Journal of Critical Care 30 (2015) 715–720

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Development and validation of a clinical prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock☆

Cristina Vazquez Guillamet, MD [a], Rodrigo Vazquez, MD [b], Scott T. Micek, PharmD [c], Oleg Ursu, PhD [d], Marin Kollef, MD [e,*]

[a] Division of Pulmonary, Critical Care, and Sleep Medicine And Division of Infectious Diseases, University of New Mexico School of Medicine, Albuquerque, NM
[b] Division of Pulmonary, Critical Care, and Sleep Medicine, University of New Mexico School of Medicine, Albuquerque, NM
[c] Division of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, MO
[d] Division of Translational Informatics, University of New Mexico School of Medicine, Albuquerque, NM
[e] Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO

ARTICLE INFO

Keywords:
Septic shock
Candida
Outcomes
Prediction
Mortality

ABSTRACT

Objective: To develop and internally validate a prediction rule for the presence of candidemia in patients with severe sepsis and septic shock (candidemia rule) that will fill the gap left by previous rules. To compare the accuracy of the available *Candida* prediction models.
Design: Retrospective cohort study.
Setting: Barnes-Jewish Hospital, St. Louis, Missouri.
Patients/Subjects: Two thousand five hundred ninety-seven consecutive patients with a positive blood culture and severe sepsis or septic shock.
Interventions: Logistic regression and a bootstrap resampling procedure were employed for model development and internal validation.
Measurements and Main Results: Two hundred sixty-six (10.2%) had blood cultures positive for *Candida* spp. Mortality was significantly higher in patients with candidemia than in patients with bacteremia (47.0% versus 28.4%; $P < .001$). Administration of total parenteral nutrition, prior antibiotic exposure, transfer from an outside hospital or admission from a nursing home, mechanical ventilation and presence of a central vein catheter were independent predictors of candidemia while the lung as a source for infection was protective. The prediction rule had an area under the receiver operating characteristic curve of 0.798 (95% CI 0.77-0.82). Internal validation using bootstrapping technique with 1000 repetitions produced a similar area under the receiver operating characteristic curve of 0.797 (bias, −0.037; root mean square error 0.039). Our prediction rule outperformed previous rules with a better calibration slope of 0.96 and Brier score of 0.08.
Conclusions: We developed and internally validated a prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock that outperformed previous prediction rules. Our study suggests that locally derived prediction models may be superior by accounting for local case mix and risk factor distribution.

1. Introduction

Invasive candidiasis has become a growing problem for hospitalized patients, especially in the critically ill where it is thought to be responsible for 17% of culture positive infections [1]. *Candida* represents the fourth most common nosocomial bloodstream infection accounting for approximately 5% to 10% of these infections [2–4]. Moreover, candidemia is typically associated with hospital mortality greater than fifty percent and increased overall healthcare costs [4–11]. Delays in initiating timely antifungal therapy, especially when septic shock is present, has repeatedly been demonstrated to be associated with excess mortality [6,7,11–14]. Such delays in therapy have placed an emphasis on identifying patients at high risk for invasive candidiasis using clinical prediction models [15–19] or *Candida* colonization [20,21]. However, few attempts have been made to externally validate these prediction models or to focus on the prediction of *Candida* infection in septic shock [22–25].

Multiple risk factors for candidemia, promoting either colonization with *Candida* or bloodstream invasion, have been described [15,16,20,21,26–31]. In the face of a rising incidence and need for timely antifungal treatment, especially in septic shock, clinicians are left with the challenge of identifying the right patients for empiric antifungal treatment. Previous prediction models focused on

☆ Financial Support/Conflicts of Interest: Dr Kollef's efforts were supported by the Barnes-Jewish hospital foundation.
* Corresponding author at: Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8052, St. Louis, MO 63110. Tel.: +1 314 454 8764; fax: +1 314 454 5571.
E-mail address: mkollef@dom.wustl.edu (M. Kollef).

http://dx.doi.org/10.1016/j.jcrc.2015.03.010
0883-9441/

invasive candidiasis and targeted only a subset of critically ill patients with prolonged intensive care unit (ICU) stay neglecting newly - admitted patients. More so, different patient characteristics and case mix require re-evaluation and updating of previous prediction models. Therefore, we set out to develop and internally validate a prediction rule that identifies patients with severe sepsis or septic shock who are at significant risk for *Candida* bloodstream infection using readily available variables. Another goal of this study was to compare the relative accuracy of the locally derived prediction model to previously described prediction rules for *Candida* bloodstream infection in our population.

2. Materials and methods

2.1. Study location and patient population

This study was conducted at a university-affiliated, urban teaching tertiary hospital: Barnes-Jewish Hospital (1250 beds). Over a 5-year period (January 2008-December 2012) all hospitalized patients with severe sepsis or septic shock and a positive blood culture were eligible for inclusion. This study was approved by the Washington University School of Medicine Human Studies Committee.

2.2. Study design and data collection

Using a retrospective cohort study design, patients were identified by the presence of a positive blood culture combined with primary or secondary *ICD-9-CM* codes indicative of sepsis and acute organ dysfunction and/or the need for vasopressors. The primary endpoint for our study was presence of candidemia. Baseline characteristics including age, gender, race, admission source, modified Acute Physiology and Chronic Health Evaluation (APACHE) II score were recorded. Possible risk factors for candidemia as previously described [15,16,20,21,26–31] were also recorded to include presence of a central vein catheter, mechanical ventilation, septic shock, prior antibiotic use, diabetes mellitus, presence of immunosuppression, total parenteral nutrition (TPN), recent surgery, and the duration of hospitalization prior to bloodstream infection.

2.3. Definitions

To be included in the study, severe sepsis and septic shock had to be temporally related (+/− 24 hours) to the positive blood cultures. Septic shock was defined by the need for vasopressors (norepinephrine, vasopressin, dopamine, epinephrine, phenylephrine). Candidemia was defined as one or more positive blood cultures for any *Candida* species. Bacteremia was defined as positive blood cultures with pathogenic bacteria (e.g. *Streptococcus pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa*). In cases where usual blood culture contaminants were isolated (e.g. coagulase-negative staphylococci, *corynebacterium* species), patients were included only if they had multiple cultures positive for the same organism or if the clinical scenario (e.g., presence of endocarditis) qualified the organism as a true pathogen.

Central vein catheters had to present for at least 48 hours prior to positive blood cultures to be considered a risk factor. Immunosuppressive conditions included hematologic malignancies, solid organ or bone marrow transplants, acquired immunodeficiency syndrome, long term or high dose administration of corticosteroids, and administration of chemotherapy and/or radiation therapy. Prior hospitalization was considered within the preceding 90 days and prior antibiotics and bloodstream infection within 30 days. Appropriate antimicrobial treatment was defined as administered agents having in vitro activity against the isolated organism(s) and being administered in the correct dose during the first 24 hours after collection of positive blood cultures.

2.4. Data analysis

Continuous variables were reported as means with standard deviations when normally distributed and as medians with inter-quartile ranges when assumptions of normal distribution were violated. *t* Test and Wilcoxon rank sum test were used to compare continuous variables. Binary and categorical data were expressed as frequencies and analyzed with the χ^2 test. To identify risk factors associated with candidemia, we performed univariable and multivariable analyses. Biologically plausible variables and known risk factors for candidemia based on published literature, and with a $P < .10$ in the univariable analysis, were considered as candidate predictors and were included in the multivariable analysis. We applied a backward selection for the multivariable logistic regression using a *P* value cutoff of .05. Missing values were less than 5% and they were excluded from the analyses.

The prediction equation was derived using the coefficients obtained from the multivariable logistic regression. We also derived a simpler, more easy to use integer score using the same coefficients. Thus the lowest coefficient obtained from the multivariable logistic regression was assigned a score of 1. The other integer values were obtained by dividing the other coefficients by the lowest coefficient and rounding to the closest integer (e.g. mechanical ventilation had a coefficient of 0.52 and was assigned an integer value of 1. TPN with a coefficient of 0.93 was assigned an integer value of $2 = 0.93/0.52$). Model discrimination was assessed using the area under the receiver operating characteristic curve (AUROC). We also tested and reported other predictive performance measures: goodness of fit using Hosmer Lemeshow test, bias, root mean square error, calibration slope and the Brier score. The candidemia prediction rule was internally validated using a bootstrap resampling procedure with 1000 repetitions which is considered the most accurate method for internal validation [32]. The same technique with computation of AUROCs, calibration slopes and Brier indexes was used for comparison and external validation of prespecified invasive candidiasis models [32]. Logistic regression coefficients were extracted from previously derived equations from the available literature [18]. Since use of corticosteroids was not personalized in our database, we considered this variable to be fully concordant with the outcome when analyzing other invasive candidiasis models. Analyses were computed using STATA/IC 11.2 (STATA Corp LP, College Station, TX) and MATLAB with the statistical toolbox installed (MATLAB version 8.3.0.532 [R2014a]; The MathWorks Inc, Natick, MA; 2014).

3. Results

Two thousand five hundred ninety-seven consecutive patients with a positive blood culture and severe sepsis or septic shock were included in our study. Two hundred sixty-six (10.2%) had blood cultures positive for *Candida* spp with *C albicans* being the dominant species (42.5%) followed by *C glabrata* (28.2%) and *C parapsilopsis* (16.2%). Polymicrobial cultures were encountered in 4 of the candidemic patients (1.5%). Mortality was significantly higher in patients with candidemia (125 patients, 47.0%) than in patients with bacteremia (662 patients, 28.4%; $P < .001$) while nursing home discharge rates were similar: 79 patients (29.7%) vs 719 patients (30.8%) ($P = .713$).

Patients with candidemia were statistically more likely to have been admitted from nursing homes or transferred from outside hospitals, to have received TPN, and to have required hemodialysis (Table 1). Patients with candidemia were also acutely sicker as evidenced by higher APACHE II scores, presence of septic shock, and need for mechanical ventilation. Longer duration of hospitalization prior to positive blood cultures, presence of a central vein catheter, and surgical intervention, to include abdominal surgery, were more prevalent in patients with candidemia (Table 1). One hundred sixty-six (62.4%) candidemic patients received inappropriate initial treatment compared to 580 (24.9%) patients without candidemia ($P < .001$).