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MAJOR ARTICLE

Creation and Assessment of a Clinical Predictive Calculator and Mortality Associated With *Candida krusei* Bloodstream Infections

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Background. *Candida krusei* bloodstream infection (CK BSI) is associated with high mortality, but whether this is due to underlying comorbidities in affected patients or the organism itself is unknown. Identifying patient characteristics that are associated with CK BSI is crucial for clinical decision-making and prognosis.

Methods. We conducted a retrospective analysis of hospitalized patients with *Candida* BSI at our institution between 2002 and 2015. Data were collected on demographics, comorbidities, medications, procedures, central lines, vital signs, and laboratory values. Multivariable logistic and Cox regression were used to identify risk factors associated with CK and mortality, respectively.

Results. We identified 1873 individual patients who developed *Candida* BSI within the study period, 59 of whom had CK BSI. CK BSI was predicted by hematologic malignancy, gastric malignancy, neutropenia, and the use of prophylactic azole antifungals, monoclonal antibodies, and β-lactam/β-lactamase inhibitor combinations. The C-statistic was 0.86 (95% confidence interval, 0.81–0.91). The crude mortality rates were 64.4% for CK BSI and 41.4% for non-CK BSI. Although CK was associated with higher mortality in univariable Cox regression, this relationship was no longer significant with the addition of the following confounders: lymphoma, neutropenia, glucocorticoid use, chronic liver disease, and elevated creatinine.

Conclusions. Six patient comorbidities predicted the development of CK BSI with high accuracy. Although patients with CK BSI have higher crude mortality rates than patients with non-CK BSI, this difference is not significant when accounting for other patient characteristics.

Keywords. *Candida krusei*; candidemia; clinical predictive model; mortality; risk factors.

Candida bloodstream infection (BSI) is the most common form of invasive candidiasis, the fourth leading cause of bloodstream infections in the United States, and the most common nosocomial BSI with non-*albicans* BSI, constituting a larger proportion of total infections in recent decades [1–3]. These species include *C. glabrata, C. tropicalis, C. parapsilosis,* and *C. krusei* (CK). Together with *C. albicans*, they make up the vast majority of *Candida* BSI. Although relatively rare, CK BSI is known to affect immunocompromised patients and is associated with the highest mortality among the *Candida* species [4–6].

The unique factors contributing to the development of infection by this organism and its clinical consequences are poorly characterized. Some predisposing factors, such as hematologic malignancy, are established in the literature as risk factors for CK BSI [7, 8]. Other risk factors including antibiotic exposure, surgery, and age exhibit a high level of heterogeneity across studies [9–12]. Most of these studies are limited by CK sample sizes of less than 35, and they often analyze for non-*albicans Candida*, which is influenced by *C. glabrata,* which has different risk factors [7–11]. In addition, few studies have addressed the question of whether the organism is directly responsible for the observed increase in mortality, or whether this association is confounded by other patient characteristics. While several authors have examined risk factors for mortality within *Candida* BSI cohorts [13], the multivariable survival models needed to definitively answer this question are lacking. Given the poor outcomes associated with CK BSI, accurately identifying patients at risk for this infection could be of benefit to clinicians.

We performed a retrospective cohort analysis of all *Candida* BSI infections at our institution over a 13-year period. The purpose of this study was to identify pertinent clinical comorbidities that could accurately predict CK BSI as well as to assess the impact of comorbidities on the elevated mortality rate seen in these patients.

METHODS

Setting

We collected data from patients admitted to Barnes Jewish Hospital between January 2002 and January 2015, a 1315-bed

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tertiary care hospital in St. Louis, Missouri. The study was approved by the Washington University in St. Louis Institutional Review Board with a waiver of consent.

Cohort Construction

Patients ≥18 years old who were hospitalized and had at least 1 blood culture positive for *Candida* were eligible for study inclusion. Subsequent *Candida* BSI episodes in the same patient within 90 days were excluded. Through a combination of automated chart extraction and medical chart review by the authors, we collected *Candida* species and a series of patient characteristics (Table 1; Supplementary Tables 1 and 2). The most extreme vital signs (highest temperature, respiratory rate, and heart rate; lowest blood pressure) measured within 24 hours preceding BSI were collected. Comorbidities were determined via ICD-9 codes (Supplementary Table 1) and included all Elixhauser comorbidities as they have been shown to be good predictors of death in acute illness [14]. We categorized

Table 1. Comparison of Characteristics Between Patients With *Candida krusei* Bloodstream Infections and Those With Non-CK Bloodstream Infections

Characteristic[a]	CK (n = 59)	Non-CK (n = 1814)	*P* Value[b]	Total (n = 1873)
Demographics				
Age, median (IQR), y	57 (21)	59 (24)	.5210	59 (24)
Female sex	25 (42.4)	869 (47.9)	.4024	894 (47.7)
Race			.0175	
White	43 (72.9)	1134 (62.5)		1177 (62.8)
African American	10 (17.0)	588 (32.4)		598 (31.9)
Other	6 (10.2)	92 (5.1)		98 (5.2)
Malignancy				
Leukemia	33 (55.9)	199 (11.0)	<.0001	232 (12.4)
Lymphoma	8 (13.6)	84 (4.6)	.0070	92 (4.9)
Hematologic	42 (71.2)	304 (16.8)	<.0001	346 (18.5)
Gastric	2 (3.4)	20 (1.1)	.1509	22 (1.2)
Other potential predisposing factors				
Bone marrow transplant	9 (15.3)	27 (1.5)	<.0001	36 (1.9)
Cancer chemotherapy	12 (20.3)	99 (5.5)	.0001	111 (5.9)
Neutropenia	17 (28.8)	120 (6.6)	<.0001	137 (7.3)
Laboratory values				
Absolute neutrophils count, median (IQR)	2.0 (11.2)	5.8 (6.2)	.0092	5.7 (6.4)
Neutropenia (ANC < 500)	23 (41.8)	150 (8.6)	<.0001	173 (9.6)
Platelets, median (IQR)	8 (78.5)	148 (175)	<.0001	143 (178)
Dichotomized creatinine (reference: ≤1)	21 (38.2)	883 (50.3)	.0771	904 (49.9)
Medications ordered within 90 days prior to *Candida* BSI				
Azole	17 (28.8)	138 (7.6)	<.0001	155 (8.3)
Fluconazole	14 (23.7)	123 (6.8)	<.0001	137 (7.3)
Voriconazole	3 (5.1)	10 (0.6)	.0068	13 (0.7)
Clotrimazole	1 (1.7)	13 (0.7)	.3622	14 (0.8)
Itraconazole	0 (0)	4 (0.2)	1.0000	4 (0.2)
Ketoconazole	0 (0)	1 (0.1)	1.0000	1 (0.05)
Monoclonal antibodies	8 (13.6)	16 (0.9)	<.0001	24 (1.3)
Antilymphocyte	5 (8.5)	10 (0.6)	<.0001	15 (0.8)
Antimyeloid	1 (1.7)	2 (0.1)	.0916	3 (0.2)
Anti-TNF	3 (5.1)	4 (0.2)	.0010	7 (0.4)
Corticosteroids	36 (61.0)	493 (27.2)	<.0001	529 (28.2)
Antiherpes antivirals	31 (52.5)	240 (13.2)	<.0001	271 (14.5)
Antimetabolites	23 (39.0)	157 (8.7)	<.0001	180 (9.6)
Calcineurin inhibitors	14 (23.7)	76 (4.2)	<.0001	90 (4.8)
Cytotoxic agents	6 (10.2)	36 (2.0)	.0016	42 (2.2)
Mitotic inhibitors	7 (11.9)	40 (2.2)	.0005	47 (2.5)
mTOR inhibitors	3 (5.1)	14 (0.8)	.0147	17 (0.9)

Descriptive statistics for additional variables are presented in Supplementary Table 2.

Abbreviations: BMI, body mass index; CK, *Candida krusei*; IQR, interquartile range; mTOR, mechanistic target of rapamycin; TNF, tumor necrosis factor; TPN, total parenteral nutrition.

[a]Unless otherwise specified, characteristics are dichotomized and reported as absolute frequency (percent).

[b]*P* values for continuous variables were based on Mann-Whitney *U* statistical tests, while categorical variable *P* values were obtained from either chi-square or Fisher exact tests, as appropriate.

[c]The most extreme vital signs (highest temperature, respiratory rate, and heart rate; lowest blood pressure) measured within 24 hours preceding BSI were collected.

continuous variables that did not follow a linear distribution, and when significantly different, odds ratios were noted for different levels of the variable in univariate analyses.

Outcomes

For logistic regression, the outcome was defined as CK BSI vs non-CK BSI. For survival analysis, we assessed 90-day all-cause mortality. Dates of death were extracted from the hospital consortium's Medical Informatics database and supplemented with information from the Social Security Death Index (SSDI). Patients with a positive *Candida* blood culture and without confirmed death who were not observed in our institution after the 90-day postdiagnosis period were censored at the date of last visit.

Statistical Analysis

Statistical analysis was performed using SAS v9.4 Software (SAS Institute Inc., Cary, NC), and all tests were 2-tailed. Survival graphs were created using SPSS V23 (IBM, Armonk, NY). For descriptive statistics, we used chi-square or Fisher exact tests for categorical variables and Mann-Whitney *U* tests for continuous variables, as the variables were not normally distributed.

We performed univariate logistic regression to evaluate the association of predisposing factors, comorbidities, medication use, and laboratory values with the development of CK BSI. We performed univariable Cox proportional hazards analysis to evaluate the association of these same factors with 90-day mortality. Variables with $P < .20$ were evaluated in the multivariable models.

We developed the multivariable models in a parsimonious manner, adding candidate variables sequentially and retaining them in the model if they were found to be significant ($P < .05$). After all relevant variables were included, those 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 the final set of predictor variables. The Cox proportional hazards model was constructed in a similar manner, with the exception that the initial model contained *Candida* species as the dependent variable, dichotomized as CK vs non-CK, and all other variables were tested in the model as confounders (changed the CK parameter estimate by at least 15% in either direction).

RESULTS

Demographics

A total of 1913 hospitalized patients were diagnosed with *Candida* BSI in the study period. Forty observations were discarded due to duplication, incomplete data collection, and not fulfilling inclusion/exclusion criteria, resulting in 1873 observations analyzed. Of these, 59 were due to CK. Absolute and relative frequency of CK BSI did not significantly change over time. CK constituted between 1.8% and 5.4% of total *Candida* BSI events between 2002 and 2015, and there has been no consistent trend over time (Supplementary Figure 1).

Significant and relevant descriptive comparison between CK and non-CK BSI can be found in Table 1, and the others in Supplementary Table 2. Age and sex distributions were similar between the 2 groups, while CK BSI was diagnosed more often in white patients (72.9% vs 62.5%). Many comorbidities were present at similar rates between the groups. However, patients with CK BSI were significantly more likely to have hematologic cancer (71.2% vs 16.8%), and were also significantly more likely to have a history of bone marrow transplant (15.3% vs 1.5%) and to have received chemotherapy (20.3% vs 5.5%). CK BSI patients were more likely to have received certain medications within the 90 days leading up to the incident infection, including azole antifungals, echinocandins, and corticosteroids.

Clinical Predictive Model

In univariate logistic regression analyses, 65 variables were found to be associated with the development of CK BSI (Supplementary Table 3).

Six variables were included in the final multivariable logistic regression model: hematologic malignancy (odds ratio [OR], 10.7; 95% confidence interval [CI], 5.1–22.4), gastric malignancy (OR, 14.7; 95% CI, 3.0–72.8), neutropenia (OR, 2.1; 95% CI, 1.1–4.1), prior azole use (OR, 2.4; 95% CI, 1.2–4.7), prior monoclonal antibody use (OR, 5.4; 95% CI, 2.0–14.9), and β-lactam/β-lactamase inhibitor use (OR, 2.4; 95% CI, 1.3–4.7) within 90 days prior to *Candida* BSI (Table 2). Prior monoclonal antibody use included all patients receiving antilymphocyte antibodies, antimyeloid antibodies, and/or anti–tumor necrosis factor antibodies. The C-statistic for this model was 0.86 (95% CI, 0.81–0.91) (Figure 1).

Mortality

Mortality was increased in CK BSI patients compared with non-CK BSI patients in univariable analysis (64.4% vs 41.4%; hazard ratio [HR], 1.8; 95% CI, 1.3–2.4) (Figure 2, Supplementary Table 4).

Five variables were included in the final multivariable Cox model: neutropenia (HR, 2.0; 95% CI, 1.6–2.5), lymphoma (HR, 1.5; 95% CI, 1.1–2.0), prior glucocorticoid use (HR, 1.4; 95% CI, 1.2–1.7), chronic liver disease (HR, 2.0; 95% CI, 1.6–2.5), and creatinine >1 mg/dL (HR, 2.1; 95% CI, 1.8–2.5) (Table 3). With the addition of these covariates, the association between CK BSI and mortality was no longer significant (HR, 1.3; 95% CI, 0.9–1.8) (Figure 2).

DISCUSSION

CK is associated with high mortality and resistance to antifungal agents; therefore, understanding the underlying risk factors for development of the infection and mortality in this population is of high clinical importance. Hematologic malignancy, gastric malignancy, neutropenia, prior azole use, prior monoclonal antibody use, and prior β-lactam/β-lactamase inhibitor use are independent risk factors for the development of CK BSI

Table 2. Clinical Predictive Calculator for *Candida krusei* vs Other *Candida* Bloodstream Infection

Variable	Parameter Estimate	Odds Ratio (95% CI)	*P* Value
Intercept	–5.1811	n/a	n
Hematologic malignancy[a]	2.3664	10.659 (5.067–22.422)	<.0001
Gastric malignancy	2.6862	14.676 (2.957–72.849)	.0010
Neutropenia[b]	0.7471	2.111 (1.091–4.086)	.0266
Prior azole use[c]	0.8623	2.369 (1.204–4.658)	.0125
Prior monoclonal antibody use[c]	1.6884	5.411 (1.964–14.910)	.0011
Prior β-lactam/β-lactamase inhibitor use[c]	0.8880	2.430 (1.251–4.722)	.0088

$$P(CK) = \frac{1}{1+e^{-(-5.1811+2.3664*X1+2.6862*X2+0.7471*X3+0.8623*X4+1.6884*X5+0.888*X6)}},$$

where X_1 = hematologic malignancy, X_2 = gastric malignancy, X_3 = neutropenia, X_4 = prior azole use, X_5 = prior monoclonal antibody use, and X_6 = prior β-lactam/β-lactamase inhibitor use.

Abbreviations: CI, confidence interval; CK, *Candida krusei*.

[a]Includes any history or diagnosis of leukemia, lymphoma, or multiple myeloma.

[b]Defined as absolute neutrophil count <500/mm^3.

[c]Medication was ordered within 90 days prior to *Candida* infection.

in our multivariable logistic regression model. The discriminating performance of this model is higher than some of the most commonly used clinical predictive models [15]. Although patients with CK BSI appear to have a higher mortality rate than non-CK BSI patients, this association is no longer significant when taking into account confounders, specifically neutropenia, lymphoma, prior glucocorticoid use, chronic liver disease, and elevated creatinine.

While CK is 1 of 5 *Candida* species composing >90% of all isolates, it is also the least common of these [1]. We found CK to constitute 3.2% of all *Candida* BSI at our institution, which is consistent with a previously published range of 0.9%–10% [7, 12, 16–18]. A systematic review of *Candida* BSI prevalence worldwide found that CK consistently made up 1%–4% of infections regardless of geographic location, with the exception of 2 studies conducted in Finland and France with proportions of 8.5% and 10.6%, respectively [19]. There is no consensus as to whether the incidence of CK is truly increasing, as results from different studies are conflicting. However, the majority of studies suggest a stable epidemiology, consistent with our findings [4, 19, 20]. It is possible that the studies that show a rise in CK are either outliers or represent localized changes in epidemiology.

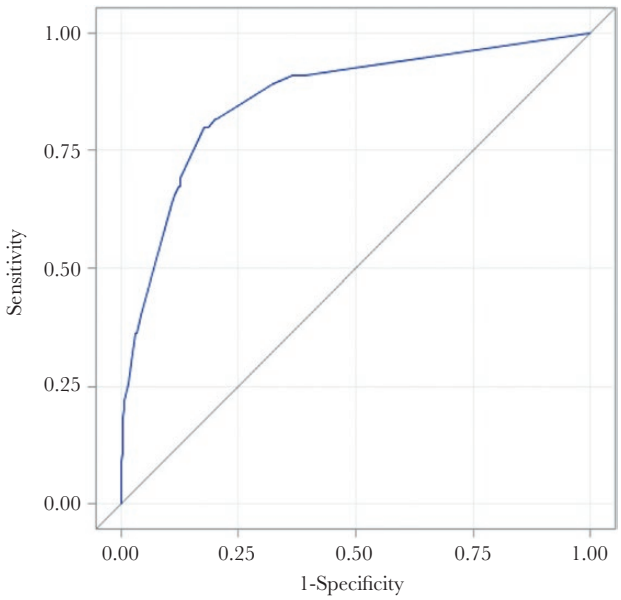

Figure 1. Receiver operating characteristic curve for the multiple logistic regression predicting *Candida krusei* bloodstream infection. The C-statistic is 0.8618 (95% confidence interval, 0.8094–0.9141). Predictor variables are hematologic malignancy, gastric malignancy, neutropenia, and prior azole, monoclonal antibody, and β-lactam/β-lactamase inhibitor use within 90 days prior to the *Candida* infection.

Several of the risk factors associated with CK BSI in our cohort have been corroborated in previous studies. Observationally, CK is disproportionately isolated in hematology units [7, 21] and neutropenia and hematologic malignancy are consistently associated with CK BSI across multiple studies [8, 11, 12, 16]. A prospective cohort of patients diagnosed with *Candida* BSI between 2004 and 2008 found that CK BSI was more common in the setting of prior use of antifungal agents, hematologic malignancy, stem cell transplantation, neutropenia, and corticosteroid therapy, although the authors did not adjust for multiple variables [22]. In our analysis, bone marrow transplantation and corticosteroid therapy were significant in univariate analyses but did not meet criteria for inclusion in multivariable analyses, appearing to have no increase in predictability in addition to hematologic malignancy and neutropenia.

We found a specific predilection for CK BSI in patients with prior azole use, which has biological plausibility given the known intrinsic resistance to fluconazole (and other azoles, to a lesser extent) in this species [20, 23, 24]. Various studies have suggested increased risk in the setting of fluconazole exposure, with 1 study demonstrating dose dependency [25–28]. Although 1 case-control analysis found no relationship between fluconazole and CK

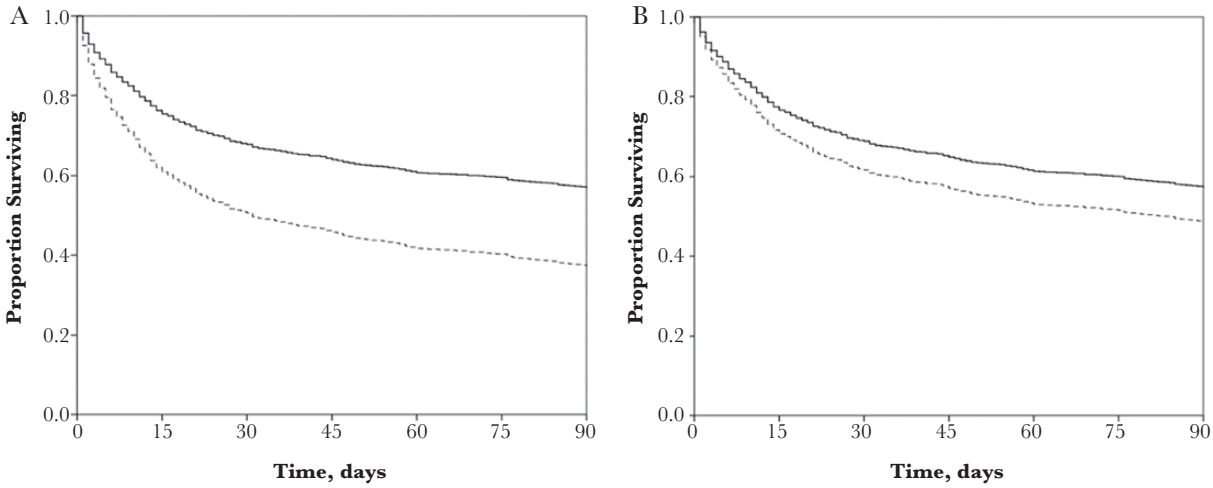

Figure 2. Univariable (A) and multivariable (B) proportional hazards model stratified by *Candida krusei* bloodstream infection (dashed) vs other *Candida* bloodstream infection (solid). Time was measured from the date of first positive culture. Patients were censored at either date of death or date last seen, as reflected in the medical chart and the Social Security Death Index. The multivariable model is adjusted for lymphoma, neutropenia, glucocorticoid use, chronic liver disease, and elevated creatinine.

BSI, this study included only 4 patients with CK [29]. Given that azole prophylaxis is often given in the setting of severe immunosuppressive disease (eg, hematologic malignancy and transplantation), some authors have suggested association rather than a true biological causation [30]. However, in 1 study limited to adult patients with leukemia or status post–bone marrow transplant, fluconazole prophylaxis was still associated with CK BSI [31]. The authors posited that emergence of a relatively low-virulence organism such as CK was aided by the suppression of other more virulent *Candida* species susceptible to fluconazole.

In addition to azoles, β-lactam/β-lactamase inhibitors and monoclonal antibodies were associated with CK BSI. Although antibiotics have been infrequently studied in this setting, 1 prior case-control study found that β-lactams, vancomycin, and aminoglycosides were associated with CK BSI, with the strongest association seen for antibiotics with anaerobic activity [10]. Presumably, antibiotics may predispose individuals to *Candida* BSI through alteration of the microbiome at sites of inoculation.

Table 3. Multivariable Proportional Hazards (Cox) Model Predicting Mortality in Patients With *Candida* Bloodstream Infection

Variable	Hazard Ratio (95% CI)	*P* Value
Candida krusei[a]	1.297 (0.909–1.849)	.1514
Neutropenia[b]	1.984 (1.593–2.472)	<.0001
Lymphoma	1.488 (1.124–1.970)	.0055
Prior glucocorticoid use[c]	1.425 (1.218–1.667)	<.0001
Chronic liver disease	2.005 (1.593–2.525)	<.0001
Elevated creatinine[d]	2.125 (1.835–2.461)	<.0001

Abbreviation: CI, confidence interval.

[a]Models *Candida krusei* in comparison with all other *Candida* species.

[b]Defined as absolute neutrophil count <500/mm^3.

[c]Medication was ordered within 90 days prior to *Candida* infection.

[d]Defined as >1 mg/dl.

However, the significance of the interaction between certain antibiotic classes and *Candida* species is unclear. Similarly, while the ability of monoclonal antibodies to significantly affect immunologic mechanisms suggests a pathway by which low-virulence organisms such as CK gain a foothold in an otherwise overly hostile environment, this area requires further investigation.

In our multivariable analysis, gastric malignancy was the only solid tumor significantly associated with the development of CK BSI. Gastrointestinal (GI) inoculation as a source of CK BSI may explain this association, as disruption of the GI barrier by tumor cells and associated inflammation could potentially lead to higher inoculation rates, although this mechanism is theoretical and may not be specific to CK [32, 33].

CK BSI was associated with higher mortality as compared with non-CK BSI in the univariate analysis (64.4% vs 41.4%; HR, 1.8; 95% CI, 1.3–2.4). The mortality in our study is generally consistent with that cited by other authors [34–36]. While mortality with CK BSI tends to be higher than non-CKI BSI in the majority of studies, this difference is often not statistically significant, likely related to low power in the setting of infrequent CK infection [8, 12, 34]. In 1 study with comparable sample sizes and species distributions, CK was found to have the highest 90-day mortality rate (52.9%) of all species when comparing them individually [22]. Another study found CK BSI to be associated with a similarly poor 90-day mortality of 46.4%, compared with 38.7% for all *Candida* BSI [12].

Our multivariable survival analysis suggests that the higher crude mortality seen with CK BSI reflects the underlying severity of illness in these patients rather than pathogenic virulence of the organism [32]. Indeed, in vitro and in vivo virulence testing has demonstrated that CK is a relatively low-virulence organism [18, 33], although several unique intrinsic mechanisms are protective against both antifungal medications and

oxidative stress [37, 38]. While hematologic malignancy predicted CK BSI, only lymphoma was an independent predictor of mortality. One possible explanation for this discrepancy may be the convergence of leukemia and neutropenia as they relate to mortality, whereas other sources of immune dysfunction in hematologic malignancy may contribute to the development of CK BSI. Regardless of their role in the initial CK BSI, liver disease, kidney dysfunction, and immunosuppression appear to be strong mediators of CK BSI–associated mortality.

This study is limited by retrospective data collection. While the database was built to maximize comprehensiveness, ICD-9 codes may not always reflect true diagnoses, leading to misclassification bias. Additionally, we were unable to identify changes in diagnostic accuracy and management over time that may have contributed to variations in mortality, although mortality in this cohort did not appear to change significantly over time. Despite a large overall sample size, our analyses were based on comparison with only 59 patients with CK BSI due to the relative infrequency of infection by this species. This limited our statistical power, although this is the largest study to look at patients with CK BSI. Finally, this study was conducted at a single tertiary care academic center and thus may not be generalizable to other populations.

In conclusion, we found that a collection of patient comorbidities could both predict the development of CK BSI and explain the increased mortality seen in these patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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