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Predicting candidemia in the internal medicine wards: a comparison with gram-negative bacteremia—a retrospectives study

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ABSTRACT

Introduction: Risk factors for candidemia in the internal medicine wards (IMW) are poorly characterized. Their elucidation might assist in early diagnosis and treatment.
Objectives: We aimed to elucidate predictors of candidemia in the IMWs comparing them to patients with gram-negative bacteremia (GNB).
Methods: A retrospective study of consecutive patients with candidemia in IMWs in Beilinson hospital (2007–2016) was performed. Patient demographics, comorbidities, and clinical characteristics were documented. The comparator group was GNB patients.
Results: Sixty-two patients with candidemia were compared with 178 patients with GNB. Candidemic patients were younger and with less body mass index > 20 kg/m^2 (73 ± 15 vs. 78 ± 10, $P = 0.01$; 44% vs. 60%, $P =$ <0.0001,respectively). In multivariate model, underweight, prior cephalosporin use, and central venous catheters (CVCs) were significantly associated with candidemia [odds ratio (OR) = 0.2, 95% confidence interval (CI) 0.07–0.4; OR = 4, 95% CI 1.3–11; and OR = 4, 95% CI 1.5–12, respectively].
Conclusion: Underweight, recent cephalosporin exposure, and CVCs were statistically significant predictors of candidemia in the IMW. Using these predictors might aid in recognizing high-risk patients for candidemia in the IMWs, leading to earlier appropriate empirical treatment.

1. Introduction

Candidemia contributes to greater mortality and prolonged hospitalizations with increased cost of care despite the advancement in antifungal therapy. It is considered the fourth most common cause of nosocomial bloodstream infection (Falcone et al., 2014).

Many laboratory- and population-based surveillance studies on candidemia are published focusing on specific populations including neonates, cancer, and surgical and intensive care unit (ICU) patients (Bassetti et al., 2013a). Data on candidemia in internal medicine wards (IMWs) are scarce. A multicenter study conducted in Italy and Spain showed that the majority of the candidemia episodes were found in the IMWs (49.6%), followed by the surgical, ICU, and the hemato-oncology ones, with the highest mortality rate reported in the internal medicine and hemato-oncology wards compared to the other ones (44.4% versus 35.4%; $P = 0.002$) (Bassetti et al., 2013b). In a recent retrospective study on 118 patients with candidemia, we demonstrated that IMWs patients were significantly older than the surgical ones, with poorer functional capacity, and more frequently were exposed to antibiotic therapy within 90 days and at onset of candidemia (Eliakim-Raz et al., 2016). These patients did not have central venous catheters (CVCs) comparable to ICU and surgical patients. It is reasonable to assume that these variables played a major role in delayed diagnosis and poor outcomes in IMWs compared to the other wards. Another important variable is inappropriate empiric therapy that consisted mostly of inadequate choice of antifungals or omission of initial empirical therapy because candidemia comprises the minority of patients who present with sepsis contrary to gram-negative bacteremia (GNB) which contributes to the majority of them (Bassetti et al., 2013a). Exploring predictors for candidemia in the IMW might assist in early diagnosis and treatment of high-risk patients. Such predictors for candidemia are poorly characterized. We are not aware of any studies comparing IMW patients with candidemia to a control group of IMW patients without candidemia to formulate a more accurate risk score in this population taking into

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account their special characteristics. Because they are common and share almost similar clinical presentation, GNB patients were chosen to be the comparators for those with candidemia in order to elucidate predictors of candidemia which is the aim of this study.

2. Methods

2.1. Subjects and study design

All consecutive hospitalized patients with candidemia (>18 years) in 6 IMWs who were diagnosed between January 2007 and September 2016were included in this retrospective study. The study was conducted at Beilinson Hospital in Petah Tikva, Israel. Data regarding demographics, comorbidities, and presenting clinical characteristics including vital signs and laboratory results were documented. For each patient, only the first episode of candidemia was included. The comparator group comprised patients with GNB who were identified in the same wards and period of the study. We choose GNB patients as comparators since they have almost similar clinical presentation with candidemic patients. All data were documented from patient's electronic and other health records. The study was approved by the hospital ethical committee. Informed consent was waived because of the retrospective, noninterventional nature of the study.

2.2. Microbiological methods

Candida isolates were detected from blood cultures using the BACTEC™ blood culture system /BACTEC™ FX system (Becton Dickinson, Inc., Sparks, MD). Isolates identification was based on Vitek 2 system (Meurman et al., 2006) or matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (Dhiman et al., 2011).

2.3. Statistical analysis

All dichotomous variables were compared by χ^2 test. Continuous data were expressed as mean ± standard deviation and compared using a *t* test. Clinically relevant variables that associated with candidemia in IMWs on univariate analysis ($P < 0.05$) were included into a logistic regression analysis.

3. Results

3.1. Study cohort

A total of 62 consecutive patients with candidemia were identified in the IMWs during the study period. *Candida albicans* isolates comprised 44% of the candidemia episodes, while the nonalbicans isolates comprised 56% (*C. tropicalis* [19%], *C. parapselosis* [18%], *C. glabrata* [16%], *C. krusei* [0%], and other species [3%]). The control group was composed of 178 patients with GNB, with *Escherichia coli* isolates comprising the majority of the episodes (59%) followed by *Klebsiella pneumoniae* [16%], *Proteous mirabilis* [14%], *Pseudomonas aeruginosa* [5%], *Acinetobacter baumannii* [2%], and others including *Enterobacter* spp., *Citrobacter* spp., and *Providencia* spp. [4%]. The baseline characteristics of the study cohort are provided in Table 1.

Patients with candidemia were significantly younger than the bacteremic ones (73 ± 15 vs. 78 ± 10, $P = 0.01$) with similar gender distribution between both groups. Higher rates of body mass index (BMI) > 20 kg/m^2 were observed in the bacteremia group. Approximately 70% of the patients in both groups were assisted in activities in daily living (ADL), and more than one-third of them have resided in a long-term health care facility. Half of the patients in both groups were hospitalized within 3 months prior to admission.

The majority of comorbidities were present at similar rates between the groups; however, candidemia was more frequently diagnosed in patients with ischemic heart disease (37% vs. 0.5%, $P = <0.0001$), with cerebrovascular disease (27% vs. 15%, $P = 0.02$), who were with decubitus ulcers (40% vs. 18%, $P = 0.0005$), and who were mechanically ventilated (39% vs. 17%, $P = 0.0008$). Furthermore, patients with candidemia were significantly more likely to have nasogastric tubes and be on total parenteral nutrition (TPN) compared with those with bacteremia (40% vs. 19%, $P = 0.0007$; 8% vs. 2%, $P = 0.02$, respectively). While urinary catheters were observed similarly between both groups, CVCs were observed more in patients with bacteremia (10% vs. 2%, $P =$

Table 1
Baseline characteristics of patients with candidemia compared with GNB in IMW.

Characteristics	Candidemia ($n = 62$)	Bacteremia ($n = 178$)	*P* value
Demographics			
Age (mean, SD)	**73 ± 15**	**78 ± 10**	**0.01**
Male gender (*n*, %)	26 (42%)	83 (47%)	0.5
BMI ≥ 20 kg/m^2 (*n*, %)	**27 (44%)**	**106 (60%)**	**<0.0001**
Assisted in ADL (*n*, %)	46 (74%)	124 (70%)	0.5
Long-term health care facility residency (*n*, %)	24 (39%)	57 (32%)	0.3
Previous ICU hospitalization (*n*, %)	3 (5%)	8 (4%)	0.8
Previous hospitalization (*n*, %)	31 (50%)	88 (49%)	0.9
Previous hospitalization duration (mean, SD)	4 ± 8	4 ± 8	1
Comorbidities			
Charlson score (mean, SD)	7 ± 2	7 ± 3	0.2
Ischemic heart diseases (*n*, %)	**23 (37%)**	**1 (0.5%)**	**<0.0001**
Congestive heart failure (*n*, %)	19 (31%)	47 (26%)	0.5
Cerebrovascular accident (*n*, %)	17 (27%)	26 (15%)	0.02
Peripheral vascular disease (*n*, %)	11 (18%)	24 (13%)	0.4
Diabetes mellitus (*n*, %)	26 (42%)	90 (51%)	0.2
Chronic kidney disease (*n*, %)	21 (34%)	41 (23%)	0.09
Hemodialysis (*n*, %)	4 (6%)	6 (3%)	0.3
Liver diseases (*n*, %)	6 (10%)	10 (6%)	0.3
Dementia (*n*, %)	12 (20%)	43 (24%)	0.4
Chronic pulmonary diseases (*n*, %)	10 (16%)	26 (15%)	0.8
Leukemia (*n*, %)	3 (5%)	6 (3%)	0.6
Lymphoma (*n*, %)	5 (8%)	13 (7%)	0.8
Solid organ tumors (*n*, %)	12 (20%)	38 (21%)	0.7
Solid organ transplant (*n*, %)	3 (5%)	8 (4%)	0.9
Bone marrow transplantation (*n*, %)	0 (0%)	3 (2%)	1
Decubitus ulcers (*n*, %)	**25 (40%)**	**32 (18%)**	**0.0005**
Abdominal surgery (*n*, %)	2 (3%)	0 (0%)	0.9
Indwelling catheters and tubes			
Nasogastric tube (*n*, %)	**25 (40%)**	**33 (19%)**	**0.0007**
Percutaneous endoscopic gastrostomy (*n*, %)	3 (5%)	3 (2%)	0.2
TPN (*n*, %)	**5 (8%)**	**3 (2%)**	**0.02**
CVCs (*n*, %)	**28 (2%)**	**17 (10%)**	**<0.0001**
Nephrostomy tubes (*n*, %)	2 (3%)	5 (3%)	0.9
Percutaneous transhepatic cholangiography (*n*, %)	1 (2%)	7 (4%)	0.4
Urinary catheters (*n*, %)	30 (48%)	97 (54%)	0.4
Mechanical ventilation (*n*, %)	**24 (39%)**	**31 (17%)**	**0.0008**
Medications			
Radiation therapy (*n*, %)	1 (2%)	9 (5%)	0.3
Active chemotherapy therapy (*n*, %)	9 (15%)	19 (11%)	0.4
Active biologic therapy (*n*, %)	2 (3%)	6 (3%)	0.9
Steroid use (*n*, %)	13 (21%)	45 (25%)	0.5
Prior cephalosporins (*n*, %)	**17 (27%)**	**27 (15%)**	**0.03**
Prior carbapenems (*n*, %)	4 (6%)	3 (2%)	0.07
Prior quinolones (*n*, %)	4 (6%)	14 (8%)	0.7
Prior metronidazole (*n*, %)	**8 (13%)**	**7 (4%)**	**0.02**
Clinical signs and laboratory results			
Temperature (°C) (mean, SD)	37.7 ± 1.7	37.6 ± 1.02	0.4
Heart rate (mean, SD)	98 ± 22	90 ± 20	0.01
Systolic blood pressure < 90 mm Hg (*n*, %)	10 (16%)	44 (25%)	0.1
White blood count (mean, SD)	15 ± 11	14 ± 11	0.7
Platelet count (mean, SD)	264 ± 159	227 ± 145	0.1
Creatinine level (mean, SD)	1.9 ± 1.5	1.6 ± 0.9	0.07
Albumin level (mean, SD)	**2.5 ± 0.6**	**3 ± 0.6**	**<0.0001**
CRP level (mean, SD)	15 ± 11	15 ± 9	0.8

<0.0001). Candidemia was frequently diagnosed in patients who were exposed to cephalosporins or metronidazole in the previous 3 months prior to admission (27% vs. 15%, $P = 0.03$ and 13% vs. 4%, $P = 0.02$, respectively). The presenting clinical parameters and laboratory results were similar in both groups, except for hypoalbuminemia which was observed more frequently in patients with candidemia (2.5 ± 0.6 vs. 3 ± 0.6, $P < 0.0001$).

On multivariate analysis of risk factors for candidemia, the only significant ones were BMI < 20 kg/m^2 [odds ratio (OR) = 0.17, 95% confidence interval (CI) 0.08–0.4], prior cephalosporins use (OR = 4, 95% CI 1.3–11), and CVC (OR = 4, 95% CI 1.5–12). Other variables were not significantly associated with candidemia including age (OR = 0.9, 95% CI 0.96–1.04), male gender (OR = 1.02, 95% CI 0.4–2), decubitus ulcers (OR = 1.2, 95% CI 0.5–3), nasogastric tube (OR = 1.4, 95% CI 0.4–5), TPN (OR = 6, 95% CI 0.7–42), mechanical ventilation (OR = 0.8, 95% CI 0.2–3), hypoalbuminemia (OR = 0.5, 95% CI 0.2–1), and prior metronidazole use (OR = 4, 95% CI 0.9–18) (Table 2).

4. Discussion

To the best of our knowledge, this is the first study to compare candidemic with gram-negative bacteremic patients hospitalized in the IMW. In this study, we found that the risk factors for candidemia in the IMW were underweight (BMI <20 kg/m^2), recent cephalosporin exposure, and CVC. Other well-known risk factors for candidemia in ICU and surgical patients including urinary catheters and TPN were not found to be statistically significant for candidemia in the IMW patients.

Recent antibiotic exposure is a well-known risk factor for candidemia mainly by altering the resident gut microbiota, in which antibiotics may selectively impair colonization resistance promoting gastrointestinal colonization with *Candida* species (Eliakim-Raz et al., 2016; Ben-Ami et al., 2012).

CVC was observed more in the bacteremic patients; however, when adjusted to other risk factors including TPN, CVC was found to be strongly associated with candidemia.

The association between body weight and candidemia was not described previously. We found that candidemic patients had significantly less BMI > 20 kg/m^2 compared to the bacteremic ones. Underweight almost reflects an underlying malnutrition state that might affect the host immunity. Inadequate innate and adaptive host defense mechanisms are strongly related to *Candida* infections (Kullberg et al., 2014).

Several studies have reported on higher mortality in candidemic patients hospitalized in the IMW as compared with those in other wards. In one study conducted in Spain and Italy, the 30-day mortality in IMW patients was 44% compared to 35% in patients from other wards (Bassetti et al., 2013b). In another study from Italy, the reported mortality rate was significantly higher in IMW patient compared to the other wards (50% vs. 36%) (Bassetti et al., 2013a). Furthermore, in our recent study, we have reported also on higher crude 30-day mortality in IMW patients compared with the surgical ones (62.7% vs. 38.7%), with a very high proportion (41%) of IMW patients with candidemia dying before receiving antifungal therapy at all and the majority of them dying before the identification of yeast in blood cultures was made (66.6%). In addition, the timing of treatment had an impact on 30-day mortality of patients with candidemia where adequate antifungal therapy within 48 h was the only significant predictor of survival in these patients ($P = 0.03$): hazard ratio 3.7 (95% CI 1.14–12.5) for therapy delayed to more than 48 h (Eliakim-Raz et al., 2016).

Several explanations for this devastating outcome might be proposed: firstly, the older age and the complex comorbidities characterizing the IMW patients compared to the surgical ones. Interestingly, in the present study, candidemic patients were younger than the bacteremic ones; however, they were sicker and more debilitated. Secondly, since candidemia and GNB have similar sepsis presentation, with GNB comprising the majority of the sepsis cases, candidemia diagnosis was overlooked. That's why we chose GNB patients as the comparator group in order to explore predictors for candidemia that might assist in early diagnosis and treatment of high-risk patients.

In the present study, recent cephalosporin exposure, CVC, and underweight were the only significant predictors of candidemia (Table 2).

The combination of age, male gender, BMI >20 kg/m^2, decubitus ulcers, nasogastric tube, TPN, mechanical ventilation, hypoalbuminemia, prior cephalosporins and metronidazole, and CVC has generated a good clinical prediction tool for candidemia with area under the receiver operating characteristic curve of 0.85 (Table 2, Fig. 1). However, this prediction model might also lead to the overprescribing of antifungals exerting a selective pressure with a shift to resistant *Candida* species, emergence of resistance, and increased costs (Bizerra et al., 2014; Cuervo et al., 2016). The use of the next-generation diagnostics with a high negative predictive value (NPV) might limit the overprescribing of antifungals by early ruling out of candidemia. A recent published pilot study estimating the diagnostic accuracy of a novel nanodiagnostic test that uses T2 magnetic resonance called "T2candida" in patients with severe sepsis and septic shock with multiple risk factors for candidemia showed that T2candida has a low positive predictive value of (25%) and a very high NPV (100%), allowing potential reduction of the duration of empiric appropriate therapy by 5 days (Giannella et al., 2018). One of

Table 2
Multivariate model for risk factors of candidemia compared with bacteremia.

variable	OR (95% CI)	*P* value
Age	0.9 (0.96–1.04)	0.9
Male gender	1.02 (0.4–2)	0.9
BMI > 20 kg/m^2	**0.2 (0.07–0.4)**	**<0.0001**
Decubitus ulcers	1.2 (0.5–3)	0.6
Nasogastric tube	1.4 (0.4–5)	0.5
TPN	6 (0.7–42)	0.1
Mechanical ventilation	0.8 (0.2–3)	0.8
Hypoalbuminemia	0.5 (0.2–1)	0.06
Prior cephalosporins	**4 (1.3–11)**	**0.01**
Prior metronidazole	4 (0.9–18)	0.051
CVC	**4(1.5–12)**	**0.005**

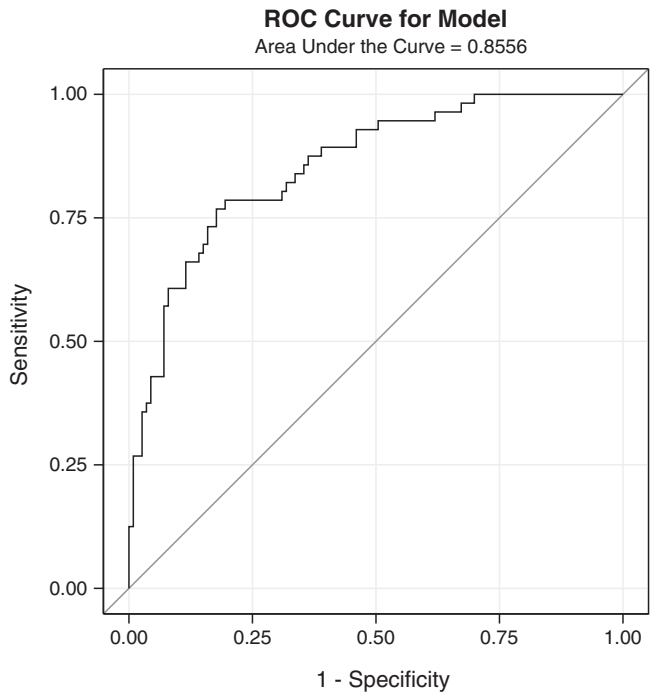

Fig. 1. Receiver operating characteristic curve for the multiple logistic regression predicting candidemia. The *C*-statistic is 0.85. Predictor variables are age, male gender, BMI >20 kg/m^2, decubitus ulcers, nasogastric tube, TPN, mechanical ventilation, hypoalbuminemia, prior cephalosporins, prior metronidazole exposure, and CVCs.

the limitations mentioned by the authors of this pilot study is that the risk factors used may not be appropriate to identify patients with candidemia and they selected them according to prior literature and local epidemiology.

Our study has several limitations. First, the retrospective nature of the study makes it vulnerable to collection bias and to potential inaccuracy in data collection. Second, it is a single-center study, limiting the generalizability of the results. Third, the small sample size might decrease the significance of the results; a larger multicenter database will increase the significance of the results and the study's external validity.

In conclusion, we found that underweight, recent cephalosporin exposure, and CVC are the only statistically significant predictors of candidemia in the IMW. Using these predictors might aid in recognizing high-risk patients for candidemia in the IMWs, leading to less underdiagnoses, and ruling out candidemia by the use of the new diagnostic test could limit the overprescribing of empiric antifungal therapy. Further studies with large multicenter database are needed to explore additional predictors for candidemia in the IMWs.

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