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MAJOR ARTICLE

Candida Infective Endocarditis: A Retrospective Study of Patient Characteristics and Risk Factors for Death in 703 United States Cases, 2015–2019

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Background. *Candida* endocarditis is a rare, sometimes fatal complication of candidemia. Past investigations of this condition are limited by small sample sizes. We used the Vizient clinical database to report on characteristics of patients with *Candida* endocarditis and to examine risk factors for in-hospital mortality.

Methods. This was a multicenter, retrospective cohort study of 703 inpatients admitted to 179 US hospitals between October 2015 and April 2019. We reviewed demographic, diagnostic, medication administration, and procedural data from each patient's initial encounter. Univariate and multivariate logistic regression analyses were used to identify predictors of in-hospital mortality.

Results. Of 703 patients, 114 (16.2%) died during the index encounter. One hundred fifty-eight (22.5%) underwent an intervention on a cardiac valve. On multivariate analysis, acute and subacute liver failure was the strongest predictor of death (odds ratio [OR], 9.2; 95% confidence interval [CI], 4.8 –17.7). Female sex (OR, 1.9; 95% CI, 1.2–3.0), transfer from an outside medical facility (OR, 1.8; 95% CI, 1.1–2.8), aortic valve pathology (OR, 2.7; 95% CI, 1.5–4.9), hemodialysis (OR, 2.1; 95% CI, 1.1–4.0), cerebrovascular disease (OR, 2.2; 95% CI, 1.2–3.8), neutropenia (OR, 2.5; 95% CI, 1.3–4.8), and alcohol abuse (OR, 2.9; 95% CI, 1.3–6.7) were also associated with death on adjusted analysis, whereas opiate abuse was associated with a lower odds of death (OR, 0.5; 95% CI, 0.2–0.9).

Conclusions. We found that the inpatient mortality rate was 16.2% among patients with *Candida* endocarditis. Acute and subacute liver failure was associated with a high risk of death, whereas opiate abuse was associated with a lower risk of death.

Keywords. *Candida*; candidemia; endocarditis.

Candida infective endocarditis (CIE) is a rare complication of candidemia with a reported in-hospital mortality of greater than 30% [1–3]. Several *Candida* species have been reported to cause candidemia, including *Candida albicans*, *Candida parapsilosis*, *Candida krusei*, *Candida dubliniensis*, *Candida lusitaniae*, and more recently the multidrug-resistant species *Candida auris* [4, 5]. Each of these may cause IE [4, 5]. Because *Candida* species are implicated in less than 2% of IE cases, our understanding of this disease entity is limited to data from small cohort studies [1–4, 6–8]. Because the incidence of candidemia in the United States is increasing, a growing number of patients is at risk for this potentially fatal complication [2, 9–11]. If risk factors for poor outcomes of CIE were defined, treatment modalities such as early valve replacement surgery or aggressive administration of antifungal therapies may be used more effectively.

Despite high mortality among patients with CIE, little is known about the clinical characteristics of this population including those that predict death. Although patients with CIE are included in several large retrospective cohort studies, their characteristics are not reported in detail [4, 6, 7]. The largest prospective study to date reports on 70 cases of CIE from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) and ICE-Plus databases [1, 2, 12]. Although these studies provided important data about the CIE population, analysis of risk factors for death was limited by small sample sizes.

In the present study, we used a US hospital discharge database of clinical and administrative information to assess the clinical characteristics of patients with CIE and to identify independent predictors of in-hospital mortality in this large cohort.

METHODS

This is a multicenter, retrospective cohort study of administrative data from the Vizient clinical database. Vizient is a consortium of 117 geographically diverse US academic medical centers and their

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300 affiliated hospitals. Participating centers submit demographic, medication, laboratory, and administrative data for all inpatient and outpatient encounters to Vizient where rigorous quality assessment is performed before entry into the clinical database.

We identified a cohort of people with at least one inpatient encounter with an *International Classification of Diseases, Tenth Revision* (ICD-10) B37.6 primary or secondary diagnosis code for CIE at a participating medical center between October 1, 2015 and April 30, 2019. We limited our primary analysis to each patient's first encounter with the ICD-10 B37.6 code during the study period, hereafter referred to as the index encounter. For each encounter, we extracted all associated diagnosis codes, procedure codes, discharge data, and demographics.

The primary outcome was all-cause inpatient mortality during the index encounter. We compared patient demographics (age, sex, race, ethnicity, insurance payer, and patient origin) and clinical characteristics of patients who were alive at discharge to those who were not alive, as recorded in the Vizient database. The clinical characteristics we considered included medical comorbidities and data regarding use of tobacco, abuse of opiates, and other illicit substances. To ascertain opiate abuse, we used the ICD-10 code F11.1. Vizient reports severity of illness (SOI) as a multilevel categorical variable with ranks of mild, medium, high, and extreme. These ranks were developed using the proprietary All Patient Refined-Diagnosis Related Group (APR-DRG) methodology developed by 3M. Scores are calculated from discharge billing codes and are based on primary and secondary discharge diagnoses, age, and preexisting conditions. The SOI ranks are then derived relative to a patient-specific APR-DRG baseline [13].

In addition to patient clinical characteristics, we were interested in the valvular interventions performed on patients in our cohort. We used procedure codes for repair, removal, or replacement of each cardiac valve to report on valvular interventions performed during the index encounter. To understand whether a prior valvular intervention or underlying valve pathology may have predisposed to intervention upon the valve during the index encounter, we examined diagnostic and procedure codes pertaining to pathology of a cardiac valve or valvular intervention, respectively, during encounters taking place within 1 year before the index encounter.

Because some of the patients in our cohort had multiple encounters during the study period, we wanted to understand whether patients who did not undergo a valvular intervention during the index encounter had such a procedure during a subsequent encounter. We used procedure codes associated with any subsequent encounters during the study period to ascertain whether additional valvular interventions were performed after the index encounter.

Demographics, diagnosis codes, and procedure codes were tabulated. Continuous variables were examined for normality. Proportions and median values with interquartile ranges were determined for categorical and continuous variables, respectively. To protect confidentiality, we were not able to report specific values for any variable with <10 subjects.

A univariate logistic regression analysis was performed to test for associations between each of the demographic and clinical variables and the outcome. A marginal screening threshold at a significance level of $P = .1$ was used for inclusion in the multivariate analysis to assess associations with in-hospital mortality. A multivariate logistic regression analysis was then performed using backward selection at a significance threshold of $P = .1$. We adjusted the final model for age, sex, race, and ethnicity.

We also examined antifungal use in a subset of patients with medication administration data available in Vizient. We performed univariate and multivariate analyses to assess the association of the use of specific antifungals and mortality using the same marginal screening threshold and backward selection technique as was used in the primary analysis. All statistical analyses were performed using Stata 15 (StataCorp LLC, College Station, TX).

RESULTS

Patient Demographics

A total of 703 patients had an index CIE inpatient encounter at 179 clinical sites between October 1, 2015 and April 30, 2019. The number of patients per site ranged from 1 to 32 with a median of 5. The cohort included 402 (57.2%) males and 301 (42.8%) females. Of 703 patients, 416 (59.2%) were non-Hispanic white, 103 (14.7%) were non-Hispanic black, 46 (6.5%) were Hispanic, 111 (15.8%) identified their race as "other," and for 27 (3.8%) race and ethnicity were unknown. Most of the patients had either Medicaid (265, 37.7%) or Medicare (260, 37.0%) as their primary insurance payer, whereas 130 (18.5%) had a private insurance payer, and 24 (3.4%) were uninsured. Three hundred forty-three (48.8%) patients were transferred to a reporting center from another inpatient facility, whereas 310 (44.1%) had a nonfacility origin, and 40 (5.7%) were admitted from an outpatient clinic. Upon admission, 498 (70.8%) had an extreme SOI index, whereas 165 (23.5%) had a major SOI index. Only 40 patients (5.7%) had a mild or moderate SOI index. The median hospital length of stay in this cohort was 19 days (interquartile range, 10–35 days). The geographic distribution of cases was fairly uniform with 210 (29.9%) patients admitted to centers in the South, 202 (28.7%) admitted to centers in the Midwest, 200 (28.5%) admitted to centers in the Northeast, and 91 (12.9%) admitted to centers in the West (Table 1).

Patient Comorbidities

Two hundred one (28.6%) patients had diabetes. Renal comorbidities were also common. A total of 219 (31.2%) patients had documented chronic kidney disease (CKD) and 73 (10.4%) were receiving hemodialysis (HD) (Table 1).

Table 1. Demographic and Clinical Characteristics of 703 Patients With *Candida* Infective Endocarditis

Subject Characteristics	N = 703
Demographics	
Age	
<18 years	23 (3.3%)
18–30 years	131 (18.6%)
31–50 years	236 (33.6%)
51–64 years	161 (22.9%)
65+ years	152 (21.6%)
Sex	
Male	402 (57.2%)
Female	301 (42.8%)
Race/Ethnicity	
Non-Hispanic white	416 (59.2%)
Non-Hispanic black	103 (14.7%)
Non-Hispanic other	111 (15.8%)
Hispanic	46 (6.5%)
Unknown	27 (3.8%)
Insurance Payer	
Private	130 (18.5%)
Medicare	260 (37.0%)
Medicaid	265 (37.7%)
Uninsured	24 (3.4%)
Other	24 (3.4%)
Region	
Northeast	200 (28.5%)
Midwest	202 (28.7%)
South	210 (29.9%)
West	91 (12.9%)
Characteristics of Index Admission	
Length of stay (days), median (interquartile range)	19.0 (10.0–35.0)
Severity of Illness Index at Admission	
Mild or moderate	40 (5.7%)
Major	165 (23.5%)
Extreme	498 (70.8%)
Origin	
Nonfacility	310 (44.1%)
Clinic	40 (5.7%)
Inpatient medical facility	343 (48.8%)
Other	10 (1.4%)
Comorbidities	
Diabetes mellitus	201 (28.6%)
Chronic kidney disease	219 (31.2%)
Hemodialysis	73 (10.4%)
Cerebrovascular disease	104 (14.8%)
Chronic obstructive pulmonary disease	74 (10.5%)
Coronary artery disease	10 (1.4%)
Other underlying heart condition	52 (7.4%)
Vascular disease	96 (13.7%)
Chronic heart failure	180 (25.6%)
Acute and subacute liver failure	55 (7.8%)
Cirrhosis	25 (3.6%)
Hepatitis B infection	20 (2.8%)
Hepatitis C infection	190 (27.0%)
Human immunodeficiency virus infection	14 (2.0%)
Connective tissue or autoimmune disease	41 (5.8%)
Hematologic malignancy or related	31 (4.4%)
Neutropenia/pancytopenia	77 (11.0%)
Solid Tumor	72 (10.2%)
Malignancy, not otherwise specified	28 (4.0%)
Solid organ transplant	22 (3.1%)
Other Risk factors	
Long-term steroid use	25 (3.6%)
Homeless	24 (3.4%)
Tobacco abuse	421 (59.9%)
Alcohol abuse	45 (6.4%)
Other illicit drug use	128 (18.2%)
Opioid abuse	213 (30.3%)
Total parenteral nutrition	47 (6.69%)

A minority of the cohort had an immunocompromising condition. Fourteen (2.0%) had human immunodeficiency virus infection, 22 (3.1%) had undergone solid organ transplantation, and 31 (4.4%) had a present or past history of hematologic malignancy. There were 77 (11.0%) patients with either disease-induced or iatrogenic cytopenia (Table 1).

One hundred ninety (27.0%) patients had documented hepatitis C, whereas 20 (2.8%) had hepatitis B infection. Twenty-five (3.6%) patients had documented cirrhosis, and 55 (7.8%) had acute or subacute liver failure (Table 1).

Social History

A majority of the patients had a history of or ongoing tobacco abuse (421, 59.9%). Use of illicit or controlled substances was also frequent, with 213 (30.3%) patients documented as having either present or past opioid abuse, and 128 (18.2%) patients had a history of use of another illicit substance (Table 1).

Valve Procedures

Of 703 patients, 158 (22.5%) underwent a valvular intervention during their index encounter. A similar proportion of patients alive at discharge underwent intervention as those died during the index encounter (23.1% vs 19.3%, $P = .370$). Of those patients who underwent a valvular intervention, 58 (36.7%) had an intervention on the aortic valve, 20 (12.7%) on the mitral valve, and 52 (32.9%) had an intervention on the tricuspid valve. Twenty-seven patients (17.1%) underwent interventions on more than 1 cardiac valve (Table 2).

Of 58 patients with an aortic valve intervention, 56 (96.6%) had documentation of valve replacement. Likewise, most patients who underwent a mitral valve intervention underwent valve replacement (18 of 20, 90.0%). Of patients who underwent tricuspid valve interventions, 42 of 52 (80.8%) underwent valve replacement. Of those patients who had intervention upon more than 1 valve, most (20 of 27, 74.1%) had aortic valve replacement in addition to intervention on at least 1 other valve (Table 2).

To understand whether a prior valvular intervention or underlying valve pathology was associated with the incidence of

Table 2. Valve Interventions Among Patients with *Candida* Infective Endocarditis During an Index Encounter

Interventions	N = 703
None recorded during index encounter	545 (77.5%)
Valve interventions, total	158 (22.5%)
Aortic Valve Intervention	58 (36.7%)
Valve replacement	56 (96.6%)
Mitral Valve Intervention	20 (12.7%)
Valve replacement	18 (90.0%)
Tricuspid Valve Intervention	52 (32.9%)
Valve replacement	42 (80.8%)
Interventions on multiple valves	27 (17.1%)
Other	1 (0.6%)

a valvular procedure during the index encounter, we examined procedure and diagnostic codes associated with encounters in the year preceding the index encounter among the 158 patients who underwent a valvular intervention. Fifty-one of these 158 patients (32.3%) who underwent a valvular intervention during the index encounter had an encounter at a reporting medical center within the preceding year. Fewer than 10 of these 51 patients had documentation of a valvular intervention or valvular pathology preceding the index encounter.

Two hundred seventy-nine patients who did not have an intervention on a cardiac valve during the index encounter were hospitalized within 1 year prior. Of these, 29 (10.4%) underwent a valvular intervention on a past admission. Thirteen of these 29 patients (44.8%) had an intervention on the aortic valve, whereas <10 patients underwent an intervention on each of the other valves.

Ninety-one (91 of 703, 12.9%) patients had more than 1 encounter recorded between October 1, 2015 and April 30, 2019. However, <10 had heart valve interventions after the index encounter; all of these were aortic valve replacements.

Risk Factors for In-Hospital Mortality

Of 703 patients, 114 (16.2%) died before discharge from the index encounter. In univariate regression analysis, transfer from another inpatient facility (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.5–3.6), CKD (OR, 1.9; 95% CI, 1.2–2.8), HD (OR, 2.3; 95% CI, 1.3–4.1), cerebrovascular disease (CVD) (OR, 2.3; 95% CI, 1.4–3.8), heart failure (HF) (OR, 1.7; 95% CI, 1.1–2.7), acute and subacute liver failure (OR, 8.1; 95% CI, 4.5–14.4), neutropenia (OR, 2.0; 95% CI, 1.1–3.5), gastrointestinal pathology (OR, 2.1; 95% CI, 1.3–3.6), alcohol abuse (OR, 2.0; 95% CI, 1.0–4.0), and underlying pathology of the aortic valve (OR, 2.2; 95% CI, 1.3–3.6) were associated with higher odds of death. Opioid abuse (OR, 0.4; 95% CI, 0.2–0.6) was associated with a lower risk of death (Supplement Table S1).

In the age- and race/ethnicity-adjusted multivariate regression model, female sex (OR, 1.9; 95% CI, 1.2–3.0), transfer from another inpatient facility (OR, 1.8; 95% CI, 1.1–2.8), underlying aortic valve pathology (OR, 2.7; 95% CI, 1.5–4.9), HD (OR, 2.1; 95% CI, 1.1–4.0), CVD (OR, 2.2; 95% CI, 1.2–3.8), acute and subacute liver failure (OR, 9.2; 95% CI, 4.8–17.7), neutropenia (OR, 2.5; 95% CI, 1.3–4.8), and alcohol abuse (OR, 2.9; 95% CI, 1.3–6.7) were significantly associated with higher odds of in-hospital death, whereas opioid abuse was associated with reduced odds of inpatient mortality (OR, 0.5; 95% CI, 0.2–0.9) (Table 3).

Antifungal Therapy

Medication administration data were available for 604 of 703 (85.9%) patients in the study cohort. Of these 604 patients, 591 (97.8%) received antifungal therapy during their index encounter. Most patients received an echinocandin (488 patients, 80.8%), and, of these, micafungin was the most commonly used (375 patients, 62.1%). Fluconazole was the most frequently administered agent (376 patients, 62.3%) (Table 4). Of 604 patients with available medication administration data, 424 (70.2%) received more than 1 antifungal agent during their index encounter; among these subjects, 173 (28.6%) received both an echinocandin and fluconazole.

We performed univariate and multivariate analyses to determine whether the selection of antifungal agent was associated with in-hospital mortality among patients with available medication administration data. In an age-, sex-, and race-adjusted multivariate analysis, fluconazole therapy was independently associated with a lower odds of in-hospital death (OR, 0.5; 95% CI, 0.3–0.8) (Supplement Tables S2 and S3).

DISCUSSION

In this study, we used administrative data from the Vizient clinical database to assemble a large cohort of CIE patients discharged from hospitals between 2015 and 2019, perhaps the largest reported in the literature to date. We found that inpatient mortality was 16.2% in a cohort of 703 patients with CIE. Opioid abuse and hepatitis C infection were common in patients with CIE, and mortality was most strongly associated with acute and subacute liver failure.

Two prospective observational cohort studies reported in-hospital mortality among patients with CIE higher than we observed. The first used data from the ICE-PCS and ICE-Plus databases and found that among 70 patients with CIE, in-hospital mortality was 36% [1].

The MYCENDO study reported on 30 CIE cases from 20 French hospitals and found mortality of 37% during the first hospitalization [3]. Although the demographics and comorbidities of patients from these studies were similar to those of patients in our cohort, the ICE-PCS/ICE-Plus and MYCENDO databases were largely or, in the case of MYCENDO, entirely composed of cases outside of the United States. Furthermore, the ICE-PCS/ICE-Plus and MYCENDO cohorts were assembled from 2000 to 2010 and 2005 to 2007, respectively. Our US

Table 3. Age-, Sex-, and Race-Adjusted Multivariable Logistic Regression for Predictors of In-Hospital Mortality Among Patients With *Candida* Infective Endocarditis

Characteristic	Odds Ratio	95% Confidence Interval	*P* Value
Age			
<18 years	Reference		
18–30 years	0.5	(0.1–2.0)	.327
31–50 years	0.4	(0.1–1.7)	.226
51–64 years	0.6	(0.2–2.3)	.461
65+ years	0.9	(0.2–3.4)	.848
Sex			
Male	Reference		
Female	1.9	(1.2–3.0)	.010
Race/Ethnicity			
Non-Hispanic white	Reference		
Non-Hispanic black	1.1	(0.5–2.1)	.847
Non-Hispanic other	1.1	(0.6–2.1)	.803
Hispanic	0.9	(0.3–2.6)	.915
Unknown	1.6	(0.6–4.6)	.337
Opioid Abuse	0.5	(0.2–0.9)	.024
Inpatient Medical Facility Origin	1.8	(1.1–2.8)	.018
Underlying Aortic Valve Pathology	2.7	(1.5–4.9)	.001
Hemodialysis	2.1	(1.1–4.0)	.033
Chronic Heart Failure	1.6	(1.0–2.6)	.069
Cerebrovascular Disease	2.2	(1.2–3.8)	.007
Acute and Subacute Liver Failure	9.2	(4.8–17.7)	<.001
Neutropenia/Pancytopenia	2.5	(1.3–4.8)	.005
Alcohol Abuse	2.9	(1.3–6.7)	.013

cohort is composed of patients admitted to a hospital more recently, between October 2015 and April 2019. These are important considerations because geographical or temporal changes in patient or disease characteristics and management may have impacted mortality. Unlike the present study, each of these prospective studies required fulfillment of specific diagnostic criteria—Duke Criteria in the case of the ICE-PCS/ICE-Plus and a similar combination of clinical and laboratory criteria in MYCENDO—for entry into the study database. In clinical practice, patients may be diagnosed with and treated for CIE, despite lack of a definitive diagnosis based on a clinical scoring system. Although fulfillment of such criteria may minimize misclassification of candidemic patients as having CIE, there is likely a population of patients treated for CIE that are excluded from these cohorts.

Table 4. Antifungal Therapy Used During Index Encounter of 604 Patients With *Candida* Infective Endocarditis Who Had Available Medication Administration Data

Available Medication Administration Data	N = 604
Received Antifungal Therapy	591 (97.8%)
Amphotericin	213 (35.3%)
Amphotericin B (Fungizone)	28 (4.6%)
Amphotericin B lipid complex (ABELCET)	27 (4.5%)
Amphotericin B liposome (AmBisome)	165 (27.3%)
Echinocandin	488 (80.8%)
Anidulafungin	30 (5.0%)
Caspofungin	86 (14.2%)
Micafungin	375 (62.1%)
Fluconazole	376 (62.3%)
Flucytozine	111 (18.4%)
Posaconazole	<10 (<1.7%)
Voriconazole	53 (8.8%)
Isavuconazole	<10 (<1.7%)

NOTE: Subjects may have received >1 drug. Some patients received more than 1 antifungal agent.

The population of patients with CIE seems to differ in important ways from the population traditionally thought of as at risk for candidemia. Although diabetes, CKD, chronic HF, hepatitis C infection, and opioid abuse occurred at high frequency in our population, lower proportions of patients had been diagnosed with hematologic malignancies, had received total parenteral nutrition (TPN), or had been treated with steroids. A recent retrospective cohort study evaluating risk factors for CIE among patients with candidemia showed a similar pattern. Although valvular heart disease was associated with a higher odds of CIE (OR, 7.66; 95% CI, 3.0–19.8), both hematologic malignancy and receipt of TPN were associated with a lower odds of CIE [8].

In our cohort, 22.5% of patients underwent a valvular intervention during their index encounter. The ICE-PCS/ICE-Plus study reports that 46% of patients underwent a valve procedure; however, it is not clear whether all of these interventions were all performed during their first admission for CIE. Our results are similar to the MYCENDO study that found that although

43% of patients ultimately underwent a valve intervention, 27% underwent surgery within 3 weeks of diagnosis.

On the multivariate regression analysis, acute and subacute liver failure was associated with the highest odds of inpatient mortality (OR, 9.2; 95% CI, 4.8–17.7). A link between acute liver failure and impaired monocyte function has been proposed, with a deficient cellular and humoral immune response resulting in immunoparesis, recurrent infection, and refractory multiple organ dysfunction [14]. It is possible that immune defects precipitated by acute liver failure resulted in worse clinical outcomes in our cohort.

Alcohol use was independently associated with an increased odds of death. Because we were unable to ascertain the cause of acute liver failure from the ICD-10 code, it is possible that this served as a mediator in the relationship between alcohol abuse and inpatient mortality. Although there was a marginal association between acute liver failure and alcohol abuse ($P = .052$), there was no evidence of confounding or effect modification between these 2 variables. Nevertheless, subclinical alcohol-related hepatic dysfunction may have resulted in unfavorable clinical outcomes in these patients.

We were unable to obtain *Candida* species data in our cohort. Infection with more resistant non-*albicans Candida* isolates may result in increased mortality [15]. Some of the significant risk factors for death in our analysis may reflect differential risk of infection by non-*albicans Candida* species. Neutropenia itself has been associated with higher incidence of non-*albicans Candida* infection, and these patients may have higher burdens of antifungal exposure that is also associated with infection by these species [16, 17]. Indwelling vascular catheters have been associated with non-*albicans* candidemia, which may explain the higher mortality among HD patients [16]. A prior study also demonstrated that a *C albicans* General-Purpose Genotype was more prevalent among females, and it was associated with higher mortality in patients ≤48 years of age [18]. It is possible that the risk association between female sex and mortality was confounded by differential risk of infection by more virulent *C albicans* genotypes.

Patients with CVD had a higher odds of death. It is possible that this variable is a surrogate marker for diminished functional status, which itself may predispose to poor clinical outcomes, or it may identify a population at elevated risk for antifungal and central line exposure, and thus infection with non-*albicans Candida* infection.

We found that transfer from an inpatient facility was associated with a higher odds of death. This may represent a subpopulation of patients with more severe disease transferred for more advanced care. Indeed, of 343 patients transferred from another inpatient facility, 254 (74%) had an "extreme" SOI score at admission.

Finally, underlying aortic valve pathology was associated with higher odds of inpatient mortality. Some studies have suggested higher mortality among patients undergoing surgical management for left-sided endocarditis compared with right-sided endocarditis [19]. More data regarding complications of endocarditis in our cohort and prevalence of native versus prosthetic valve infection are needed to better understand this risk factor.

It was surprising to find that a diagnosis of opioid abuse was associated with lower odds of inpatient mortality. We hypothesized that opioid abusers may be younger with fewer comorbidities, which may explain their favorable clinical outcomes. However, we did not find there was significant interaction between opioid abuse and age. We cannot rule out that there may have been an interaction or confounding between opioid abuse and some characteristic not included among the variables we considered in our analysis.

We found that echinocandins and fluconazole were the most frequently prescribed antifungal agents, reflecting guideline-recommended antifungal therapy [9]. In many cases, patients received both agents during the course of their index encounter.

We found a significantly lower odds of in-hospital death among patients who received fluconazole. However, death during the initial hospitalization for CIE may not be an appropriate endpoint for comparing the effectiveness of antifungal agents. Furthermore, it is difficult to interpret this result in the absence of species or susceptibility data.

Our study had several limitations. This was a retrospective examination of administrative data, and our results may have been affected by unmeasured confounding. Our cohort was identified using the ICD-10 code B37.6 (Candidal Endocarditis), which has not been validated in a study comparing the code to "gold standard" clinical diagnostic criteria. Because the performance characteristics of this diagnostic code are unknown, it is possible that our results were influenced by misclassification bias. We were not able to report which *Candida* species caused infections in our cohort or to report the antifungal susceptibilities of causative *Candida* isolates. Therefore, we could not determine the appropriateness of the choice of antifungal therapy. Our study used ICD-10 codes to evaluate patient characteristics. Our ability to evaluate potentially important risk factors for inpatient mortality among patients with CIE was limited by detail provided in these codes. For example, we could not evaluate valve type (native vs prosthetic) as a risk factor for inpatient morality because the B37.6 ICD-10 code does not make this distinction. We were also unable to evaluate many complications of CIE as the risk factors for death because we could not infer from the diagnostic codes that a particular complication was related to infection. Finally, our study does not include follow-up after the index encounter discharge, which may have resulted in an underestimation of mortality related to CIE.

CONCLUSIONS

In this study, we reported on the clinical characteristics of a large cohort of patients with CIE. We found that these patients often had many comorbid conditions. More importantly, many of these patients had a history of opioid abuse, which highlights a population in which clinicians must maintain a high index of suspicion for CIE. We performed a multivariate analysis and found that acute and subacute liver failure was the strongest predictor of inpatient mortality. Further study is needed to elaborate on this association.

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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