Published in final edited form as:

Mycoses. 2019 July ; 62(7): 554–561. doi:10.1111/myc.12917.

Creation and Assessment of a Clinical Predictive Model for Candidemia in Patients with Candiduria

Katie Wang^a, Kevin Hsueh^b, Ryan Kronen^{b,c}, Charlotte Lin^b, Ana S. Salazar^b, William G. Powderly^b, and Andrej Spec^b

^aSaint Louis University School of Medicine, Saint Louis, MO

^bDivision of Infectious Diseases, Department of Medicine, Washington University School of Medicine, Saint Louis, MO

^cDepartment of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

Abstract

Background—Candidemia is the most common clinical presentation of invasive candidiasis and is a major cause of morbidity and mortality. Candiduria is a predictor for candidemia; however, patient characteristics that are associated with concurrent candidemia in the setting of candiduria are unclear. Identifying these characteristics could aid in the early detection of systemic disease.

Methods—We performed a retrospective cohort analysis of hospitalized patients with candiduria at our institution over a 13-year period. Our evaluation of patient characteristics included demographics, comorbidities, medications, procedures, devices, vital signs, and laboratory values. We developed a multivariable logistic model to identify factors associated with candidemia in patients with candiduria.

Results—We identified 4,240 patients with candiduria, 263 (6.2%) of whom had candidemia. Predictors for increased risk of candidemia with candiduria included hospitalizations greater than 12 days, central venous catheter, parenteral nutrition, hematological and gynecological malignancy, and receipt of β -lactam/ β -lactamase inhibitors. Vital signs and laboratory values associated with candidemia included elevated heart rate, temperature, and creatinine, along with neutropenia and neutrophilia. Factors that demonstrated a decreased risk of candidemia included diabetes mellitus, gastrostomy, and urinary catheter with antibiotic use. The c-statistic was 0.741 (95% CI, 0.710 – 0.772).

Conclusion—We identified a set of clinical characteristics that can predict the presence of candidemia with candiduria.

Corresponding Author Andrej Spec, MD, MSCI, Assistant Professor, Infectious Disease, Associate Director, Infectious Disease Clinical, Research Unit, 4523 Clayton Ave., Campus Box 8051, St Louis, MO, 63110-0193, T: 314.747.1725, F: 314.454.8294, andrespec@wustl.edu. **Alternate Corresponding Author** Katie Wang, BS, Saint Louis University School of Medicine in St. Louis, 1402 South Grand Blvd., St Louis, MO, 63104-1004, T: 608.354.9390, katie.wang@health.slu.edu.
Author Contributions: AS, KW, KH, and WGP conceived the ideas; ASS, RK, and CL collected the data; AS, KW, and KH analyzed the data, AS and KW led the writing, KH, RK, CL, ASS, and WGP contributed significantly to the writing.

Conflict of Interest: WGP has received research support from Merck & Co. and serve on the advisory board for Merck & Co. and Gilead Sciences. AS has received research support from Astellas, Scynexis, Cidera, MeraVista and Mayne and consulting fees from Mayne, Scynexis, Astellas, Viamet and Minnetronix. ASS, CL, KH, KW, and RK declare that they have no relevant conflict of interest.

Keywords

Candida spp; candidemia; systemic infection; colonization; risk factors; protective factors; candiduria; clinical prediction model

Introduction

Candiduria is a frequent finding amongst hospitalized patients with a global incidence rate of 27.4 per 1, 000 patient admissions^{1, 2}. The presence of yeast in the urine commonly represents benign colonization of the urinary tract or perineum, but can also be a sentinel of a hematogenous infection^{3–5}. Candidemia, the most common form of invasive candidiasis, is associated with an attributable mortality rate of 38–49% and is responsible for prolonged hospital stays and high healthcare expenditure^{6–9}.

Colonization with *Candida* is an independent risk factor for nosocomial candidemia^{8, 10–12}. Researchers have constructed clinical prediction tools to assess *Candida* colonization and identify patients at risk for invasive disease, with the *Candida* colonization index (CI) being one of the most widely studied^{11, 13}. Later studies found candiduria to correlate to a CI 0.5, the threshold value that places patients at higher risk for infection versus colonization^{11, 14}. Yet, the decision to initiate or forgo treatment when *Candida* species is detected in the urine remains controversial³. In most patients, candiduria is not a precipitant of candidemia, but multivariate analyses have confirmed it to be a risk factor for invasive disease^{4, 5, 15}. Clinical characteristics that are associated with candidemia in the setting of established candiduria have not been fully explored^{5, 15}. Identification of these patient characteristics would help clinicians to differentiate patients with candiduria from those with concomitant disease and to determine an appropriate treatment course.

To accomplish this goal, we performed a retrospective cohort analysis of patients with candiduria over a 13-year period. Our goal was to identify relevant patient comorbidities that could accurately predict the presence of candidemia in the setting of candiduria.

Methods

Cohort Construction

We collected data from patients admitted between January 2002 and January 2015 to Barnes Jewish Hospital, a 1,323-bed tertiary care hospital in St. Louis, MO. We confirm that the ethical policies of the journal have been adhered to and that the Washington University in St. Louis Institutional Review Board approved the study with a waiver of consent. All hospitalized patients with candiduria, defined as the presence of candida or yeast in at least one urine culture, were included in the study. Patients with urine cultures positive for non-*candida* yeast were removed from the study.

Data extracted from medical records included *Candida* species, duration of hospitalization, demographics, vital signs, in-hospital procedures and surgeries, cancer, laboratory values (absolute neutrophils, absolute lymphocytes, white blood cells, alanine aminotransferase, aspartate aminotransferase, amylase, lipase, total and direct bilirubin, creatinine, platelets,

hemoglobin) and medications ordered within 90 days leading up to a positive urine culture. We defined the heart rate and temperature as the maximum heart rate 48 hours prior to or 24 hours after a positive urine culture was collected, along with the maximum temperature 24 hours prior to or after a positive urine culture, respectively. We defined neutropenia as an absolute neutrophil count (ANC) less than 1,500/mm³ and neutrophilia as an ANC greater than 9,500/mm³ based on our institution's upper threshold value¹⁶.

We defined comorbidities based on ICD-9 codes and included Elixhauser comorbidities along with diabetes, organ transplants, and cancers as previously defined¹⁷. Additional factors evaluated for predisposition of candidemia included recent use of central venous catheter (CVC), recent use of ventilator, recent total parenteral nutrition (TPN), receipt of hemodialysis, HIV infection, burns, radiation therapy and chemotherapy. We combined urinary catheter and recent antibiotic use into one variable to evaluate for their synergistic effect on the development of candidemia. We categorized continuous variables and combined different levels within a variable to better model the underlying distribution.

Outcomes

We used the presence of candidemia as the primary outcome in both univariable and multivariable analyses. Candidemia was defined as having at least one positive blood culture for *Candida* drawn from any venous or arterial access site 48 hours prior to or after a positive urine culture. For patients with multiple episodes of candiduria or candidemia, only the first episode was incorporated in the database.

Statistical Analysis

We performed statistical analysis using SPSS V23 (IBM, Armonk, NY) and all tests were two-tailed with $p < 0.05$ considered significant. For descriptive statistics, we used Chi-square or Fisher's exact tests for categorical variables and Mann-Whitney U tests for continuous variables as the data were not normally distributed.

We performed univariable analysis to assess the risk of concomitant candiduria and candidemia in association with patient demographic and clinical characteristics. Criteria for evaluation in multivariable analysis included variables with $p < 0.2$, and those with strong plausibility in previous literature, including but not limited to renal failure, solid malignancies, and bone marrow transplant^{18–20}. 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 ($p < 0.05$). After all relevant variables were included, those that were no longer found to be significant were sequentially removed from the model.

We then generated a c-statistic and receiver operating characteristic (ROC) curve using the final set of predictor variables.

Results

Demographics

During the study period, 4,878 hospitalized patients were diagnosed with candiduria. We excluded 638 cases from analysis due to incomplete data collection. Of the remaining 4,240 cases, 263 (6.2%) of them were positive for concurrent candidemia. A total of 3,698 (92.9%) of the 3,977 patients with candiduria alone had blood cultures drawn within 48 hours prior to or after a positive urine culture.

Demographic characteristics and relevant factors associated with concomitant candiduria and candidemia are outlined in Table 1 and Supplementary Table 1. Age and race were not associated with differences in the rate of candidemia among the study population. Female gender was associated with a lower risk of candidemia with candiduria compared to male gender (4.6% vs 8.0%; $p < 0.001$).

Univariable Logistic Regression

In univariable logistic regression analyses, we found 71 variables to be predictors of candidemia in the setting of candiduria (Supplementary Table 1). Candidemia was more prevalent in patients with candiduria caused by non-*albicans* species (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.2–3.1; $p = 0.007$). Concomitant candidemia was also more likely to be diagnosed in patients with a hospital stay greater than 12 days (OR 2.1, 95% CI, 1.7–2.7; $p < 0.001$), a CVC (OR, 2.0; 95% CI, 1.6–2.6; $p < 0.001$), receipt of TPN (OR, 1.5; 95% CI, 1.2–2.0; $p = 0.002$), hematological malignancy (OR, 2.4; 95% CI, 1.6–3.5; $p < 0.001$), and prior antibiotic use (OR, 1.7; 95% CI, 1.3–2.4; $p = 0.002$). On evaluation of vital signs and laboratory values, candidemia was more prevalent among patients with an elevated heart rate (OR, 2.5; 95% CI, 1.9–3.1; $p < 0.001$), temperature (OR, 2.4; 95% CI, 1.8–3.0; $p < 0.001$) and creatinine (OR, 1.6; 95% CI, 1.2–2.0; $p < 0.001$), and a lower hemoglobin level (OR, 2.6; 95% CI, 1.9–3.5; $p < 0.001$).

Gastrostomy dependency (OR, 0.4; 95% CI, 0.2–1.0; $p = 0.045$) and diabetes (OR, 0.7; 95% CI, 0.5–0.9; $p = 0.004$), and hypertension (OR 0.6; 95% CI, 0.5–0.8; $p < 0.001$) were associated with a lower risk for candidemia.

Clinical Predictive Model

The multivariable logistic regression model consisted of 15 variables (Table 2). Eleven variables demonstrated an increased risk for candidemia, including hospital stay greater than 12 days (OR 1.4, 95% CI, 1.04–1.8; $p = 0.027$), presence of a CVC (OR, 1.8; 95% CI, 1.4–2.4; $p < 0.001$), receipt of TPN (OR, 1.5; 95% CI, 1.1–2.0; $p = 0.005$), hematological malignancy (OR, 2.1; 95% CI, 1.4–3.2; $p < 0.001$), and gynecologic malignancy (OR, 1.7; 95% CI, 1.03–2.9; $p = 0.037$). Vital signs and laboratory values included elevated heart rate (OR, 1.9; 95% CI, 1.4–2.4; $p < 0.001$), temperature (OR, 1.8; 95% CI, 1.3–2.3; $p < 0.001$) and creatinine (OR, 1.8; 95% CI, 1.4–2.3; $p < 0.001$), along with neutropenia (OR, 1.8; 95% CI, 1.1–3.1; $p = 0.021$) and neutrophilia (OR, 1.6; 95% CI, 1.2–2.1; $p = 0.003$). The only medication that remained significant in the final model was prior β -lactam/ β -lactamase inhibitor use (OR, 1.6; 95% CI, 1.2–2.2; $p = 0.002$).

Variables associated with a decreased risk for candidemia in the final model included female gender (OR, 0.5; 95% CI 0.4–0.7; $p < 0.001$), gastrostomy dependency (OR, 0.4; 95% CI, 0.2–0.9; $p = 0.035$), diabetes (OR, 0.6; 95% CI, 0.5–0.9; $p = 0.006$), and urinary catheter with prior antibiotic use (OR, 0.5; 95% CI, 0.3–0.97; $p = 0.039$). The c-statistic for this model was 0.741 (95% CI, 0.710 – 0.772) (Figure 1).

Discussion

Although *Candida* species in the urine rarely disseminates into the bloodstream, candiduria has a positive association with candidemia⁴. Prior investigations on the risk factors for candidemia generally focus on patients in the intensive care units or as a comparison between *C. albicans* versus non-*albicans* species infection^{9, 12, 21, 22}. To the best of our knowledge, this is the first study to assess potential patient factors that influence the risk of concurrent candidemia with candiduria.

While candiduria is highly prevalent in hospitalized patients, the presence of concomitant candidemia is infrequently encountered^{1, 4}. Our study revealed that out of the 4,240 patients with candiduria, only 263 cases (6.2%) had concomitant candidemia. This aligns with current epidemiological studies, which calculate the incidence of candidemia in the presence of candiduria to be 1.3–10%^{23, 24}.

Our multivariable analysis demonstrated a decreased risk of candidemia in the setting of candiduria with female gender. Candiduria by itself is typically more prevalent in the female population because of a shorter urethra and a high likelihood (10–65%) of vulvovestibular colonization with *Candida*^{4, 25}. Accordingly, women with candiduria in our study outnumbered the men (63.9% vs 36.1%).

Hospital stay greater than 12 days was an independent risk factor for concomitant candidemia with candiduria. Medical interventions that invariably accompany an extended hospital course, including but not limited to exposure to antibiotics and invasive therapies, are likely driving this association rather than the length of stay itself.

Although not a variable studied before in candidemia risk assessments, our analysis identified gastrostomy to be associated with less risk for concomitant candidemia and candiduria. This could be related to the fact that those patients with a gastrostomy would likely be receiving TPN if they were without a gastrostomy tube. This finding is novel and would benefit from further study.

Other investigators have suggested both hematologic malignancies and solid tumors to be predictors of candidemia, which is consistent with our findings in candiduric patients^{19, 26}. Specifically, we found gynecologic malignancies to be the class of solid tumors associated with candidemia in the setting of candiduria. Current literature reports that candidemia in patients with solid tumors is more likely to occur in the setting of recent surgery¹⁹. Multiple studies are in consensus that abdominal surgery is the main factor driving this association due to *Candida* colonization and translocation from the gastrointestinal tract^{10, 27}. In contrast, there is limited research available regarding gynecologic surgeries in relation to *Candida* infections. Furthermore, epidemiological evidence suggests that vaginal

colonization by *Candida* can be found in up to 20–30% of women²⁸, and surgical manipulation of the vaginal tract may disrupt the balance between host colonization and infection, subsequently allowing *Candida* to gain entry into the bloodstream.

On analysis of laboratory values, we found elevated creatinine level to be independently associated with candiduria with concomitant candidemia. While few authors have investigated the relationship between creatinine level and candidemia, kidney dysfunction is a commonly recognized variable in *Candida* studies. Previous literature found an increased risk for candidemia in the setting of chronic renal failure (OR 4.48 –11.5), although one study was unable to adjust for other variables due to a limited sample size^{20, 29}. One cohort analysis of SICU patients suggested acute renal failure to be a risk factor for the onset of candidemia (RR 4.2)³⁰. Chronic kidney disease failed to demonstrate significance in our univariable analysis, suggesting that the elevated creatinine is more likely to represent acute renal failure.

Our multivariable analysis determined both neutropenia and neutrophilia to be clinical predictors of candiduria with candidemia. Retrospective analyses found that neutropenia was present in 8–11.6% of patients diagnosed with candidemia^{31, 32}. In comparison, neutropenia was present in 8.7% of our patient population. While neutrophils are important for early clearance of infection, prolonged neutrophilia may be associated with a high fungal burden and be indicative of an uncontrolled systemic infection.

Additional indicators of systemic infection, including elevated heart rate and temperature, were also clinical predictors of candidemia in our study. Aberrations in either white cell count, heart rate, or temperature may suggest a clinical picture consistent with a systemic inflammatory host response³³. A retrospective cohort study evaluated the inflammatory response of 60 patients with candidemia and found that greater than 90% of patients fulfilled the Systemic Inflammatory Response Syndrome (SIRS) criteria on the day of the first positive blood culture³⁴.

In regards to antibiotics, we found β -lactam/ β -lactamase inhibitors to be significantly associated with elevated rates of candidemia in candiduric patients. Antibiotics can selectively alter intestinal microbial flora in such a way that facilitates the growth and dissemination of *Candida* species³⁵. Multiple investigations have illustrated this link between antibiotics and candidemia, yet there is a paucity of studies further delineating the class of antibiotics responsible for this association^{9, 20, 35}. The limited research available also show conflicting results; some studies showed that exposure to vancomycin and piperacillin-tazobactam was associated with *C. glabrata* or *C. krusei* candidemia yet another study found the same antibiotics to be noncontributory^{17, 36, 37}. In one study, antibiotics with anaerobic activity appeared to predispose to candidemia; however, *C. glabrata* accounted for the majority of the sample and the results may not apply to *Candida* species as a group³⁸.

Neither urinary catheter or prior antibiotic exposure contributed significantly to our model, but when combined together demonstrated a decreased risk of candidemia in candiduric patients. This finding is likely because they increase urinary colonization synergistically. Urinary catheterization provides a direct portal of entry into the bladder, allowing microbes to

establish infection either via an extraluminal or intraluminal pathway^{25, 39}. While β -lactam/ β -lactamase inhibitor use is associated with an increased risk for candidemia likely by its influence on the intestinal microbial flora, prior antibiotic exposure altogether may have a greater effect on the lower genital tract, altering the microbiome and increasing *Candida* colonization²⁵. This factor combined with urinary catheter confers additional risk for candiduria, which translates to a decreased risk for candidemia in our final model.

Our study has several limitations. First, we used a retrospective design which allowed us to analyze a large patient sample over a broad time period, but also has inherent weaknesses and predisposes to several types of information bias and selection bias. The ICD-9 codes used to construct the database may not reflect true diagnoses, contributing to misclassification bias. Our study was also restricted to a single institution with discrepancies that may exist between our patient population and the general population.

In conclusion, we found a set of clinical comorbidities that can predict the presence of candidemia with concomitant candiduria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank Cherie Hill and Dorothy Sinclair for their contribution to the patient database.

Funding

This study was funded by Astellas Pharma Global Development, Inc., through an investigator sponsored grant (MYCA-15L03). Astellas Pharma Global Development, Inc., was not involved in study design, implementation, data analysis, manuscript drafting, or the final approval for publication. This was the sole responsibility of the authors. In addition, research reported in this publication was supported by the Washington University Institute of Clinical and Translational Sciences grant UL1TR002345 from the National Center for Advancing Translational Sciences (NCATS) and the National Cancer Institute grant T32CA190194 of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH or Astellas Pharma Inc.

References

1. Drogari-Apiranthitou M, Anyfantis I, Galani I, et al. Association Between Candiduria and Candidemia: A Clinical and Molecular Analysis of Cases. *Mycopathologia*. 2017.
2. Bougnoux ME, Kac G, Aegerter P, et al. Candidemia and candiduria in critically ill patients admitted to intensive care units in France: incidence, molecular diversity, management and outcome. *Intensive Care Med*. 2008;34(2):292–299. [PubMed: 17909746]
3. Alfouzan WA, Dhar R. Candiduria: Evidence-based approach to management, are we there yet? *J Mycol Med*. 2017.
4. Kauffman CA. Candiduria. *Clin Infect Dis*. 2005;41 Suppl 6:S371–376. [PubMed: 16108001]
5. Binelli CA, Moretti ML, Assis RS, et al. Investigation of the possible association between nosocomial candiduria and candidaemia. *Clin Microbiol Infect*. 2006;12(6):538–543. [PubMed: 16700702]
6. Antinori S, Milazzo L, Sollima S, et al. Candidemia and invasive candidiasis in adults: A narrative review. *Eur J Intern Med*. 2016;34:21–28. [PubMed: 27394927]
7. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis*. 2003;37(9):1172–1177. [PubMed: 14557960]

8. Wey SB, Mori M, Pfaller MA, et al. Hospital-acquired candidemia. The attributable mortality and excess length of stay. *Arch Intern Med.* 1988;148(12):2642–2645. [PubMed: 3196127]
9. Ding X, Yan D, Sun W, et al. Epidemiology and risk factors for nosocomial *Non-Candida albicans* candidemia in adult patients at a tertiary care hospital in North China. *Med Mycol.* 2015;53(7):684–690. [PubMed: 26229153]
10. Eggimann P, Pittet D. *Candida* colonization index and subsequent infection in critically ill surgical patients: 20 years later. *Intensive Care Med.* 2014;40(10):1429–1448. [PubMed: 24934813]
11. Pittet D, Monod M, Suter PM, et al. *Candida* colonization and subsequent infections in critically ill surgical patients. *Ann Surg.* 1994;220(6):751–758. [PubMed: 7986142]
12. Jorda-Marcos R, Alvarez-Lerma F, Jurado M, et al. Risk factors for candidaemia in critically ill patients: a prospective surveillance study. *Mycoses.* 2007;50(4):302–310. [PubMed: 17576324]
13. Toya SP, Schraufnagel DE, Tzelepis GE. Candiduria in intensive care units: association with heavy colonization and candidaemia. *J Hosp Infect.* 2007;66(3):201–206. [PubMed: 17573156]
14. Sellami A, Sellami H, Makni F, et al. [Candiduria in intensive care unit: significance and value of yeast numeration in urine]. *Ann Fr Anesth Reanim.* 2006;25(6):584–588. [PubMed: 16626924]
15. Bross J, Talbot GH, Maislin G, et al. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. *Am J Med.* 1989;87(6):614–620. [PubMed: 2589396]
16. Boxer LA. How to approach neutropenia. *Hematology Am Soc Hematol Educ Program.* 2012;2012:174–182. [PubMed: 23233578]
17. Kronen R, Hsueh K, Lin C, et al. Creation and Assessment of a Clinical Predictive Calculator and Mortality Associated With *Candida krusei* Bloodstream Infections. *Open Forum Infect Dis.* 2018;5(2):ofx253. [PubMed: 29450209]
18. Yapar N Epidemiology and risk factors for invasive candidiasis. *Ther Clin Risk Manag.* 2014;10:95–105. [PubMed: 24611015]
19. Bergamasco MD, Garnica M, Colombo AL, et al. Epidemiology of candidemia in patients with hematologic malignancies and solid tumours in Brazil. *Mycoses.* 2013;56(3):256–263. [PubMed: 23043234]
20. Barberino MG, Silva N, Reboucas C, et al. Evaluation of blood stream infections by *Candida* in three tertiary hospitals in Salvador, Brazil: a case-control study. *Braz J Infect Dis.* 2006;10(1):36–40. [PubMed: 16767314]
21. Alvarez-Lerma F, Nolla-Salas J, Leon C, et al. Candiduria in critically ill patients admitted to intensive care medical units. *Intensive Care Med.* 2003;29(7):1069–1076. [PubMed: 12756441]
22. Serefhanoglu K, Timurkaynak F, Can F, et al. Risk factors for candidemia with non-albicans *Candida* spp. in intensive care unit patients with end-stage renal disease on chronic hemodialysis. *J Formos Med Assoc.* 2012;111(6):325–332. [PubMed: 22748623]
23. Storfer SP, Medoff G, Fraser VJ, et al. Candiduria - Retrospective Review in Hospitalized-Patients. *Infect Dis Clin Pract.* 1994;3(1):23–29.
24. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis.* 2000;30(1):14–18. [PubMed: 10619726]
25. Lundstrom T, Sobel J. Nosocomial candiduria: a review. *Clin Infect Dis.* 2001;32(11):1602–1607. [PubMed: 11340532]
26. Ortega M, Marco F, Soriano A, et al. *Candida* species bloodstream infection: epidemiology and outcome in a single institution from 1991 to 2008. *J Hosp Infect.* 2011;77(2):157–161. [PubMed: 21216030]
27. Mikamo Hiroshige KK, Sato Yasumasa, Izumi Koji, Tamaya Teruhiko. Pelvic Abscess and Fungemia Caused by *Candida glabrata*. *Journal of Infection and Chemotherapy.* 1996(2):294–296. [PubMed: 29681385]
28. Achkar JM, Fries BC. *Candida* infections of the genitourinary tract. *Clin Microbiol Rev.* 2010;23(2):253–273. [PubMed: 20375352]
29. Bassetti M, Trecarichi EM, Righi E, et al. Incidence, risk factors, and predictors of outcome of candidemia. Survey in 2 Italian university hospitals. *Diagn Microbiol Infect Dis.* 2007;58(3):325–331. [PubMed: 17350205]

30. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. *The National Epidemiology of Mycosis Survey*. *Clin Infect Dis*. 2001;33(2):177–186. [PubMed: 11418877]
31. Teo JQ, Candra SR, Lee SJ, et al. Candidemia in a major regional tertiary referral hospital - epidemiology, practice patterns and outcomes. *Antimicrob Resist Infect Control*. 2017;6:27. [PubMed: 28293420]
32. Yang ZT, Wu L, Liu XY, et al. Epidemiology, species distribution and outcome of nosocomial *Candida* spp. bloodstream infection in Shanghai. *BMC Infect Dis*. 2014;14:241. [PubMed: 24886130]
33. Balk RA. Systemic inflammatory response syndrome (SIRS): where did it come from and is it still relevant today? *Virulence*. 2014;5(1):20–26. [PubMed: 24280933]
34. Wisplinghoff H, Seifert H, Wenzel RP, et al. Inflammatory response and clinical course of adult patients with nosocomial bloodstream infections caused by *Candida* spp. *Clin Microbiol Infect*. 2006;12(2):170–177. [PubMed: 16441456]
35. Ben-Ami R, Olshtain-Pops K, Krieger M, et al. Antibiotic exposure as a risk factor for fluconazole-resistant *Candida* bloodstream infection. *Antimicrob Agents Chemother*. 2012;56(5):2518–2523. [PubMed: 22314534]
36. Lin MY, Carmeli Y, Zumsteg J, et al. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and *Candida krusei* fungemia: a case-case-control study. *Antimicrob Agents Chemother*. 2005;49(11):4555–4560. [PubMed: 16251295]
37. Chow JK, Golan Y, Ruthazer R, et al. Factors associated with candidemia caused by non-albicans *Candida* species versus *Candida albicans* in the intensive care unit. *Clin Infect Dis*. 2008;46(8):1206–1213. [PubMed: 18444857]
38. Lee I, Fishman NO, Zaoutis TE, et al. Risk factors for fluconazole-resistant *Candida glabrata* bloodstream infections. *Arch Intern Med*. 2009;169(4):379–383. [PubMed: 19237722]
39. Padawer D, Pastukh N, Nitzan O, et al. Catheter-associated candiduria: Risk factors, medical interventions, and antifungal susceptibility. *Am J Infect Control*. 2015;43(7):e19–22. [PubMed: 25920705]

Figure 1. Receiver operating characteristic (ROC) curve for the multiple logistic regression predicting concurrent candidemia and candiduria. The c-statistic is 0.741 (95% CI 0.710 – 0.772).

Table 1.

Select Baseline Characteristics of 4,240 Candiduric Patients by Presence of Candidemia, 2002–2015

Characteristic ^a	Candidemia (N=263)	No Candidemia (N=3,977)	p-value ^b	Total (N=4,240)
Demographics				
Age, median (IQR)	64 (23)	64 (24)	0.486	64 (24)
Female sex	132 (50.2)	2,608 (65.6)	<0.001	2,740 (64.6)
Race			0.073	
White	167 (63.5)	2,732 (68.7)		2,899 (68.4)
African American	83 (31.6)	1,054 (26.5)	0.073	1,137 (26.8)
Other	13 (4.9)	191 (4.8)		204 (4.8)
Comorbidities				
Hypertension	111 (42.2)	2,387 (60.0)	<0.001	2,498 (58.9)
Diabetes	67 (25.5)	1,460 (36.7)	0.004	1,527 (36.0)
Coronary artery disease	70 (26.6)	1,185 (29.8)	0.668	1,255 (29.6)
Chronic liver disease	30 (11.4)	404 (10.2)	0.310	434 (10.2)
Chronic kidney disease	57 (21.7)	921 (23.2)	0.993	978 (23.1)
Malignancy				
Any	130 (49.4)	1,773 (44.6)	0.016	1,903 (44.9)
Leukemia	17 (6.5)	136 (3.4)	0.005	153 (3.6)
Hodgkin's lymphoma	3 (1.1)	22 (0.6)	0.198	25 (0.6)
Non-Hodgkin's lymphoma	19 (7.2)	135 (3.4)	<0.001	154 (3.6)
Hematologic ^c	35 (13.3)	259 (6.5)	<0.001	294 (6.9)
Gynecologic ^d	19 (7.2)	288 (7.2)	0.777	307 (7.2)
Other Potential				
Predisposing Factors				
Non- <i>albicans</i> species	20 (7.6)	174 (4.4)	0.040	194 (4.6)
<i>C. glabrata</i>	12 (4.6)	113 (2.8)		125 (2.9)
<i>C. krusei</i>	1 (0.4)	6 (0.2)		7 (0.2)
<i>C. parapsilosis</i>	4 (1.5)	19 (0.5)		23 (0.5)
<i>C. tropicalis</i>	2 (0.8)	27 (0.7)		29 (0.7)
Others	1 (0.4)	9 (0.2)		10 (0.2)
Hospital stay >12 days	124 (47.1)	1,218 (30.6)	<0.001	1,342 (31.7)
Bone marrow transplant	1 (0.4)	14 (0.4)	0.889	15 (0.4)
Cancer chemotherapy	8 (3.0)	80 (2.0)	0.191	88 (2.1)
Radiation therapy	6 (2.3)	60 (1.5)	0.258	66 (1.6)
TPN within prior 30 days	105 (39.9)	1,299 (32.7)	0.002	1,404 (33.1)
Gastrostomy	5 (1.9)	197 (5.0)	0.045	202 (4.8)
Devices				
Ventilator	13 (4.9)	220 (5.5)	0.871	233 (5.5)
Permanent central line	109 (41.4)	1,155 (29.0)	<0.001	1,264 (29.8)

Characteristic ^a	Candidemia (N=263)	No Candidemia (N=3,977)	p-value ^b	Total (N=4,240)
Temporary central line	114 (43.3)	1,022 (25.7)	<0.001	1,136 (26.8)
Dialysis catheter	31 (11.8)	258 (6.5)	0.002	289 (6.8)
Urinary catheter	16 (6.1)	349 (8.8)	0.224	365 (8.6)
Central venous catheter ^e	152 (57.8)	1,657 (41.7)	<0.001	1,809 (42.7)
Urinary catheter and antibiotic use ^f	15 (5.7)	276 (6.9)	0.616	291 (6.9)
Vital Signs				
Temperature				
>39 °C	52 (19.8)	355 (8.9)	<0.001	407 (9.6)
Heart rate >120 beats/min	121(46.0)	1,037 (26.1)	<0.001	1,158 (27.3)
Respiratory rate				
20–30 breathes/min	49 (18.6)	947 (23.8)	0.225	996 (23.5)
>30 breathes/min	50 (19.0)	502 (12.6)	<0.001	552 (13.0)
Select Laboratory Values				
Absolute neutrophils count				
<1,500/mm ³	23 (8.7)	162 (4.1)	<0.001	185 (4.4)
>9,500/mm ³	82 (31.2)	1,025 (25.8)	0.002	1,107 (26.1)
Hemoglobin <9 g/dL	226 (85.9)	2,766 (69.5)	<0.001	2,992 (70.6)
Platelets <150 K/ mm ³	155 (58.9)	1,703 (42.8)	<0.001	1,858 (43.8)
Creatinine >1.3 mg/dL	124 (47.1)	1,494 (37.6)	<0.001	1,618 (38.2)
Medications Ordered Within 90 Days Prior to <i>Candida</i> BSI				
Azole	19 (7.2)	268 (6.7)	0.552	287 (6.8)
Caspofungin	3 (1.1)	7 (0.2)	0.005	10 (0.2)
Corticosteroids	86 (32.7)	999 (25.1)	0.001	1,085 (25.6)
Anti-herpes antivirals	29 (11.0)	282 (7.1)	0.007	311 (7.3)
Carbapenems	58 (22.1)	585 (14.7)	<0.001	643 (15.2)
Cytotoxic agents	5 (1.9)	32 (0.8)	0.053	37 (0.9)
Glycopeptide antibiotics	131 (49.8)	1,714 (43.1)	0.003	1,845 (43.5)
Nitroimidazoles	84 (31.9)	97 (2.4)	<0.001	181 (4.3)
Penicillins	26 (9.9)	244 (6.1)	0.007	270 (6.4)
Penicillin/β-lactamase inhibitors	67 (25.5)	669 (16.8)	<0.001	736 (17.4)
Polymyxin	3 (1.1)	21 (0.5)	0.174	24 (0.6)
Any prior antifungal use	50 (19.0)	608 (15.3)	0.037	658 (15.5)
Any prior antibiotic use	239 (90.9)	3,458 (86.9)	0.001	3,697 (87.2)

^aUnless otherwise specified, characteristics are dichotomized and reported as absolute frequency (percent).

^bp-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.

^cIncludes any history or diagnosis of leukemia or lymphoma

^dIncludes any history or diagnosis of malignancy of the uterus, cervix, ovary, or other female genital sites

^eIncludes the presence of a permanent or temporary central line or a dialysis catheter

^fMedication was ordered within 90 days prior to *Candida* infection.

NOTE: Descriptive statistics for additional variables are presented in Supplementary Table 1. Abbreviations: IQR, interquartile range; TPN, total parenteral nutrition

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Clinical Predictive Model for Candiduria with Candidemia vs Candiduria Alone

Variable	Parameter Estimate	Odds Ratio (95% CI)	p-value
Intercept	-3.754	n/a	n
Hospital length of stay > 12 days	0.310	1.363 (1.036, 1.795)	0.027
Hematologic malignancy ^a	0.754	2.126 (1.394, 3.242)	<0.001
Gynecologic malignancy ^b	0.554	1.740 (1.034, 2.927)	0.037
Central venous catheter ^c	0.599	1.821 (1.398, 2.372)	<0.001
Total parenteral nutrition	0.415	1.514 (1.136, 2.017)	0.005
Prior β -lactam/ β -lactamase inhibitor use ^d	0.494	1.639 (1.203, 2.233)	0.002
Heart rate >120 beats/min	0.618	1.856 (1.408, 2.446)	<0.001
Temperature			
>39 °C	0.570	1.769 (1.343, 2.330)	<0.001
Absolute neutrophil count			
<1,500/mm ³	0.606	1.833 (1.096, 3.065)	0.021
>9,500/mm ³	0.445	1.560 (1.164, 2.093)	0.003
Creatinine >1.3 mg/dL	0.583	1.791 (1.372, 2.337)	<0.001
Sex (Female)	-0.609	0.544 (0.414, 0.713)	<0.001
Diabetes mellitus	-0.445	0.641 (0.465, 0.883)	0.006
Gastrostomy	-0.984	0.374 (0.150, 0.932)	0.035
Urinary catheter and prior ^d antibiotic use	-0.639	0.528 (0.288, 0.968)	0.039

^aIncludes any history or diagnosis of leukemia or lymphoma^bIncludes any history or diagnosis of malignancy of the uterus, cervix, ovary, or other female genital sites^cIncludes the presence of a permanent or temporary central line or a dialysis catheter^dMedication was ordered within 90 days prior to *Candida* infection.

Abbreviations: CI, confidence interval