	…
Diabetes mellitus, *n* (%)	6 (12.8)	433 (23.7)	.080	439 (23.4)
Chronic kidney disease, *n* (%)	8 (17.0)	297 (16.3)	.890	305 (16.3)
Chronic liver disease, *n* (%)	3 (6.4)	124 (6.8)	1	127 (6.8)
Chronic heart failure, *n* (%)	22 (46.8)	763 (41.8)	.491	785 (41.9)
Malignancy				
Hematologic malignancy[b], *n* (%)	1 (2.1)	345 (18.9)	.004	346 (18.5)
Solid organ malignancy, *n* (%)	9 (19.1)	640 (35.0)	.024	649 (34.7)
Other potential predisposing factors				
Valvular heart disease, *n* (%)	17 (36.2)	394 (21.6)	.017	411 (21.9)
TPN, *n* (%)	6 (12.8)	489 (26.8)	.031	495 (26.4)
Presence of CVC, *n* (%)	17 (36.2)	482 (26.4)	.135	499 (26.6)
Removal of CVC	…	…	.935	…
≤72 hours, *n* (%)	14 (29.8)	471 (25.8)	…	485 (25.9)
>72 hours, *n* (%)	4 (8.5)	141 (7.7)	…	145 (7.7)
Neutropenia[c], *n* (%)	0 (0)	137 (7.5)	.045	137 (7.3)
Bone marrow transplant, *n* (%)	0 (0)	36 (2.0)	1	36 (1.9)
Cancer chemotherapy, *n* (%)	0 (0)	111 (6.1)	.110	111 (5.9)
Exposure to corticosteroid within 90 days prior to candidemia, *n* (%)	6 (12.8)	523 (28.6)	.002	529 (28.2)
Any inpatient GI procedure, *n* (%)	4 (8.5)	168 (9.2)	1	172 (9.2)
Laboratory values	…	…	…	…
Absolute neutrophil count, as cells/mm^3, median (IQR)	6.3 (3.9–10.1)	5.7 (3.1–9.4)	.261	5.7 (3.1–9.5)
Platelet count, as 10^3/μl, median (IQR)	157 (105–286)	143 (53–233)	.063	143 (55–233)
Candida spp. isolated	…	…	.013	…
Candida albicans, *n* (%)	28 (59.6)	889 (48.7)	…	917 (49.0)
Non-*albicans Candida*	…	…	…	…
C. glabrata, *n* (%)	2 (4.2)	388 (21.3)	…	390 (20.8)
C. parapsilosis, *n* (%)	7 (14.9)	297 (16.3)	…	304 (16.2)
C. tropicalis, *n* (%)	6 (12.8)	133 (7.3)	…	139 (7.4)
C. krusei, *n* (%)	0 (0)	59 (3.2)	…	59 (3.2)
Others, *n* (%)	4[d] (8.5)	60[e] (3.3)	…	64 (3.4)
Duration of candidemia in days, median (IQR)	3 (2.0–5.5)	3 (2.0–4.0)	.052	3 (2.0–4.0)
Persistent candidemia, *n* (%)	27 (57.4)	711 (38.9)	.010	738 (39.4)
Onset of candidemia	…	…	.032	…
Community-acquired, *n* (%)	27 (57.4)	763 (41.8)	…	790 (42.2)
Nosocomial, *n* (%)	20 (42.6)	1063 (58.2)	…	1083 (57.8)

CIE, candida infective endocarditis; IQR, interquartile range; TPN, total parenteral nutrition; CVC, central venous catheter; GI, gastrointestinal.

[a] *P* values for continuous variable were calculated using Mann-Whitney *U* statistic tests, while *P* values for categorical variable were obtained using either χ^2 or Fisher exact tests, as appropriate.

[b] Included leukemia, lymphoma, and multiple myeloma.

[c] Absolute neutrophil count of < 1500 cells/mm^3.

[d] *C. dubliniensis* (2), *C. lusitaniae* (1), and *Candida* spp. (1).

[e] *C. dubliniensis* (20), *C. lusitaniae* (16), *C. guilliermondii* (13), *C. kefyr* (3), and *Candida* spp. (8).

goodness of fit test was performed to evaluate calibration of the model. Kaplan-Meier analyses, conducted using log-rank tests, were used to determine the relationship of survival time between the two groups. All tests were two-sided with a $P < .05$ considered to be statistically significant.

Results

Demographics

A total of 1873 hospitalized patients diagnosed with candidemia from January 2002 to January 2015 were eligible for this study.

Of these, 47 (2.5%) cases were identified to have CIE. Comparison of selected significant demographic characteristics, comorbidities, and risk factors between CIE and non-CIE groups are summarized in Table 1, and the others in Supplementary Table 1. The sex and age distributions were similar among the two groups. Patients with CIE were significantly more likely to have valvular heart disease (36.2% vs. 21.6%, $P = .017$), community-acquired candidemia (57.4% vs. 41.8%, $P = .032$), and persistent candidemia (57.4% vs. 38.9%, $P = .010$). However, patients with CIE were significantly less likely to have hematologic malignancy (2.1% vs. 18.9%, $P = .004$), solid organ malignancy (19.1% vs. 35.0%, $P = .024$), neutropenia (0 vs. 7.5%, $P = .045$), to receive TPN (12.8% vs. 26.8%, $P = .031$), or have exposure to glucocorticoids in the 90 days prior to being diagnosed with candidemia (12.8% vs. 28.6%, $P = .002$). We identified 630 patients (33.6%) with a CVC at the time of diagnosis with candidemia. Of these, 77.8% and 77.0% had their CVCs removed within 72 hours in CIE and non-CIE groups, respectively.

Mycological and diagnostic data

In total, *C. albicans* was the most common species in both CIE ($n = 28$, 59.6%) and non-CIE ($n = 889$, 48.7%) groups. The next most common species isolated were *C. glabrata* ($n = 390$, 20.8%) and *C. parapsilosis* ($n = 304$, 16.2%); the distribution of other *Candida* spp. is shown in Table 1. The median duration of candidemia was 3 days in both CIE and non-CIE groups, with an interquartile range of 2.0–5.5 and 2.0–4.0 days, respectively. For patients diagnosed with CIE, 28 (59.6%) underwent both transthoracic (TTE) and transesophageal echocardiography (TEE), 10 (21.3%) had TTE alone, and 9 (19.1%) had only TEE performed. Of the patients who underwent both TTE and TEE, 75.0% ($n = 21$ of 28) were diagnosed on TEE after an initial negative TTE and 25.0% ($n = 7$ of 28) on both TTE and TEE. Overall, the distribution of valves involved in CIE were 38.5% mitral, 35.9% aortic, 23.1% tricuspid, and 2.5% pulmonary.

For the non-CIE group, 55.9% ($n = 1020$ of 1826) of the patients had echocardiography performed; 79.8% had TTE ($n = 814$ of 1020) alone, 5.0% had TEE ($n = 51$ of 1020) alone, and 15.2% had both TTE and TEE ($n = 155$ of 1020).

Logistic regression models

In univariable analyses, we assessed fifty two variables associated with the development of CIE in patients with candidemia (Supplementary Table 2). CIE was more prevalent in patients with valvular heart disease (odds ratio [OR], 7.95; 95% confidence interval [CI], 3.16–20.02) and community-acquired candidemia (OR, 1.88; 95% CI, 1.05–3.38). Predictors that were associated with a decreased risk for CIE included hematologic malignancy (OR, 0.09; 95% CI, 0.01–0.68), infection with *C. glabrata* (OR, 0.17; 95% CI, 0.04–0.68), an exposure to glucocorticoids within 90 days prior to candidemia (OR, 0.37; 95% CI, 0.15–0.86), receipt of TPN (OR, 0.40; 95% CI, 0.17–0.95), solid organ malignancy (OR, 0.44; 95% CI, 0.21–0.91), and temperature (OR, 0.68; 95% CI, 0.51–0.90).

Table 2. Multivariable logistic regression predicting *Candida* infective endocarditis in patients with candidemia.

Variable	Adjusted odd ratio (95% CI)	*P* value
Valvular heart disease	7.66 (2.95, 19.84)	<.0001
Infection with *Candida glabrata*	0.17 (0.04, 0.69)	.013
Hematologic malignancy[a]	0.09 (0.01, 0.68)	.019
Receipt of TPN	0.38 (0.16, 0.91)	.030

CI, confidence interval; TPN, total parenteral nutrition.
[a]Included leukemia, lymphoma, and multiple myeloma.

The final multivariable logistic regression model consisted of four variables (Table 2). Valvular heart disease (adjusted odds ratio [aOR], 7.66; 95% CI, 2.95–19.84) was the only predictor associated with an increased risk for CIE. Variables associated with a decreased risk for CIE in the final model included hematologic malignancy (aOR, 0.09; 95% CI, 0.01–0.68), infection with *C. glabrata* (aOR, 0.17; 95% CI, 0.04–0.69), and receipt of TPN (aOR, 0.38; 95% CI, 0.16–0.91). The c-statistic for this model was 0.732 (95% CI, 0.68–0.79) and Hosmer-Lemeshow goodness of fit test was 0.74.

Mortality

The crude 90-day mortality for CIE was 48.9%, which was similar to the overall non-CIE mortality of 41.9% ($P = .338$). There was no difference in survival between the two groups ($P = .719$). This did not change with a multivariable model (data not shown).

Discussion

Candidemia is one of the most common BSI in the United States with an estimated 25 000 cases annually.[21,22] CIE is a rare but important complication of candidemia because of its high mortality and relapse rate.[3,11,12] Therefore, distinguishing patients with uncomplicated candidemia from those with concurrent infective endocarditis has important therapeutic and prognostic implications. However, our understanding of the incidence of CIE in candidemic patients has been limited to three small cohorts[11,12,23] and focused primarily on nosocomial candidemia in patients with prosthetic valves.[12] In our large-scale cohort of all candidemic inpatients, only 47 cases (2.5%) out of 1873 patients with *Candida* BSI were identified to have CIE according to modified Duke criteria. This incidence rate was comparable to similar epidemiologic studies, which reported a range of 1.9–5.9%.[11,23]

Identification of high-risk patient populations for CIE in the setting of candidemia is clinically challenging and the diagnostic utility of echocardiography among patients with candidemia remains a controversial topic among major guidelines.[2,15] Although prior investigators have suggested that prosthetic heart valve and an unidentifiable portal of entry for nosocomial candidemia were potential risk factors for CIE in candidemic patients, these analyses were not adjusted for known and important covariates such as underlying comorbidities.[11,12] To the best of our knowledge, this is the first study assessing potential risk factors of CIE among patients with candidemia using a logistic regression model in a large database of inpatients without focusing on a specific patient population.

Our multivariable analysis demonstrated that patients with underlying valvular heart disease (including both native and prosthetic valvular disease) have a more than sevenfold increase in risk of developing CIE in the setting of candidemia. This finding is consistent with prior prospective observational studies that have demonstrated that underlying cardiac valvular abnormalities were present in 26% to 64% of patients diagnosed with CIE.[3,14,24] The pathogenic mechanisms by which CIE develops in the setting of candidemia is not fully understood. It is postulated, based on animal models, that damaged valvular endothelium predisposes to fibrin-platelet complex formation which promotes adherence of *Candida* leading to formation of vegetations.[25–27] It is also suggested that prosthetic materials serve as a foci for *Candida* infection.[28] One cohort analysis of nosocomial candidemia in patients with prosthetic heart valves found 25% of the patients had prosthetic valve endocarditis.[12] In another study, up to 36.4% of the patients diagnosed with CIE had valvular prostheses.[11]

Notably, we found three predictors associated with a lower risk of CIE in the setting of candidemia including receipt of TPN, the presence of hematologic malignancy, and infection with *C. glabrata*. TPN is a common risk factor for candidemia and an *in vivo* study demonstrated that lipid emulsion in the TPN solution enhances candidal virulence determinants such as germination and biofilm formation on the silicone-elastomer catheter.[29] Nevertheless, the incidence of CIE among candidemic patients on TPN is unknown. Several large observational studies have illustrated the link between CIE and risk factors such as prosthetic heart valves, structural valvular disorders, prior IE, injection drug use, and indwelling CVCs.[3,14,24] Use of TPN has not been well-implicated as a cause for CIE.[3,14,24] In our cohort, 26.4% of the candidemic patients received TPN. The relatively higher incidence of candidemia in patients receiving TPN (as recognized in the literature but not specifically studied in our cohort) and an overall low incidence of CIE translated to a decreased risk for CIE in our final model.

Hematologic malignancy was another factor associated with lower risk of CIE in patients with candidemia. Although immune dysfunction and neutropenia increases the risk of *Candida* BSI, CIE is relatively uncommon in the setting of granulocytopenia or defective immunity.[30] A similar observation has been shown in patients with hematologic malignancy and *Staphylococcus aureus* bacteremia.[31,32] The underlying immunologic mechanism for this lower risk of endocarditis remains unknown, though it is posited that concomitant thrombocytopenia may prevent fibrin-platelet complex and vegetation formation.[32] Early detection and treatment of candidemia in immunocompromised patients may also contribute to a lower incidence of infective endocarditis.[32]

Lastly, our data suggest that patients with *C. glabrata* BSI are at lower risk for developing CIE. Previous studies have found that the different *Candida* spp. have varying virulence mechanisms which result in different infectious complications and presentations.[33] Although the mechanisms by which CIE develops in humans remain to be fully elucidated, neutrophil extracellular traps (NETs), which are part of the innate immune response, have been shown to promote and expand vegetation formation by entrapping bacteria-platelet aggregations on injured heart valves in the setting of *Streptococcus mutans* endocarditis.[34] Studies of NETs in *Candida* spp. have demonstrated that the hyphal (but not yeast) forms of *C. albicans* stimulate NET production in response to disseminated candidal infection.[35] The inability of *C. glabrata* to transform into the hyphal form may result in a less robust NET formation by the host. It has also been demonstrated that biofilm formation by *C. glabrata* plays a role in NET inhibition.[36] These combined factors may explain the lower incidence of endocarditis in patients with *C. glabrata* BSI. The other plausible explanation for this observation is the emergence of *C. glabrata* due to selective pressure provided by common use of fluconazole for prophylaxis among high risk groups.[37,38] In our cohort, there are inherently significant more high risk patients with underlying malignancy and on immunosuppressive therapy in the non-CIE group, which may translate to a decreased risk for CIE in our final model.

This study is limited as a retrospective analysis of a cohort from a single tertiary academic center in the Midwest United States and our results may not be generalizable to other populations. Despite a large cohort of patients with candidemia, our analysis was based on 47 cases of CIE due to the rarity of this disease entity, which limits our statistical power. It is possible that misclassification bias may exist in the proportion of TEE being performed among the two study groups. Nevertheless, previous studies have found that patients with *Candida* infective endocarditis usually have large vegetations and TTE has a good sensitivity in diagnosing *Candida* infective endocarditis.[14,24] Additionally, undertreatment of invasive or complicated candidiasis (e.g., infective endocarditis) would result in high rates of relapse,[13] which would have been captured in our cohort as the median follow-up was over 2 years. Finally, we were not able to capture intravenous drug use secondary to lack of consistent documentation of this condition.

In conclusion, our study provides clarity on the risk factors for CIE in patients with *Candida* BSI. Valvular heart disease was the only factor associated with a greater risk of CIE while TPN use, hematologic malignancy, and *C. glabrata* BSI were associated with a decreased risk for CIE. Given the already low baseline incidence of CIE in patients with *Candida* BSI and reduced risk in certain patient populations, expensive and invasive diagnostic cardiac imaging may not be warranted in patients with a lower risk profile for endocarditis and alternative infection sources for candidemia. Our study highlights opportunities for diagnostic stewardship and cost savings through avoidance of unnecessary testing.

Supplementary material

Supplementary material are available at *MMYCOL* online.

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Declaration of Interest

W.G.P. has received research support from Merck & Co. and serves on the advisory board for Merck & Co. and Gilead Sciences. A.S. has received research support from Astellas, Scynexis, Cidera, MeraVista, and Mayne and consulting fees from Mayne, Scynexis, Astellas, Viamet, and Minnetronix. All other authors report no conflicts of interests relevant to this article.

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