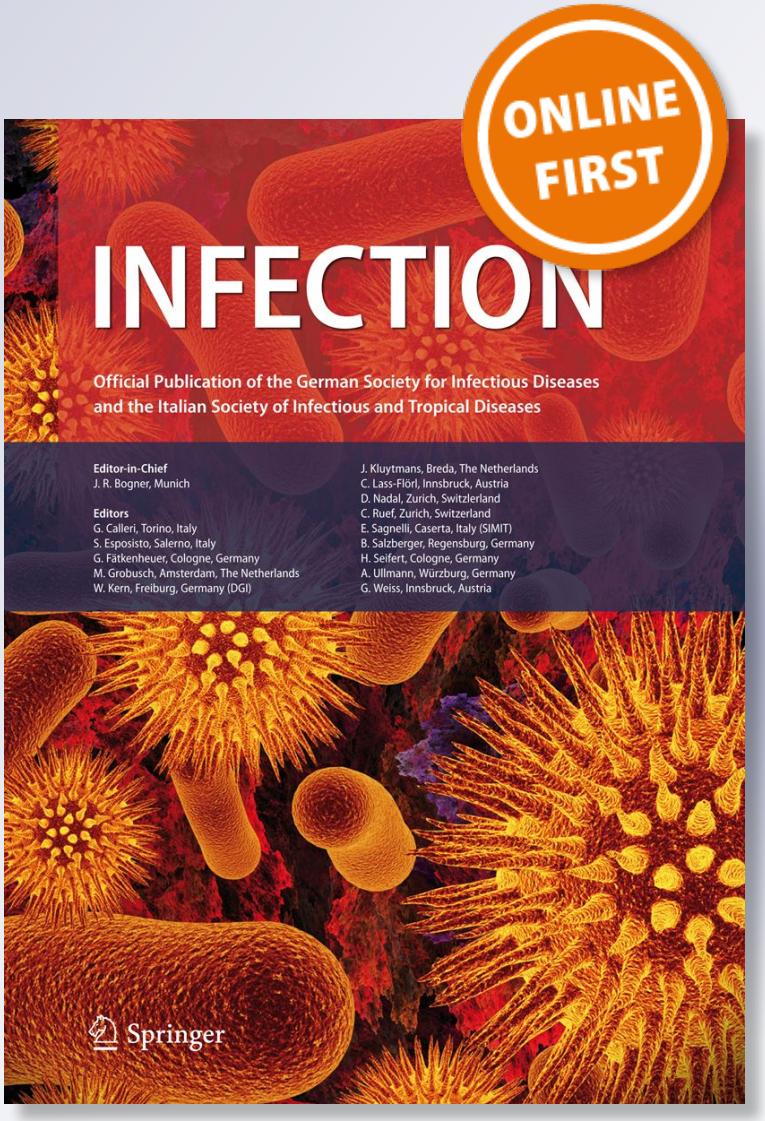
A prediction rule for early recognition of patients with candidemia in Internal Medicine: results from an Italian, multicentric, case–control study

on behalf of GISA/FADOI Candida Study Group

Infection
A Journal of Infectious Diseases

ISSN 0300-8126

Infection
DOI 10.1007/s15010-018-1162-0



Springer

Infection
https://doi.org/10.1007/s15010-018-1162-0

ORIGINAL PAPER

A prediction rule for early recognition of patients with candidemia in Internal Medicine: results from an Italian, multicentric, case–control study

Emanuela Sozio[1] · Filippo Pieralli[2] · Anna Maria Azzini[3] · Giancarlo Tintori[4] · Federica Demma[5] · Gianluca Furneri[5] · Francesco Sbrana[6] · Giacomo Bertolino[7] · Simona Fortunato[8] · Simone Meini[9] · Damiano Bragantini[3] · Alessandro Morettini[10] · Carlo Nozzoli[10] · Francesco Menichetti[8] · Ercole Concia[3] · Carlo Tascini[11] · on behalf of GISA/FADOI Candida Study Group

Received: 17 March 2018 / Accepted: 5 June 2018

Abstract

Purpose Increasing prevalence of candidemia in Internal Medicine wards (IMWs) has been reported in recent years, but risk factors for candida bloodstream infection in patients admitted to IMW may differ from those known in other settings. The aim of this study was to identify risk factors and define a prediction rule for the early recognition of the risk of candidemia in IMW inpatients.

Methods This was a multicentric, retrospective, observational case–control study on non-neutropenic patients with candidemia admitted to IMWs of four large Italian Hospitals. Each eligible patient with candidemia (case) was matched to a control with bacteremia. Stepwise logistic regression analyses were performed.

Results Overall, 300 patients (150 cases and 150 controls) were enrolled. The following factors were associated with an increased risk of candidemia and weighted to build a score: total parenteral nutrition (OR 2.45, $p = 0.008$; 1 point); central venous catheter (OR 2.19, $p = 0.031$; 1 point); peripherally inserted central catheter (OR 5.63, $p < 0.0001$; 3 points), antibiotic treatment prior (OR 2.06; $p = 0.059$; 1 point) and during hospitalization (OR2.38, $p = 0.033$; 1 point); neurological disability (OR 2.25, $p = 0.01$; 1 point); and previous hospitalization within 3 months (OR 1.56, $p = 0.163$; 1 point). At ROC curve analysis, a final score ≥ 4 showed 84% sensitivity, 76% specificity, and 80% accuracy in predicting the risk of candidemia.

Conclusions The proposed scoring system showed to be a simple and highly performing tool in distinguishing bloodstream infections due to Candida and bacteria in patients admitted to IMW. The proposed rule might help to reduce delay in empirical treatment and improve appropriateness in antifungal prescription in septic patients.

Keywords Candidemia · Internal medicine wards · Prediction rule · Risk factors

Introduction

Candidemia is an important cause of bloodstream infections (BSIs), leading to significant mortality and morbidity in health-care settings. The global incidence of candidemia increased fivefold in the past 15 years, and *Candida* spp. are currently between the fourth and the sixth most common nosocomial bloodstream isolates found in studies from the United States and Europe [1–9], representing around the 9% of all nosocomial BSIs [1]. In Italy, its incidence is estimated between 0.8 and 2.53 episodes per 1000 hospital admission [10, 11]. That variability may reflect the different profile of risk factors for candidemia, including demographics, patients' case mix, and different use of invasive procedures [12].

A retrospective cohort study conducted in Intensive Care Unit (ICU) among patients with candidemia shown that candidemia acquired after 48-h ICU stay had significantly more frequent undergone previous surgery and organ failures with cardiovascular, renal, central nervous, and coagulation

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s15010-018-1162-0) contains supplementary material, which is available to authorized users.

✉ Emanuela Sozio
emanuela.sozio@gmail.com

Extended author information available on the last page of the article

systems than candidemia acquired before ICU admission or during the first 48-h [13].

In recent years, an increasing number of Candida BSIs (up to 59% of all nosocomial candidemia) has been observed in patients admitted to Internal Medical Wards (IMWs), where patients are usually old, with multiple comorbidities, and often have multiple risk factors for candidemia [10, 11, 14–18]. Prediction rules for invasive candidiasis, such as the Candida score and Ostrosky-Zeichner score, have been formulated to predict the risk in surgical and medical patients admitted to ICU [19–24]. However, no risk score has been expressly carried out to identify the patients admitted to IMWs at risk of candidemia.

Aim of this study was to identify risk factors for candidemia and develop a prediction rule to assist clinicians to the early recognition of the risk of Candida bloodstream infection in septic patients admitted in IMWs.

Materials and methods

Study design and population

In this multicenter, retrospective, case–control study were included all consecutive adult patients with candidemia admitted in IMWs of Pisa, Firenze, and Verona Hospitals (Italy), between February 2012 and August 2015. Only cases occurred in IMWs were included.

Cases were retrospectively identified through the microbiology laboratory database; in the case of more than one episode of candidemia in the same patient, only the first episode of candidemia was considered for the study.

For each case, one control in the same IMW, reporting bacteremia and matched for age (±5 years), sex, date of hospital admission, and duration of hospitalization (±20 days) at time of first positive blood culture, was selected in a 1:1 ratio. To ensure comparable periods of risk exposure in both groups, each control had a length of hospitalization similar to the time at risk of case (defined as the number of days from hospital admission to candidemia occurrence). Neutropenic patients (absolute neutrophil count of < 1000 cells/mm^3) were excluded. This study was exempt from institutional review board oversight because of its retrospective nature and the anonymity of pooled data.

Data

Cases and controls clinical records were used to collect demographic and clinical data; comorbidities were assessed by the Charlson comorbidity index. Information about invasive devices (central venous catheter—CVC; peripherally inserted central catheter—PICC; bladder catheter—BC; nasogastric tube—NGT), total parenteral nutrition (TPN), acute pancreatitis, broad-spectrum antibiotic and antifungal treatment in the previous 30 days, concomitant antibiotic therapy, steroids or other immunosuppressant treatment, major surgical interventions in previous 3 months, dialysis and *C. difficile* infection (CDI), and data about therapy and laboratory were recorded. Candida colonization defined both by the Candida score and the Ostrosky-Zeichner prediction rule was collected as well [19, 20].

In cases and controls, all risk factors were assessed at the onset of candidemia/bacteremia (date of collection of the blood sample subsequently resulted positive). All collected data have been de-identified to preserve participant's anonymity and confidentiality.

Definitions

A case of candidemia was defined as a patient with at least one blood culture yielding Candida species.

A case of bacteremia was defined as at least one blood culture yielding a Gram-negative or Gram-positive bacteria; in case of coagulase-negative *staphylococci*, at least two consecutive blood culture sets yielding the same strains were required. Blood cultures positive for more than one species were excluded.

We included patients with fever and/or other clinical signs of infection (basing on SIRS criteria). Clinical severity at the diagnosis of candidemia/bacteremia was assessed according to sepsis grading purposed by the Surviving Sepsis Campaign [25].

Microbiology laboratory methods

Blood cultures were processed using the automated blood culture system BacT/Alert 3D (BioMerieux Inc., Marcy-l'Etoile, France). Positive cultures were sub-cultured and identified to the species level by VitekMS or Vitek2 (BioMerieux; Marcy-l'Étoile, France). Susceptibility testing was performed using Vitek2 system and interpreted according to EUCAST criteria effective during the study period.

Statistical analysis

Standard descriptive statistics were used to analyze patients' characteristics at baseline. All continuous variables were expressed as mean and standard deviation (SD). Categorical data were presented as percentages. For the unadjusted analysis, univariate logistic regressions were run. Variables associated with a p value < 0.20 [23, 26, 27] were considered significant and included in multivariate analysis. For the adjusted analysis, multivariate logistic models were realized to identify independent predictors of candidemia. The model with the highest performance was selected. Sensitivity analysis was performed to test the robustness of the

selected model. A candidemia scoring system was created by rounding the odds ratios (ORs) of the chosen model [28, 29]. ROC curve was used to determine the optimal cutoff score to discriminate between the two states "high risk of candida" and "high risk of any bacterial infection".

More details on statistical analysis are shown in Supplementary Materials.

Results

A total of 300 patients with candidemia or bacteremia (150 cases and 150 controls) were included in the study.

Candida albicans was the most commonly documented species (58.7%), followed by *C. parapsilosis* (22%), *C. tropicalis* (7.3%), *C. glabrata* (6.7%), *C. krusei* (2%), *C. famata* (2%), and *C. lusitaniae* (1.3%).

Among controls, Gram-negative strains were 51% and the other 49% were Gram-positive.

The median age of the whole population was 76 years; sex distribution was balanced, with 48.7% of women.

Diagnostic criteria for severe sepsis/septic shock were present in 48.3% of patient population.

In Table 1 are described demographic and clinical features of the enrolled population.

In general, candidemia was a delayed event with respect to bacteremia, since it occurred after a mean of 9 days from admission (9 days ± 10.96, CI 7.27–10.80) versus a mean of 3.7 days for bacteremia (3.72 days ± 8.33, CI 2.37–5.06) ($p < 0.001$).

Table 1 Comparison of patients with candidemia (cases) and patients with bacteremia (controls) admitted in internal medical wards

Variables	Global population ($N = 300$)	Patients with candidemia (cases) ($N = 150$)	Patients with bacteremia (controls) ($N = 150$)
Age [mean; median (SD)]	73.5; 76.8 (14.8)	74.3; 77.7 (14.6)	72.6; 76.1 (15.0)
Sex (female)	146 (48.7%)	73 (48.7%)	73 (48.7%)
Diagnostic criteria for severe sepsis/septic shock	145 (48.3%)	86 (57.3%)	59 (39.3%)
Fever	260 (86.7%)	123 (82.0%)	137 (91.3%)
Charlson score [mean; median (SD)]	5.3; 5 (3.5)	6.1; 6 (3.4)	4.5; 4 (3.4)
Ostrosky-Zeichner score	95 (31.7%)	65 (43.3%)	30 (20.0%)
Candida score [mean; median (SD)]	1.8; 2 (1.4)	2.3; 2 (1.3)	1.3; 1 (1.2)
Days to blood culture [mean; median (SD)]	6.4; 2.0 (10.1)	9.0; 5.5 (11.0)	3.7; 0.0 (8.3)
Hospitalizations in the previous 3 months	178 (59.3%)	108 (72.0%)	70 (46.7%)
Previous antibiotic treatment	177 (59.0%)	117 (78.0%)	60 (40.0%)
Previous *C. difficile* infection	19 (6.3%)	15 (10.0%)	4 (2.7%)
Previous antifungal treatment	20 (6.7%)	11 (7.3%)	9 (6.0%)
Immunosuppressants	22 (7.3%)	7 (4.7%)	15 (10.0%)
Steroids during hospitalization	121 (40.33%)	75 (50.0%)	46 (30.7%)
Antibiotics during hospitalization	187 (62.3%)	122 (81.3%)	65 (43.3%)
TPN	107 (35.7%)	83 (55.3%)	24 (16.0%)
NGT	64 (21.3%)	45 (30.0%)	19 (12.7%)
PICC	87 (29%)	70 (46.7%)	17 (11.3%)
CVC	92 (30.7%)	49 (32.7%)	43 (28.7%)
BC	190 (63.6%)	116 (77.3%)	74 (49.3%)
Chronic kidney disease	68 (22.7%)	25 (16.7%)	43 (28.7%)
Diabetes mellitus	95 (31.7%)	42 (28.0%)	53 (35.3%)
Liver disease	31 (10.3%)	18 (12.0%)	13(8.7%)
Cancer	78 (26.0%)	42 (28.0%)	36 (24.0%)
Dementia	59 (19.7%)	43 (28.7%)	16 (10.7%)
Cerebrovascular disease	86 (28.7%)	57 (38.0%)	29 (19.3%)
Severe functional impairment as Hemiplegia	37 (12.3%)	26 (17.3%)	11 (7.3%)
Ischemic heart disease	50 (16.7%)	17 (11.3%)	33 (22.0%)
Peripheral vascular disease	67 (22.3%)	41 (27.3%)	26 (17.3%)
Congestive heart failure	44 (14.7%)	18 (12.0%)	26 (17.3%)

TPN total parenteral nutrition, *PICC* peripherally inserted central catheter, *CVC* central venous catheter, *BC* bladder catheter, *NGT* nasogastric tube

By a first comparison between cases and controls, factors significantly associated with a moderate to strong risk of candidemia were: TPN (OR = 6.50; $p < 0.001$); presence of an intravascular device such as PICC or CVC (OR = 5.75; $p < 0.001$), with a very strong association with PICC (OR = 6.84; $p < 0.001$) respect to CVC (OR = 1.20; $p = 0.4530$); previous antibiotic therapy (OR = 5,31; $p < 0.001$) and antibiotic treatment during hospitalization (OR = 5.69; $p < 0.001$); *C. difficile* infection in the previous 30 days (OR = 4.05; $p = 0.0150$); BC (OR = 3.5; $p < 0.001$); presence of neurological disability such as cerebrovascular disease, dementia, hemiplegia (OR = 3.0; $p < 0.001$); hospitalization in the previous 3 months (OR = 2.94; $p = 0.0150$), and presence of a NGT (OR = 2.95; $p < 0.001$).

Table 2 describes univariate (unadjusted) analysis of risk factors for candidemia and bacteremia in our population.

The OR of all the variables resulted significant at the 0.20 level were rounded and used as points assigned to each variable (see more details on Supplementary Materials). From these data and with respect to the better performing statistical model, we deduced a very strong risk of candidemia in patients with PICC, and a moderate to strong risk in patients receiving TPN, previously hospitalized, in those with previous and/or concomitant antibiotic therapy, in the presence of a CVC or affected by neurological disability.

Table 3 shows the OR of all the variables of the better performing statistical model (see more details on Supplementary Materials).

Using the best performing statistical model (see more details on Supplementary Materials), a new prediction rule for candidemia for septic patients hospitalized in IMWs was built up. Table 4 summarizes this score and the points assigned to each variable.

Using ROC curve analysis, the threshold to define a high risk for candidemia was a score greater or equal than 4. A patient with a final score ≥ 4 was at high risk to be affected by candidemia; a patient reporting a final score < 4 was at high risk to be affected by bacteremia.

Table 5 summarizes performances of the score.

A score ≥ 4 correctly identified 126 out of 150 candidemias (84% true positive) and misidentified as fungal infections 36/150 bacteremias (24% false positive). On the other hand,

Table 2 Univariate (unadjusted) analysis of risk factors for candidemia and bacteremia in Internal Medicine Wards

Variables	Candidemia ($N = 150$), %	Bacteremia ($N = 150$), %	OR	95% CI	*p* value
TPN	55.3	16.0	6.50	3.78–11.19	< 0.0001
Intravascular devices (PICC and CVC)	79.3	40.0	5.75	3.45–9.61	< 0.0001
PICC	46.7	11.3	6.84	3.76–12.45	< 0.0001
Previous antibiotic therapy	78.0	40.0	5.31	3.20–8.82	< 0.0001
Antibiotics during hospitalization	81.3	43.3	5.69	3.38–9.60	< 0.0001
BC	77.3	49.3	3.50	2.13–5.77	< 0.0001
Neurological Disability[a]	54.7	28.7	3.00	1.86–4.84	< 0.0001
Hospitalization in the previous 3 months	72.0	46.7	2.94	1.82–4.75	< 0.0001
NGT	30.0	12.7	2.95	1.63–5.35	< 0.0001
Steroids during hospitalization	50.0	30.7	2.26	1.41–3.62	0.0001
Chronic kidney disease	16.7	28.7	0.50	0.28–0.87	0.0140
Previous *C. difficile* infection	10.0	2.7	4.05	1.31–12.52	0.0150
Fever	82.0	91.3	0.43	0.21–0.87	0.0200
Immunosuppressants	4.7	10.0	0.44	0.17–1.11	0.0830
Diabetes mellitus	28.0	35.3	0.71	0.44–1.16	0.1730
Liver disease	12.0	8.7	1.43	0.68–3.05	0.3450
Cancer	28.0	24.0	1.23	0.73–2.06	0.4300
CVC	32.7	28.7%	1.20	0.74–1.97	0.4530
Previous antifungal therapy	7.3	6.0	1.24	0.49–3.08	0.6440
Cardiovascular disease[c]	40.0	39.3	1.02	0.65–1.63	0.9600
Female sex	48.7	48.7	1.00	0.63–1.58	1.0000
Age ≥ 63.07[b]	80.0	74.0	1.41	0.82–2.41	0.2180

TPN total parenteral nutrition, *PICC* peripherally inserted central catheter, *CVC* central venous catheter, *BC* bladder catheter, *NGT* nasogastric tube

[a]Presence of at least one of the following conditions: cerebrovascular disease, dementia, and hemiplegia

[b]Threshold obtained using ROC curve

[c]Presence of at least one of the following conditions: ischemic heart disease, congestive heart failure, and peripheral vascular disease

Table 3 Selected model and candidemia prediction rule

Variable	OR	*p* value	Rounded coefficient
Hospitalizations in the previous 3 months	1.56	0.1630	2
Previous antibiotic treatment	2.06	0.0590	2
Antibiotics during hospitalization	2.38	0.0330	2
Immunosuppressant	0.40	0.1030	0
CVC	2.19	0.0310	2
PICC	5.63	0.0000	6
TPN	2.45	0.0080	2
Neurological disability	2.25	0.0100	2
Kidney failure	0.68	0.2780	NS
Fever	0.71	0.4740	NS
Steroids	1.14	0.6740	NS
Clostridium difficile infection	1.35	0.6560	NS
Constant	1.56	0.1630	-

All the variables assumed value 1 if Yes; 0 otherwise

CVC central venous catheter, *PICC* peripherally inserted central catheter, *TPN* total parenteral nutrition, *NS* not significant so not considered in the scoring system

Table 4 Risk score for candidemia in patients hospitalized in IMWs

Risk factor	Points
PICC	+3
CVC	+1
TPN	+1
Neurological disability[a]	+1
Hospitalization in the previous 3 months	+1
Previous antibiotic therapy	+1
Antibiotics during hospitalization	+1

PICC peripherally inserted central catheter, *CVC* central venous catheter, *TPN* total parenteral nutrition

[a]Presence of at least one of the following conditions: cerebrovascular disease, dementia, and hemiplegia

it misidentified as bacterial infections 24 out of 150 candidemias (16% false negative). PICC was absent in all of these false negative patients.

Discussion

The incidence of candidemia is growing in patients admitted to IMWs because of demographic changes, with growing numbers of frail elderly patients affected by multiple comorbidities, and the increasing use of invasive procedures and complex surgical techniques that subsequently increase the risk of health-care-associated infections [1–12].

Thus, candidemia is an important challenge for Internists, who should be aware of it, since the high mortality and morbidity rates prolonged hospitalization and increased costs for the entire health-care system [6, 30].

Despite the increasing incidence of candidemia in patients admitted in IMW, there is to date scant evidence on the characterization of risk factors on this specific population.

In this study, we describe risk factors independently associated with an increased risk of candidemia in a population of patients admitted and entirely managed in an IMW.

At the ultimate analysis, the presence of a central venous line, TPN, hospitalization during the previous 3 months, previous (within 1 month) or ongoing antibiotic therapy, and severe neurological disability (including dementia and invalidating stroke) represent factors independently associated with a significant increasing risk for candidemia. All these factors increase the probability of candidemia by a factor of 2, whereas the presence of a PICC increases that probability by a factor of 5.

Available data about risk profiles for candidemia mainly derive from ICU and surgical wards, where patients' characteristics are deeply different from those of patients admitted in IMWs, for the burden of comorbidities, and demographic and health-care-related factors.

For these and other reasons, scores designed for ICU or surgical patients (i.e., Ostrosky-Zeichner and Leon candida score) [19, 20] are realistically unsuitable for the application in IMWs, where a large part of candidemias occur, and our results seem of value adding new insight in a setting for which data are currently lacking.

To predict the risk of candidemia in IMWs setting, we derived a prediction rule that showed a high NPV (82.6%) with a favorable PPV (77.8%), a global accuracy of 80%, and a good performance in terms of sensitivity (84%) and specificity (76%).

This prediction rule would have permitted to correctly identify 126 out of 150 candidemias (84% of true positives) and to misidentify as fungal infection 36/150 bacteremias (24% of false positives). On the contrary, it would have misidentified as bacterial infections, 24/150 candidemias (16% of false negatives). We consider this latter group of utmost importance, because even in the presence of a documented fungemia they would have been probably misinterpreted and not treated with antifungal agents, according to this score, at least until blood culture turned positive.

A score greater or equal than 4 would be able to discriminate patients that would need an early empiric antifungal therapy, but we suggest that all septic patients should anyway start an empirical antibiotic therapy, since even with a score ≥ 4 about 25% of patients with BSI due to bacteria could be misidentified as fungal infection.

Table 5 Performance of the proposed score

Prediction rule for a score ≥ 4		
Number of observed	Number of predicted	
	Candidemia	Bacteremia
Candida BSIs ($N = 150$)	126	24
Bacterial BSIs ($N = 150$)	36	114
Performance indicators		
PPV	77.8%	
NPV	82.6%	
Sensitivity	84.0%	
Specificity	76.0%	
Accuracy	80.0%	

PPV positive predictive value, *NPV* negative predictive value

Then, our score could be useful as a decision support for the Internists in starting an empiric antifungal therapy in addition to antibiotic therapy in front of a patient with sepsis.

If the score is lower than 4, the antifungal therapy could be delayed, since the high NPV (82.6%).

Of note, PICC was absent in all the 24 falsely negative patients. The presence of a PICC was associated with the greatest risk of candidemia at multivariate analysis: it independently increased the probability of candidemia more than 5 times. As previously shown by Tascini et al. [33], PICC is a much stronger risk factor for candidemia than for bacteremia, probably since it is a long standing device and mainly predispose to the adherence of biofilm-producing yeasts instead of bacteria.

In our series, even other classical risk factors were related to a significant increasing risk of candidemia. At multivariate analysis CVC, TPN, previous or current antibiotic therapy, and hospitalization within 3 months from the index event, increased the risk of candidemia roughly two times with respect to bacteremia. All these are known risk factors for candidemia and may reflect the frailty and complexity of the elderly people admitted to IMWs [31–33].

It is known that *Candida* species are an important cause of invasive infection at the extremes of age, and the elderly population, which is increasing worldwide, is particularly vulnerable due to high frequency of comorbidities, aging-related physiological changes, polypharmacy [34–36].

In the referral studies by Ostrosky-Zeichner and Leon on prediction rules for invasive candidiasis inside ICU and surgical settings, the mean age of enrolled patients was 59 and 60 years, respectively [19, 20]. In our study, the mean age of enrolled patients was 74 years with a median of 77 years, closely reflecting current demographics of patients seen in clinical practice. Our study, representing real-world general medicine inpatients, can provide additional data on a very frail population at a higher risk of death and complications independently of severity and origin of infection.

In general, multiple factors account for the increased susceptibility of older patients to infections, including immune senescence, institutionalization, and concomitant chronic comorbidities [12]. All these factors expose subjects to endogenous or exogenous candidemia, both throughout mucosal barrier damage and extensive exposure to broad-spectrum antibiotics or invasive medical devices, procedures and treatments, such as TPN [11, 34, 37, 38]. Of note, TPN is a widely recognized risk factor for candidemia [39], and it is a matter of fact that the presence of lipid emulsions and glucose in TPN formulations promotes the production of *Candida*'s biofilm [40–42], making infusion lines and catheters the ideal place for yeasts' colonization and replication. Moreover, prolonged fasting due to lack of enteral nutrition reduces physiological peristalsis and promotes alteration of the intestinal barrier, thus facilitating the translocation into bloodstream of intestinal microorganisms, including *Candida* spp [43].

Also Luzzati et al. [18] in a study on candidemia in IMWs found that risk factors significantly associated with candidemia onset were the presence of a CVC and TPN with an increasing gradient sustained by the increasing duration of treatment.

More recently, Falcone et al. [44], studying risk factors for candidemia in a multicenter case–control study, identified independent risk factors and derived a score that was subsequently tested in a validation cohort. At multivariate analysis risk factors for candidemia resulted: *Clostridium difficile* infection, diabetes mellitus, TPN, chronic obstructive pulmonary disease (COPD), concomitant intravenous glycopeptide therapy, presence of PICC, previous antibiotic therapy, and immunosuppressive therapy.

In our cohort, factors of increased risk of candidemia were quite similar, with the exception of *C. difficile*

infection (which was significant only at unadjusted analysis), immunosuppressive therapy, glycopeptide therapy, and comorbidities such as diabetes and COPD.

In our study, a factor significantly associated to the risk of candidemia was the presence of neurological disability, defined as stroke or dementia causing substantial functional impairment in daily activities. To the best of our knowledge, this is the first time that neurological disability is shown as a risk factor for candidemia. Even if originally this observation is not surprising, since we can argue that neurological disability caused by severe stroke or advanced dementia portrays a fragile subject with substantial loss of functional autonomy, often malnourished or at risk of malnutrition, needing supportive measures, and frequently administered through a PICC. Patients with significant neurological disability often reside in long-term care facilities, where the exposure to broad-spectrum antibiotics, a known risk factor for candidemia, is frequent and may contribute to increasing the risk of candidemia.

The interpretation of the main differences among identified risk factors in our study with respect to others may be various. We could hypothesize the different profile of the hospitalized population of different Italian regions and the different attitudes of different IMWs to a peculiar type of medical patients, that finally shows a different risk toward candidemia (i.e., oncological, hematological, subintensive, and post-surgical).

Importantly, the main difference among our series and the others is the selection of control cases.

Specifically, in our population both cases and controls are patients with BSIs, whereas sepsis was not a criterion for selection of controls in the studies by Luzzati and Falcone [18, 44]. In our opinion, this is a main and important difference, since we deem fundamental trying to identify risk factors for candidemia starting from the point of view of a potential septic syndrome, which constitute the starter for the initial clinical suspicion, as it was the cohort in our study represented by patients with BSIs. This condition could be a selection bias together with the fact that, primarily due the retrospective nature of the study, it is not possible to define exactly the grading of the septic state of patients. This study identifies renal failure or cancer, such as the presence of fever, treatments with steroids, and Clostridium difficile infection, as risk factors for both candidemic and bacteriemic patients. We do not state that these risk factors do not play a major role as a risk factor for infections due to Candida, but that does not allow us to identify the likelihood of a candidemia in a patient who has an infection.

We are aware that the prediction rule proposed requires a prospective validation in a larger patient cohort, which could possibly consider both bacterial and fungal sepsis and negative controls.

Although the limits of this work, we believe it could help the internist physician in the challenge of early recognition of a candidemia to start a timely empirical antifungal therapy combined with empiric antibiotic therapy. Infact, as shown in several studies, prompt diagnosis for a timely treatment could be difficult in older patients (lack of fever or other clinical signs of systemic infection) [45]. But it is crucial in candidemic patients, being mortality higher in case of a delay in antifungal treatment's prescription [3, 11]. This score could help to promptly start empirical antifungal therapy in patients at risk for candidemia and could help physicians to select patients that should undergo integrative non-cultural tests, such as mannan–antimannans and/or beta-D-glucan, in an appropriate manner for a better definition of the probability of candidemia. Also procalcitonin levels could be very useful to further discriminate between bacterial and fungal bloodstream infections, but for the retrospective design of our study, these data resulted lacking in many enrolled patients, so we could not analyze it and incorporate into our score [46].

This study has strengths and limitations. Among the first ones, we underline the use of real-world data, the inclusion of patients with BSIs both in cases and controls, the evaluation of a large number of predictors, the availability of the information at admission time, and the conduction of sensitivity analyses. However, the study has some limitations as well. In clinical trials, randomization is intended to balance the distribution of both known and unknown confounding factors in the compared groups. This is rarely possible in observational studies and a systematic bias could be generated even when cases are matched with controls. Even if the 1:1 matching adopted in this cohort could reflect the distribution of candidemia and bacterial infections in the real practice, the scoring system should be tested in a more balanced dataset. Selection bias might have occurred because patients with missing data were excluded and the multivariate analysis was restricted to patients who had complete data set. In addition, couples of variables were dichotomized. Although this strategy simplifies the creation of a risk score, the use of continuous variables has the potential to provide more refined information. Despite a comparison with the existing test was performed, the smaller size of the cohort implies that these results should be reproduced in a larger one to achieve more robust results and compare to other scoring systems. Finally, even if sensitivity analyses were conducted, the presence of a testing set should have made more rigorous the model validation process. For all these reasons, further insights are needed and the proposed score should be used to drive perspective validations.

Conclusions

The proposed scoring system obtained by the identification of risk factors for candidemia in patients admitted to IMW for bloodstream infections showed to be a simple and highly performing tool in distinguishing candida and bacterial sepsis through sensitivity analyses. The proposed rule might help to identify patients in IMWS at high risk of candidemia, guide the indication for non-cultural testing, reduce the delay in empirical treatment, and improve appropriateness in antifungal prescription. Due to the retrospective nature of the study, prospective validations in larger patient cohorts are needed to confirm these preliminary findings.

Funding No financial support was received.

Compliance with ethical standards

Conflict of interest CT has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck, and Astellas. All other authors: none to declare.

References

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39:309–17.
2. Marchetti O, Bille J, Fluckiger U, et al. Epidemiology of candidaemia in Swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis. 2004;38:311–20.
3. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of Candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother. 2005;49:3640–5.
4. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 2013;173:2039–46.
5. Cleveland AA, Farley MM, Harrison LH, et al. Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011. Clin Infect Dis. 2012;55:1352–61.
6. Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis. 2005;41:1232–9.
7. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med. 1988;148:2642–5.
8. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev. 2007;20:133–63.
9. Puig-Asensio M, Padilla B, Garnacho-Montero J, et al. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect. 2014;20:O245–54.
10. Bassetti M, Merelli M, Righi E, et al. Epidemiology, species distribution, antifungal susceptibility, and outcome of Candidemia across five sites in Italy and Spain. J Clin Microbiol. 2013;51:4167–72.
11. Bassetti M, Taramasso L, Nicco E, Molinari MP, Mussap M, Viscoli C. Epidemiology. Species distribution, antifungal susceptibility and outcome of nosocomial Candidemia in a Tertiary Care Hospital in Italy. PLoS One. 2011;6:e24198.
12. Luzzati R, Merelli M, Ansaldi F, et al. Nosocomial candidemia in patients admitted to medicine wards compared to other wards: a multicentre study. Infection. 2016;44:747–55.
13. Ylipalosaari P, la-Kokko TI, Karhu J, et al. Comparison of the epidemiology, risk factors, outcome and degree of organ failures of patients with candidemia acquired before or during ICU treatment. Crit Care. 2012;16(2):R62.
14. Milazzo L, Peri AM, Mazzali C, et al. Candidaemia observed at university hospital in Milan (northern Italy) and review of published studies from 2010 to 2014. Mycopathologia. 2014;178:227–41.
15. De Rosa FG, Corcione S, Filippini C, et al. The effect on mortality of fluconazole or echinocandin treatment in candidemia in internal medicine wards. PLoS One. 2015;10:e0125149.
16. Hii IM, Chang HL, Lin LC, et al. Changing epidemiology of candidemia in a medical center in middle Taiwan. J Microbiol Immunol Infect. 2015;48:306–15.
17. Guimaraes T, Nucci M, Mendonca JS, et al. Epidemiology and predictors of a poor outcome in elderly patients with candidemia. Int J Infect Dis. 2012;16:e442–7.
18. Luzzati R, Cavinato S, Giangreco M, et al. Peripheral and total parenteral nutrition as the strongest risk factors for nosocomial candidemia in elderly patients: a matched case–control study. Mycoses. 2013;56:664–71.
19. León C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("Candida score") for early antifungal treatment in non-neutropenic critically ill patients with Candida colonization. Crit Care Med. 2006;34:730–7.
20. Ostrosky-Zeichner L, Sabel C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis. 2007;26:271–6.
21. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol. 2005;43:235–43.
22. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg. 1994;220:751–8.
23. Dunning J, Au JK, Millner RW, Levine AJ. Derivation and validation of a clinical scoring system to predict the need for an intra-aortic balloon pump in patients undergoing adult cardiac surgery. Interact Cardiovasc Thorac Surg. 2003;2:639–43.
24. Faiz S, Neale B, Rios E, et al. Risk-based fluconazole prophylaxis of Candida bloodstream infection in a medical intensive care unit. Eur J Clin Microbiol Infect Dis. 2009;28:689–92.
25. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2013;39:165–228.
26. Imtiaz R, Hawken S, McCormick BB, Leung S, Hiremath S, Zimmerman DL. Diabetes mellitus and younger age are risk factors for hyperphosphatemia in peritoneal dialysis patients. Nutrients. 2017;9:2.
27. Hon HH, Wojda TR, Barry N, et al. Injury and fatality risks in aeromedical transport: focus on prevention. J Surg Res. 2016;204:297–303.
28. Piombo AC, Gagliardi JA, Guetta J, et al. A new scoring system to stratify risk in unstable angina. BMC Cardiovasc Disord. 2003;3:8.

29. Soto A, Solari L, Agapito J, et al. Development of a clinical scoring system for the diagnosis of smear-negative pulmonary tuberculosis. Braz J Infect Dis. 2008;12:128–32.
30. Falagas ME, Aostolou KE, Pappas VD. Attributable mortality of candidemia. Eur J Clin Microbiol Infect Dis. 2006;25:419–25.
31. Peres-Bota D, Rodriguez-Villalobos H, Dimopoulos G, Melot C, Vincent JL. Potential risk factors for infection with *Candida* spp. in critically ill patients. Clin Microbiol Infect. 2004;10:550–5.
32. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis. 1995;20:1531–4.
33. Tascini C, Sozio E, Tintori G, et al. Peripherally inserted central catheter as a predominant risk factor for candidemia in critically ill patients in internal medicine wards in Italy. Intensive Care Med. 2015;41:1498–9.
34. Luzzati R, Cavinato S, Deiana ML, Rosin C, Maurel C, Borelli M. Epidemiology and outcome of nosocomial candidemia in elderly patients admitted prevalently in medical wards. Aging Clin Exp Res. 2015;27:131–7.
35. Laupland KB, Gregson DB, Church DL, Ross T, Elsayed S. Invasive Candida species infections: a 5 year population-based assessment. J Antimicrob Chemother. 2005;56:532–7.
36. Barchiesi F, Orsetti E, Mazzanti S, et al. Candidemia in the elderly: what does it change? PLOS ONE. 2017;12:e0176576.
37. Falcone M, Concia E, Iori I, et al. Identification and management of invasive mycoses in internal medicine: a road-map for physicians. Intern Emerg Med. 2014;9:501–11.
38. Tortorano AM, Prigitano A, Lazzarini C, et al. A 1-year prospective survey of candidemia in Italy and changing epidemiology over one decade. Infection. 2013;41:655–62.
39. McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. Crit Care Med. 2014;42:2600–10.
40. Shin JH, Kee SJ, Shin MG, et al. Biofilm production by isolates of Candida species recovered from nonneutropenic patients: comparison of bloodstream isolates with isolates from other sources. J Clin Microbiol. 2002;40:1244–8.
41. Branchini ML, Pfaller MA, Rhine-Chalberg J, Frempong T, Isenberg HD. Genotypic variation and slime production among blood and catheter isolates of *Candida parapsilosis*. J Clin Microbiol. 1994;32:452–6.
42. Swindell K, Lattif AA, Chandra J, Mukherjee PK, Ghannoum MA. Parenteral lipid emulsion induces germination of *Candida albicans* and increases biofilm formation on medical catheter surfaces. J Infect Dis. 2009;200:473–80.
43. Pappo I, Polacheck I, Zmora O, Feigin E, Freund HR. Altered gut barrier function to Candida during parenteral nutrition. Nutrition. 1994;10:151–4.
44. Falcone M, Tiseo G, Tascini C, et al. Assessment of risk factors for candidemia in non-neutropenic patients hospitalized in internal medical wards: a multicentre study. Eur J Int Med. 2017;41:33–8.
45. Tascini C, Falcone M, Bassetti M, et al. Candidemia in patient with body temperature below 37 °C and admitted to internal medicine wards: assessment of risk factors. Am J Med. 2016;129:1330.e1–6.
46. Pieralli F, Corbo L, Torrigiani A, et al. Usefulness of procalcitonin in differentiating Candida and bacterial blood stream infections in critically ill septic patients outside the intensive care unit. Intern Emerg Med. 2017;12:629–35.

Affiliations

Emanuela Sozio[1] · Filippo Pieralli[2] · Anna Maria Azzini[3] · Giancarlo Tintori[4] · Federica Demma[5] · Gianluca Furneri[5] · Francesco Sbrana[6] · Giacomo Bertolino[7] · Simona Fortunato[8] · Simone Meini[9] · Damiano Bragantini[3] · Alessandro Morettini[10] · Carlo Nozzoli[10] · Francesco Menichetti[8] · Ercole Concia[3] · Carlo Tascini[11] · on behalf of GISA/FADOI Candida Study Group

1 Emergency Department, North-West District, Tuscany HealthCare, Spedali Riuniti Livorno, Viale Alfieri 36, 57100 Leghorn, Italy

2 Intermediate Care Unit, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

3 Infectious Disease Unit, Azienda Ospedaliera Universitaria Integrata di Verona, p.Le LA Scuro, Verona, Italy

4 Emergency Medicine Unit, Nuovo Santa Chiara University Hospital, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

5 Health Economics and Outcome Research Department-EBMA Consulting, Milan, Italy

6 Fondazione Toscana Gabriele Monasterio, Pisa, Italy

7 Pharmaceutical Department, Ospedale di Sassuolo, Modena, Italy

8 Infectious Diseases Clinic, Nuovo Santa Chiara University Hospital, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

9 Department of Internal Medicine, S.M. Annunziata Hospital, Florence, Italy

10 Internal Medicine Unit, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

11 First Division of Infectious Diseases, Cotugno Hospital, Azienda Ospedaliera dei Colli, Naples, Italy