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Original Article

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

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