Assessment of risk factors for candidemia in non-neutropenic patients hospitalized in Internal Medicine wards: A multicenter study

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ABSTRACT

Background: An increasing prevalence of candidemia has been reported in Internal Medicine wards (IMWs). The aim of our study was to identify risk factors for candidemia among non-neutropenic patients hospitalized in IMWs.

Methods: A multicenter case–control study was performed in three hospitals in Italy. Patients developing candidemia (cases) were compared to patients without candidemia (controls) matched by age, time of admission and duration of hospitalization. A logistic regression analysis identified risk factors for candidemia, and a new risk score was developed. Validation was performed on an external cohort of patients.

Results: Overall, 951 patients (317 cases of candidemia and 634 controls) were included in the derivation cohort, while 270 patients (90 patients with candidemia and 180 controls) constituted the validation cohort. Severe sepsis or septic shock, recent *Clostridium difficile* infection, diabetes mellitus, total parenteral nutrition, chronic obstructive pulmonary disease, concomitant intravenous glycopeptide therapy, presence of peripherally inserted central catheter, previous antibiotic therapy and immunosuppressive therapy were factors independently associated with candidemia. The new risk score showed good area under the curve (AUC) values in both derivation (AUC 0.973 95% CI 0.809–0.997, $p < 0.001$) and validation cohort (0.867 95% CI 0.710–0.931, $p < 0.001$). A threshold of 3 leads to a sensitivity of 87% and a specificity of 83%.

Conclusion: Non-neutropenic patients admitted in IMWs have peculiar risk factors for candidemia. A new risk score with a good performance could facilitate the identification of candidates to early antifungal therapy.

1. Introduction

Hospital-acquired *Candida* bloodstream infections (BSI) represent around the 9% of all nosocomial BSI [1]. Spanish data report an annual incidence of 8.1 cases/100,000 inhabitants, 0.89/1000 admissions and 1.36/10,000 patient-days [2]. Candidemia has been extensively studied in neutropenic patients with hematological malignancies or in non-neutropenic ones admitted to intensive care units (ICUs) [3,4,5]. Moreover, candidemia has been frequently reported in patients undergoing abdominal surgery with anastomotic leakage or repeated laparotomies, and *Candida* spp. account for approximately 3% of all surgical-related peritoneal infections [4].

In recent years, a shift in candidemia hospital epidemiology has been observed, with an increasing number of episodes (up to 59% of

Abbreviations: ANC, absolute neutrophil count; AROC, average receiver operating characteristic curves; AUC, area under the curve; BSI, bloodstream infections; CDI, *Clostridium difficile* infection; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CVC, total parenteral nutrition; IBD, inflammatory bowel disease; ICU, intensive care units; IMW, Internal Medicine wards; IQ, interquartile ranges; NPV, negative predictive value; OR, odds ratio; PICC, peripherally inserted central catheter; PPV, positive predictive value; ROC, receiver operating characteristic curves; SD, standard deviation.

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nosocomial episodes) reported in patients cared for in Internal Medicine wards (IMWs) [6–12]. Patients residing in IMWs are usually old, with multiple comorbidities, and may present multiple risk factors for candidemia.

An early identification of patients presenting with risk factors for candidemia is crucial because may help to generate a timely and appropriate diagnostic and therapeutic approach. The aim of our study is to assess the role of specific risk factors for nosocomial candidemia in non-neutropenic patients residing in IMWs.

2. Methods

2.1. Study population and study design

This retrospective multicenter case-control study was performed in three tertiary-care hospitals, located in the Central Italy: Policlinico Umberto I, "Sapienza" University, Rome (1100 beds), San Giovanni-Addolorata Hospital, Rome (700 beds), Azienda Ospedaliera Universitaria Pisana, Pisa (800 beds). The study included cases observed from December 2012 to December 2014. The local ethics committee ("Ethics Committee *Sapienza*") approved the study. According to local and national policies, we attempted to obtain an informed consent from survived patients that we were able to contact by phone or ambulatory visit; among remaining patients it was waived.

Patients aged ≥18 years cared for in IMWs with a definite diagnosis of candidemia were included in the study and represented the case group. IMWs included all medical wards other than surgical or intensive care wards (general medicine, cardiology, pulmonology, nephrology, rheumatology). Patients hospitalized in hematology and/or oncology wards were excluded. Candidemia was defined by at least one positive blood culture yielding *Candida* spp. in a patient with fever and/or other clinical signs of infection [13]. For patients with 2 or more episodes of candidemia, the subsequent episode was considered as a new (incident) episode if it occurred after at least 30 days from the previous one; in this case, we re-evaluated risk factors for each candidemia episode [14].

For each case, two controls matched for age (±2 years), date of hospital admission and duration of hospitalization were selected (cases:controls ratio 1:2). Matching for duration of hospitalization was performed calculating the time between the day of admission and candidemia occurrence (first positive blood culture) of the index case (duration categories: ≤7, 8–14, 15–21, 22–30, >30 days) and choosing two controls with the same time of hospital stay. To ensure comparable periods of risk exposure in both groups, each control had a length of hospitalization similar to the time at risk of cases (defined as the number of days from hospital admission to candidemia occurrence). Exclusion criteria were candidemia documented outside IMWs, age < 18 years and presence of neutropenia [defined as absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 h] [14]. Moreover, we excluded patients with diagnosis of any hematological malignancy. Age < 18 years, presence of neutropenia and hematological malignancy were exclusion criteria also for control patients. In this cohort of patients, risk factors independently associated with candidemia were identified and were used to develop a new clinical risk score. The score was further validated on an external cohort of patients hospitalized in IMWs in the tertiary-care University Hospital of Trieste (840 beds), sited in the Northern Italy. All cases were collected in the same period in the derivation and validation cohort. In both populations, the same abovementioned inclusion, exclusion and matching criteria were applied.

2.2. Data collection and study definitions

Demographic data, underlying diseases, reason for hospital admission and severity of illness of patients with definite diagnosis of candidemia were retrospectively reviewed by each investigator of the four study centers on a standardized report form. The variables considered were: age, sex, time at risk (defined as the number of hospital days from the admission in IMWs to the date of the first positive blood culture for *Candida* spp.), comorbidities assessed by the Charlson comorbidity index. Information about diabetes mellitus, chronic liver disease, malignancies, chronic obstructive pulmonary disease (COPD), chronic renal failure, inflammatory bowel disease (IBD), acute pancreatitis, total parenteral nutrition (TPN) [15], central venous catheter (CVC) or peripherally inserted central catheter (PICC), surgery in the previous 30 days, *Clostridium difficile* infection (CDI), and concomitant antibiotic therapy (defined as exposure to antibiotics from at least 48 h before diagnosis of candidemia) were also collected. CDI was defined as the presence of diarrhea, defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours and a stool test result positive for the presence of toxigenic *C. difficile* or its toxins. In the candidemia group, all risk factors were assessed at the onset of candidemia (date of positivity of blood cultures). On the same hand, in the control group risk factors were collected after a period of hospitalization as long as the time at risk of cases; this period could be named "pseudo-date of diagnosis". According to these matching criteria, cases and controls had comparable pre-exposure periods. Blood cultures were processed using the automated blood culture system BacT/Alert 3D (Biomérieux Inc., Marcy l'Etoile, France). Confirmation of *Candida* spp. identification was performed by use of Vitek-2 system (Biomérieux Inc.). Immunosuppressive therapy was defined as use of steroids (prednisolone >0.5 mg/kg/d or equivalent for >1 month), chemotherapy or anti-tumor necrosis factor therapy within the past 3 months. Previous antibiotic therapy was defined as exposure to antibiotics for at least 48 h in the 30 days preceding candidemia, while concomitant antibiotic therapy was defined as use of antibiotic at the time of candidemia onset. Recent CDI was defined as CDI occurring in the 30 days before candidemia. Severe sepsis or septic shock occurring during the days of candidemia were defined according to the Surviving Sepsis Campaign criteria [16]. Data about in-hospital survival were also collected.

2.3. Study endpoint and statistical analysis

The goal of our study was to identify risk factors independently associated with the development of nosocomial candidemia in non-neutropenic patients hospitalized in IMWs. Moreover, we aimed to develop a clinical score to identify patients with high risk of nosocomial candidemia in IMWs.

Continuous variables were compared by Student's *t*-test if normally distributed and the Mann–Whitney *U* test if non-normally distributed. Categorical variables were evaluated using χ [2] or the two-tailed Fisher's exact test. Values for continuous and categorical variables are expressed as the mean ± standard deviation (SD) or median (interquartile ranges) (IQR) and percentage of the group from which they are derived, respectively. Multivariate analysis to identify independent risk factors for development of candidemia was performed using a conditional logistic regression model, to take into account matching. All variables were considered for the multivariate analysis. At multivariate analysis the predictors were selected via a stepwise selection procedure optimizing the Akaike Information Criterion. It shall be noted that if the initial pool of variables available for model selection at multivariate analysis was restricted only to variables significant at univariate analysis, the same final multivariate model was obtained. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association.

A new score predicting the risk of nosocomial candidemia was developed. The score values were derived by rounding the beta coefficients (logarithm of the odds-ratios). We evaluated discrimination using average receiver operating characteristic curves (AROC). AROC is used to take into account the fact that data are matched. First, covariate-specific ROC curves are estimated by means of a non-parametric

estimation procedure [17], then these are averaged [18]. We proposed a threshold based on maximization of Youden index. We calculated the area under the curve (AUC) and the sensitivity and specificity for the cut-off point of the score. Given that we are working with case-control data, positive predictive value (PPV) and negative predictive value (NPV) cannot be evaluated. However, based on the adaptation for incidence of candidemia in our previous case series we provided the positive predictive value (PPV) and the negative predictive value (NPV) of this score. To validate the model, we applied the derived risk score to patients in the validation cohort. Statistical significance was established at ≤0.05. All reported *p* values are 2-tailed. The results obtained were analyzed using commercially available statistical software packages (SPSS, version 20.0; SPSS, Inc., Chicago, IL and R, version 3.0.2; R development core team, Vienna, Austria).

3. Results

A total of 951 patients (317 cases of candidemia and 634 controls) were included in the study. Among the 317 candidemic episodes, 165 (52%) were observed in Policlinico Umberto I, 113 (35.6%) in Azienda Ospedaliera Universitaria Pisana and 39 (12.3%) in San Giovanni-Addolorata Hospital. *C. albicans* was the most commonly documented species (51.4%), followed by *C. parapsilosis*-group (17.7%), *C. tropicalis* (9.8%), *C. glabrata* (7.6%), *C. krusei* (2.5%), others (11%); five patients (1.6%) had mixed *Candida* infection. The median time at risk in patients with candidemia was 6 (IQR 2–15) days. In-hospital mortality among patients with candidemia was 40.4%.

Table 1 describes the demographic and clinical features of patients with and without candidemia. The median age was 76 (IQR 68.5–84) years in patients with candidemia and 75 (IQR 69–84) years in controls. Patients with candidemia had more frequently a CVC or PICC inserted, a higher rate of diabetes mellitus, COPD, IBD, acute pancreatitis, history of recent CDI and previous antibiotic therapy, and were more likely to receive concomitant antibiotics, chemotherapy and immunosuppressive therapy.

Table 2 describes univariate and multivariate analyses of risk factors for candidemia in our population. The multivariate analysis identified severe sepsis or septic shock (OR 12.544, 95% CI 5.426–29.00, $p < 0.001$), recent CDI (OR 9.287, 95% CI 3.166–27.241, $p < 0.001$), diabetes mellitus (OR 7.306, 95% CI 3.905–13.666, $p < 0.001$), TPN (OR 6.266, 95% CI 3.240–12.119, $p < 0.001$), COPD (OR 6.029, 95% CI 2.982–12.188, $p < 0.001$), concomitant intravenous glycopeptide therapy (OR 5.863, 95% CI 2.138–16.078, $p < 0.001$), PICC inserted (OR 5.125, 95% CI 2.595–10.118, $p < 0.001$), previous antibiotic therapy (OR 3.315, 95% CI 1.975–5.565, $p < 0.001$) and immunosuppressive therapy (OR 2.131, 95% CI 1.316–3.451 $p = 0.002$) as factors independently associated with the risk of nosocomial candidemia.

Table 3 summarizes the *Candida* score and the points assigned to each variable. The score ranges from 0 to 14. The threshold to define low risk for nosocomial candidemia was 3. When the score was ≤3 the percentage of candidemia was 6.5%, while this prevalence increased to 66.4% with a score >3. The threshold 3 lead to a sensitivity of 87% and a specificity of 83%. The PPV and the NPV adapted for prevalence of candidemia is 0.095% and 0.997 respectively.

Table 4 shows the number of patients with candidemia, the sensitivity and the specificity of the proposed tool for each score. When the score is >5 the specificity is >95%.

Fig. 1 (panel A) shows the AROC curve of this score system in the derivation cohort. The AUC of our model was high (0.973 95% CI 0.809–0.997, $p < 0.001$).

The performance of the score was evaluated in the validation cohort. This cohort of patients consisted of 270 patients (90 patients with candidemia and 180 controls). Demographics and clinical characteristics of the validation cohort are listed in Table S1 while comparison of demographics and underlying disease between the derivation and the validation cohort is reported in Table S2 (see Supplementary material).

Table 1
Comparison of patients with candidemia and patients without candidemia admitted in Internal Medicine wards (derivation cohort).

	Patients with candidemia $N = 317$ (%)	Patients without candidemia $N = 634$ (%)	*p*-Value
Male	148 (46.7%)	358 (56.5%)	***0.004***
Age, median (IQR)	76 (68.5–84)	75 (69–84)	0.982
Diabetes mellitus	175 (55.2%)	195 (30.8%)	<***0.001***
IBD	15 (4.7%)	5 (0.8%)	<***0.001***
Chronic renal failure	94 (29.7%)	140 (22.1%)	***0.011***
COPD	83 (26.2%)	61 (9.6%)	<***0.001***
Solid cancer	55 (17.4%)	128 (20.2%)	0.295
Organ transplantation	1 (0.3%)	1 (0.2%)	0.617
Recent *Clostridium difficile* infection	57 (18%)	17 (2.7%)	<***0.001***
Previous surgery	35 (11%)	68 (10.7%)	0.883
Acute pancreatitis	3 (0.9%)	2 (0.3%)	0.205
Previous hospitalization	86 (27.1%)	146 (23%)	0.165
Previous antibiotic therapy	15 (55.2%)	143 (22.6%)	<***0.001***
Concomitant antibiotic therapy	235 (74.1%)	399 (62.9%)	<***0.001***
Multiple concomitant antibiotics	52 (16.4%)	70 (11%)	***0.020***
Type of concomitant antibiotic			
Penicillin	1 (0.3%)	10 (1.6%)	0.086
β lactam/β lactamase inhibitors	106 (33.4%)	136 (21.5%)	<***0.001***
Cephalosporin	19 (6%)	77 (12.1%)	***0.003***
Carbapenem	43 (13.6%)	51 (8%)	***0.007***
Glycopeptide	43 (13.6%)	14 (2.2%)	<***0.001***
Fluoroquinolone	36 (11.4%)	90 (14.%)	0.223
Aminoglycoside	11 (3.5%)	15 (2.4%)	0.325
Other	23 (7.3%)	30 (4.7%)	0.110
Immunosuppressive therapy	179 (56.5%)	189 (29.8%)	<***0.001***
Non steroidal immunosuppressive therapy	50 (15.8%)	43 (6.8%)	<***0.001***
Steroids	129 (40.7%)	146 (23%)	<***0.001***
Chemotherapy	48 (15.1%)	58 (9.1%)	***0.006***
CVC	73 (23%)	60 (9.5%)	<***0.001***
PICC	112 (35.3%)	40 (6.3%)	<***0.001***
TPN	143 (45.1%)	58 (9.1%)	<***0.001***
Charlson comorbidity index, median (IQR)	7 (6–9)	5 (4–6)	<***0.001***
Severe sepsis or septic shock	111 (35%)	20 (3.2%)	<***0.001***
In-hospital mortality	128 (40.4%)	76 (12%)	<***0.001***

COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease; CVC = central venous catheter; PICC = peripherally inserted central catheter; TPN = total parenteral nutrition, IQR = interquartile ranges.
Bold type indicates statistically significant *p*-values.

As shown in Fig. 1 (panel B) AUC of AROC curve in the validation cohort was 0.867 (95% CI 0.710–0.931, $p < 0.001$).

4. Discussion

To our knowledge, this is the first study that systematically assessed the risk factors for candidemia in non-neutropenic, non-ICU patients residing in IMWs. Our study reveals that IMW patients have some inedited risk factors for candidemia, which seem to be peculiar for this setting of patients.

Candidemia in non-neutropenic patients has been long considered as a clinical syndrome occurring in ICU or in patients undergoing abdominal surgery with anastomotic leakage [19]. However, an increasing number of episodes of candidemia are nowadays diagnosed in medical wards. A study by Bassetti et al. conducted in five sites in Italy and Spain between 2008 and 2010 showed that 49.7% of a total of 995 candidemia episodes occurred in IMWs [9]. On the same hand, Luzzati et al. showed that 68% of all episodes of nosocomial candidemia in elderly patients were diagnosed in IMWs [20], and two additional studies conducted in other countries between 2006 and 2012 reported similar

Table 2
Univariate and multivariate analysis of risk factors for candidemia in Internal Medicine wards (derivation cohort).

	Univariate analysis				Multivariate analysis			
		95.0% CI				95.0% CI		
	OR	Lower	Upper	*p*-Value	OR	Lower	Upper	*p*-Value
Male sex	0.675	0.515	0.885	0.004				
Diabetes mellitus	2.774	2.100	3.665	<0.001	7.306	3.905	13.666	<0.001
IBD	6.248	2.250	17.352	<0.001				
Chronic renal failure	1.487	1.096	2.019	0.011				
COPD	3.332	2.316	4.794	<0.001	6.029	2.982	12.188	<0.001
Recent CDI	7.957	4.542	13.939	<0.001	9.287	3.166	27.241	<0.001
Previous antibiotic therapy	4.232	3.169	5.651	<0.001	3.315	1.975	5.565	<0.001
Ongoing antibiotic therapy	1.688	1.252	2.275	0.001				
Multiple concomitant antibiotics	1.581	1.073	2.329	0.020				
Concomitant β lactam/β LI	1.840	1.362	2.485	<0.001				
Concomitant cephalosporin	0.461	0.274	0.777	0.003				
Concomitant carbapenem	1.794	1.166	2.759	0.007				
Concomitant IV glycopeptide therapy	6.950	3.740	12.915	<0.001	5.863	2.138	16.078	<0.001
Immunosuppressive therapy	3.054	2.309	4.040	<0.001	2.131	1.316	3.451	0.002
Steroids	2.294	1.715	3.067	<0.001				
Non-steroidal immunosuppressive th.	2.574	1.670	3.967	<0.001				
Chemotherapy	1.772	1.177	2.667	0.006				
CVC	2.862	1.971	4.156	<0.001				
TPN	8.162	5.757	11.571	<0.001	6.266	3.240	12.119	<0.001
PICC	8.113	5.469	12.036	<0.001	5.125	2.595	10.118	<0.001
Severe sepsis/septic shock	16.542	10.018	27.317	<0.001	12.544	5.426	29.001	<0.001

IBD = inflammatory bowel disease; COPD = chronic obstructive pulmonary disease; CDI = *Clostridium difficile* infection; β LI = β lactamase inhibitors; IV = intravenous; CVC = central venous catheter; TPN = total parenteral nutrition; PICC = peripherally inserted central catheter.

results (prevalence of candidemia in IMWs ranging from 47.8% to 52%) [11,12].

Patients hospitalized in IMWs have some "traditional" risk factors for candidemia, including immunosuppressive therapy, previous antibiotic therapy, diabetes mellitus and severe sepsis or septic shock at presentation [21]. Among inedited risk factors, it is noteworthy that CDI, diagnosed in the previous 30 days, is a strong factor associated with nosocomial candidemia in IMWs patients.

Patients with recent CDI could be at high risk to develop candidemia for several reasons. First, the presence of recent CDI could be interpreted as a surrogate marker of clinical frailty and previous healthcare exposures. Furthermore, patients with CDI are more likely to receive multiple antibiotic therapies. Taken together, all these factors could contribute to the development of candidemia. However, CDI could also represent a factor increasing the risk of candidemia by other independent mechanisms. It has been demonstrated that CDI may be involved in *Candida* translocation causing severe mucosal injury and disruption of the intestinal epithelial barrier [22–24], and we previously found that severe CDI is associated with the risk of subsequent candidemia [13,25–26]. Then, we may assume that the impairment of gastrointestinal mucosa due to CDI play a pivotal role as predisposing factors for candidemia in patients residing in IMWs.

Of interest, we also found a significant relationship between candidemia and concomitant intravenous glycopeptide therapy. Two studies analyzing pediatric patients cared for in ICUs identified the use of a glycopeptide as a risk factor for candidemia [27–28], and a similar result was obtained in a matched case-control study on elderly patients with nosocomial candidemia [13]. This phenomenon may be explained by the fact that vancomycin decreases the total anaerobic gut bacterial populations, increasing the enteric bacilli population levels and allowing *Candida albicans* to proliferate in the gut [29].

Intravascular devices are established risk factors for candidemia. The PICC (but not the CVC) resulted at the multivariate analysis a factor independently associated with candidemia in our cohort. PICC use has become a common practice in non-ICU settings for administration of antibiotics, chemotherapy and parenteral nutrition, but if PICC is associated with a lower risk of BSI than other devices is still debated [30]. In children, PICC for ≥21 days and TPN were factors independently associated with central line–associated BSI and the most common pathogens were coagulase-negative staphylococci followed by *Candida parapsilosis* [31]. Tascini et al. recently confirmed the presence of PICC was common in patients with very early-onset candidemia in IMWs [32].

Finally, the association between COPD and candidemia could be partially explained by the large use of antibiotic and steroidal immunosuppressive therapy in these patients.

Diagnosis of candidemia in patients residing in IMWs may be challenging for physicians, because the heterogeneity of patients population

Table 3
Risk score for candidemia in patients hospitalized in IMWs.

Risk factor	Points
Severe sepsis/septic shock	+2.5
Recent *Clostridium difficile* infection	+2
Diabetes mellitus	+2
TPN	+1.5
COPD	+1.5
Concomitant glycopeptide therapy	+1.5
PICC	+1.5
Previous antibiotic therapy	+1
Immunosuppressive therapy	+0.5

IMWs = Internal Medicine wards; TPN = total parenteral nutrition; PICC = peripherally inserted central catheter.

Table 4
Distribution of single risk-predictive score and corresponding number of patients with candidemia, sensitivity and specificity in the derivation cohort.

Predictive score value	No. of patients with candidemia	No. of patients without candidemia	Total no. of patients	Sensitivity	Specificity
1	2 (6.1%)	31 (93.9%)	33	99%	41%
2	13 (9.8%)	120 (90.2%)	133	96%	57%
3	28 (51.9%)	26 (48.1%)	54	87%	83%
4	25 (64.1%)	14 (35.9%)	39	69%	91%
5	30 (66.7%)	15 (33.3%)	45	52%	95%
6	30 (90.9%)	3 (9.1%)	33	33%	98%
7	13 (76.5%)	4 (23.5%)	17	20%	99%
8	8 (88.9%)	1 (11.1%)	9	11%	99%
9	9 (100%)	–	9	4%	100%
≥10	5 (100%)	–	5	2%	100%

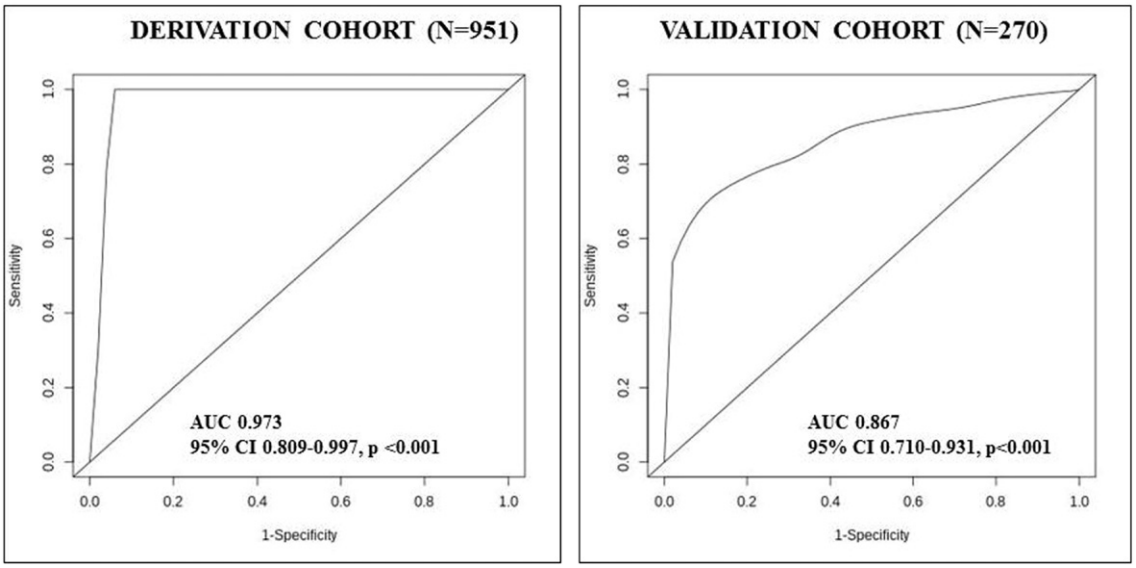

Fig. 1. ROC curve of *Candida* score in the derivation and in the validation cohort.

and the lack of specific symptoms. Furthermore, about 50% of episodes of candidemia in this setting are not associated with fever [33], and the diagnosis may be delayed. Since the mortality for candidemia doubles if antifungal therapy is not delivered within the first 24 h [34–35], the knowledge of specific risk factors, along with the use of diagnostic techniques such as serum beta-D glucan, could be useful for physicians to exclude the presence of candidemia or, conversely, to early recognize patients with suspected candidemia. The proposed risk score has a dual clinical significance. Patients with a negative risk score (≤3) have a low probability of candidemia, and because the high NPV this tool could be used by clinicians to avoid unnecessary empirical antifungal therapy. Conversely, since the specificity of the score increases if the total score is high (>5), it can be used to support the decision to start empirical/pre-emptive antifungal therapy in IMWs patients presenting with systemic inflammatory response syndrome.

Our study have some strengths, but also some limitations. The major strengths of our study are that it considered the specific risk factors for candidemia in a large population of patients hospitalized in IMWs, and the data source were from a multicenter cooperation. Moreover, we proposed a new risk score showing a good performance. The score was also validated in an external population of patients hospitalized in a tertiary-care hospital located in a different geographic area and its good reliability was confirmed. As shown in Supplementary material, the external validation cohort represent a different but plausibly related population. This could be interpreted as a strength of our study because confirms the good generalizability of our risk model.

However, some limitations should be acknowledged: because the retrospective design of the study some information may be missed, including demographic informations, previous diagnostic tests, and data regarding *Candida* multi-site colonization. Moreover, although a standard form was used, data were extracted by four different investigators at each study center, and this may introduce a bias in the collection of data. However, we were able to study a large number of candidemic patients in four tertiary-care centers from different regions and to date this is the largest study performed in the setting of IMWs.

Another study limitation is that both *Candida albicans* and non-*albicans* species were jointly analyzed, although specific risk factors associated with candidemia due to different *Candida* species have been previously reported [4]. However, the aim of our study was to provide a clinical tool easy to apply at bedside in patients with signs and symptoms of BSI prior to the blood cultures results rather than to analyze risk factors for different *Candida* species. Future studies, specifically designed, will differentiate between risk factors for *albicans* vs non-*albicans Candida* spp. among IMWs patients.

In conclusion, we have reported that in patients admitted to IMWs risk factors for candidemia are partially different from those already established in patients cared for in ICUs or in surgical wards. Severe sepsis or septic shock, recent CDI, diabetes mellitus, TPN, COPD, concomitant intravenous glycopeptide therapy, presence of PICC, previous antibiotic therapy and immunosuppressive therapy are factors directly associated with candidemia in non-neutropenic patients admitted to IMWs. The recognition of these risk factors is necessary to identify patients requiring early antifungal therapy. To facilitate this identification, a “nine items” risk score for candidemia in IMWs can be easily used in the clinical practice.

Conflict of interest

The author(s) declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejim.2017.03.005.

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