Journal of
Anesthesia and Intensive Care

ScienceAssist International

Research Article | Open Access

The Association of *Candida Auris* Invasive Candidiasis with Hospital Mortality - A Propensity Score Weighted Cohort Analysis and Clinical Predictive Model Development

Paula Carmona[1,2,*], Guido Mazzinari[1,2], Iratxe Zarragoikoetxea[1,2], Clara Pascual[3], María Victoria Johannessen[3], Marta López-Cantero[1], Miguel Ángel Chiveli[1], Pilar Argente[4]

[1]Consultant of Anesthesiology and Critical Care Medicine, HuiP la Fe, Valencia, Spain
[2]Research Group in Perioperative Medicine, Biomedical Research Institute la Fe, Valencia, Spain
[3]Resident of Anesthesiology and Critical Care Resident at HuiP La Fe, Valencia, Spain
[4]Associate Professor of Valencia University, Head of Department of Anesthesiology and Critical Care at HUiP La Fe, Valencia, Spain

***Correspondence:** Paula Carmona García, MD PhD, MSc, Hospital Universitario y Politécnico la Fe, Avinguda de Fernando Abril Martorell 106 ,46026, Valencia, Spain, Tel: +34 669344529; E-mail: paulac_g@hotmail.com

Received: June 11, 2021; Accepted: June 22, 2021; Published: June 29, 2021

Abstract

Objectives: The main objective was to assess if invasive candidiasis (IC) caused by *Candida Auris* is associated with higher mortality compared to non-Auris IC etiology. The secondary objective was to identify which factors are associated with mortality in a population of surgical intensive care unit (SICU) patients with IC.

Methods: Retrospective propensity score weighted cohort study and predictive risk model estimation with elastic net regularization.

Results: 107 patients developed IC. 61 (57%) had a *C.auris* etiology and 46 (43%) had other *Candida spp* etiology. The overall hospital mortality rate was 48.6% and 49.2% and 47.8% in the *C.auris* and other *Candida spp*. IC cohort respectively. The association of *C.auris*–related IC with mortality was not significant (odds ratio (OR) 1.12 [95%CI 0.46 to 2.75, P = 0.99]. The *C.auris*–related IC survival time ratio was not significant [1.47 95%CI 0.85 to 2.55, P=0.99]. Predictive risk model feature selection selected the following variables as predictors: age, APACHE II score, renal replacement therapy, septic shock, pulmonary, kidney, and hemodynamic complications during ICU stay. The predictive model Area Under Curve (AUC) was 0.88 [95%CI 0.82 to 0.95, P < 0.001]

Conclusions: Mortality in patients admitted with IC in SICU remains high. *C.auris* etiology was not associated with increased hospital mortality nor higher survival time compared to *non–Auris*–related IC. The development of septic shock with hemodynamic, respiratory, and renal compromise are the main risk factors for mortality.

Keywords: Invasive candidiasis; Candidemia; *Candida Auris*; Critical Care; Risk Factors; Multidrug Resistant Yeast

INTRODUCTION

Candida Auris is an emerging yeast with high transmissibility, high antifungal treatment resistance, and difficult microbiological identification [1, 2]. Containing *C.auris* outbreaks in intensive care units (ICUs) is arduous as it colonizes patients indefinitely, generates invasive disease, and persists in the healthcare environment [3].

Most patients who develop invasive candidiasis (IC) are fragile, often immunosuppressed, and with severe comorbidities. Indeed, surgical ICU (SICU) patients are particularly at risk of developing IC since they frequently undergo aggressive surgeries, receive multiple antibiotic treatments or artificial nutrition, require extracorporeal circulatory assistance devices, and suffer from severe metabolic diseases [4].

While IC is associated with high overall mortality, it is unclear whether a *C.auris*–related IC is associated with higher mortality compared to an IC caused by other *Candida species* (spp.). Also, while risk factors associated with IC occurrence have been studied [5], the factors associated with increased mortality in patients with IC remain to be elucidated. Identifying mortality predictors could be the key to implementing specific measures to reduce IC mortality.

This study aimed to assess whether IC caused by *C.auris* is associated with increased mortality and to identify mortality predictors in patients with IC. Our primary objective was the association of *C.auris* IC etiology with mortality compared to *non–Auris* IC etiology. Our secondary objective was to build a predictive model with mortality predictors in patients with IC.

MATERIALS AND METHODS

This study was a single-center retrospective cohort and predictive model development analysis, which followed the statement for strengthening the reporting of observational studies in epidemiology (STROBE) (http://www.strobe-statemenent.org) and transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD). The statistical analysis plan was predefined, and the study was registered at clincaltrials.gov (NCT04484376). Hospital Universitario y Politécnico la Fe Ethical Committee, Valencia, approved the study protocol (MLC-ANT-2019-01).

Inclusion and Exclusion Criteria

We included patients over 18 years with Candida–related IC diagnosis admitted to the SICU between May 2016 and October 2018. We excluded patients with: [1] *Candida spp*. colonization without IC, and [2] patients admitted to the medical ICU (MICU). Data were collected from the SICU electronic health record system (ICCA Philips, Eindhoven, The Netherlands) and included baseline characteristics, comorbidities, complications, and ICU management (full details on collected variables in the eMethods in the Supplement).

Definitions

In-hospital mortality was defined as death during the hospital stay. Attributable mortality was defined as death caused by IC unless the treating physician considered a different cause [6]. IC was defined as the isolation of *Candida spp*. at least in one culture from blood, bronchoalveolar lavage, pleural, intraabdominal, or spinal fluid after 48 h of admission to the critical care unit up to 72h after ICU discharge. Sepsis was defined as documented infection with a change ≥ 2 in the baseline Sequential Organ Failure Assessment (SOFA) score. Septic shock was defined as sepsis requiring administration of vasopressor, mean arterial pressure < 65 mmHg, and serum lactate > 2 $mmol \cdot L^{-1}$ [7]. A detailed list of all used definitions is reported in the Supplement.

Microbiological Methods

All Candida isolates were identified by their biochemical features (AuxaColor2TM, Bio Rad Laboratories, Marnes la Coquette, France) and proteomic profiling (VITEK MS IVD and VITEK MS Research Use Only -RUO-version, bio Mérieux, Marcy l'Etoile, France) according to manufacturer instructions. Definitive *C.auris* identification was performed by internal transcribed spacer (ITS) sequencing using ITS3-ITS4 and ITS2-ITS5 primers using GenomeLab GeXP™ (Beckman Coulter, Fullerton, CA, USA) equipment. The obtained sequences obtained were compared with those in the Microbial Genomes Basic Local alignment search tool (BLAST) (http://www.ncbi.nlm.nih.gov/guide/sequence-analysis/). Molecular identification was confirmed in the Spanish Mycology Reference Laboratory using ITS1-ITS4 primers. If identification diverged, the reference laboratory identification prevailed.

Statistical Analysis Plan

We estimated the potency for small to large effects of *C.auris*–related IC on hospital mortality, corresponding to a Cohen's h of 0.2 to 0.6. Assuming an IC baseline mortality rate of 30% [6], a sample of 107 patients had a power of 80% and 90% to detect a mortality difference of 13% and 16%, respectively, with an alpha error of 0.05 and a two-tailed test of significance. (Supplementary Figure 1).

We reported continuous variables as median and 25^{th}–75^{th} percentiles and categorical variables as numbers and percentages. Distributions normality was assessed by inspecting quantile-quantile plots, and a two-sample t-test or Wilcoxon rank-sum test was used accordingly for univariate analysis. For categorical variables, we used the Chi-square test or Fisher exact test. Statistical uncertainty was expressed by showing the 95%–confidence intervals (CI). In the case of >, 5% missing data in any variable, values imputation was performed using the R software mice package.

A weighted logistic regression model was estimated to determine if *C.auris*–related IC was associated with hospital mortality compared to *non–Auris*–related IC.

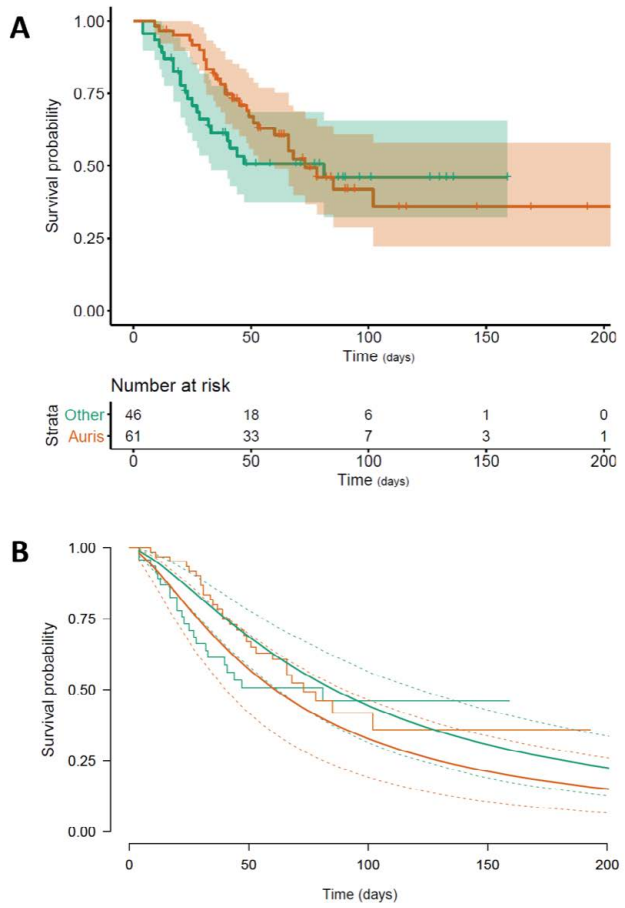

Figure 1: Panel A: Kaplan Meier survival curve estimated fro hospital mortality. Orange: *C. auris*–related IC patients; Green: *non–auris*–related IC patients. Shaded areas represent the 95% confidence band. **Panel B:** Accelerated Failure Time weighted survival model estimation superimposed to the Kaplan Meier estimator. Orange: *C. auris*–related IC patients; Green: *non–auris*–related IC patients. Dashed lines: 95% Confidence boundaries.

An inverse probability weighting (IBW) factor computed from the covariate–balancing propensity score (CBPS) method was introduced in the model to simultaneously optimize group assignment prediction and confounders influence. The CBPS procedure sets mean independence between group assignment and covariates to ensure covariate balancing and estimate the PS with the generalized method of moments (GMM) method [8]. The PS was calculated including the group assignment as the primary exposure variable. The variables that entered the PS calculation are detailed in the eMethods in the Supplement. We assessed PS balance with the R cobalt package.

We also evaluated the effect of *C.auris*–related IC versus *non–Auris*–related IC on survival by estimating a weighted survival model using the same PS weighting procedure described above. Depending on whether proportional hazard assumptions were met by checking Schonfeld scaled residuals and deviance, we carried out the estimation with a weighted Cox model or with a log-logistic accelerated failure time model to consider the diminishing effect of IC on mortality over time.

Multivariable logistic regression was estimated to determine the factors influencing mortality in patients with IC. The candidate variables were the same used for PS calculation, and the selection process was performed using elastic net regularization with the glmnet and R caret package. This method combines the L1 and L2 penalties of the lasso and ridge methods [9, 10] The discriminative performance of the model was estimated using the area under the curve (AUC) of the receiver-operator curve (ROC). In addition, the model calibration plot and the residuals diagnosis based on scaled quantile residuals were carried out. The internal validation of the model was evaluated by bootstrapping using 500 repetitions and estimating the naïve curve's optimism.

To further unravel *C.auris* association with hospital mortality, we performed the following posthoc sensitivity analysis. First, we fitted a logistic regression on a PS matched cohort to reduce the estimates' bias [11]. Second, we fitted an IPW logistic regression weighted on IBTW computing the PS with a generalized boosted model method to explore the non–linear relationship between exposure variable and covariate [12]. Third, we performed a feature selection procedure with an elastic net regularization method before CBPS estimation to assess if non–parsimonious PS specifications led to overfitting and inflated variance of the estimates [13]. Matching and regularization procedures details are reported in the eMethods in the Supplement.

Statistical significance was set at P-value <0.05 for two-tailed tests. We performed corrections for multiple comparisons with the Holm-Bonferroni step–down procedure. Analyses were performed with R 4.0.2 (The R Foundation for Statistical Computing, www.r-project.org).

RESULTS

Of 107 patients with IC, 61 (57.0%) and 46 (43%) had a *C.auris* and other *Candida spp*. IC etiology, respectively. The inclusion flowchart is reported in (Supplementary Figure 2). Missing data proportion was always < 5%. Demographic and clinical characteristics are presented

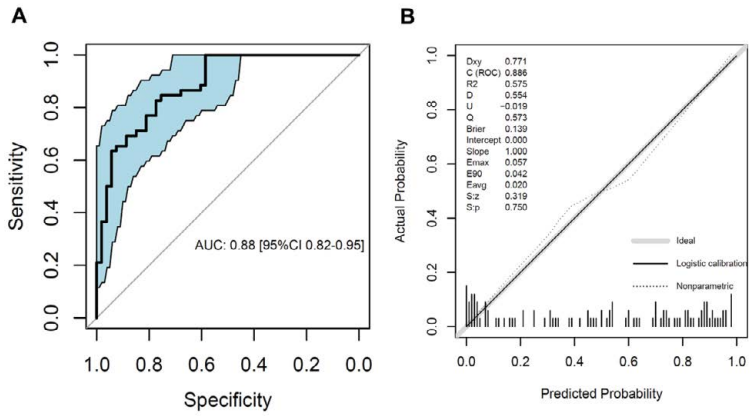

Figure 2. Panel A: ROC curve of the elastic net predictive model for hospital mortality in patients with invasive fungal disease. Light blue bands are the bootstrapped confidence bands. Abbreviations: AUC: Area under curve; CI, Confidence interval. **Panel B:** Calibration plot of the elastic net predictive model for hospital mortality in patients with invasive fungal disease. Dxy, Somers' D_{xy} rank correlation between p and y; C, c–statistic; R_2, Nagelkerke-Cox-Snell-Maddala-Magee R-squared index; D, Discrimination index; U, Unreliability index; Q, quality index; Brier, Brier score; Emax, maximum absolute difference in predicted and locally weighted smoothing calibrated probabilities; Eavg, average in the same absoulute difference; E90, the 0.9 quantile of the same difference; S:z, Spiegelhalter Z-test for calibration accuracy; s:p, Spiegelhalter test *P* value.

in Table 1 and (Supplementary 1). *C. albicans* and *C. parapsilosis* were the most frequent species in the *Candida spp*. cohort, and bloodstream infection was the most frequent infection source. Hospital mortality rate of 48.6% overall, and 49.2% and 47.8% in the *C.auris* and other *Candida spp*. IC cohort, respectively. Overall attributable mortality to Candida–related IC was 29.9%, and 30.2% and 28.2% in the *C.auris* and other *Candida spp*. IC cohort, respectively.

Association between IC Etiology and Mortality

The association of *C.auris*–related IC with mortality was not significant compared to *non–Auris*–related IC. The odds ratio (OR) estimated from the IPW logistic model was 1.12 [95%CI 0.46 to 2.75, P = 0.99] (Table 2). The *C.auris*–related IC survival time ratio estimated with the multivariable accelerated failure time model was not significant [1.47 95%CI 0.85 to 2.55]. The survival curves are shown in Figure 1.

Predictive Risk Model Feature Selection

The elastic net procedure selected seven variables: age, APACHE II score, renal replacement therapy (CVVHDF), septic shock, pulmonary, kidney, and hemodynamic complications during ICU stay. The coefficients and adjusted ORs are presented in Table 2. The predictive model with the elastic net selected variables AUC was 0.88 [95%CI 0.82 to 0.95, P < 0.001]. The ROC curve and calibration plot are presented in Figure 2. Simulated residuals and scaled residuals plot showed a good fit (Supplementary Figure 3). After bootstrapped internal validation, the model still showed acceptable accuracy with an AUC of 0.86 and optimism of 0.05.

Sensitivity Analyses

We did not find any significant association between *C.auris*–related IC and hospital mortality compared to *non–Auris*–related IC (Table 2). Generalized boosted IPW logistic regression estimation for mortality showed an OR of 1.06 [95%CI 0.49 to 2.28, P = 0.99] for *C.auris*–related IC. After feature selection and CBPS estimation, the OR for mortality for *C.auris*–related IC was 0.89 [95%CI 0.34 to 2.21, P = 0.99]. The elastic net selected variables for PS calculation are reported in the eMethods in the Supplement. After matching, the resulting cohort consisted of 22 patients in both *C.auris* and *non–Auris*–related IC cohorts. Baseline characteristics between groups were balanced (Supplementary Table 2 and Supplementary Figure 4). OR for mortality in the matched analysis was 1.10 [95%CI 0.33 to 3.74, P = 0.99] for *C.auris*–related IC. Balance assessment for the various PS estimations is reported in (Supplementary Figure 5-7).

DISCUSSION

The results of this study can be summarized as follows: In patients with IC, (i) *C.auris* etiology is not associated with increased hospital mortality, and (ii) mortality predictors are mainly related to illness severity.

This study has several strengths. First, we analyzed data from a large, sufficiently powered *C.auris* outbreak.

Table 1. Baseline characteristics.

	Overall (n = 107)	**Candida auris** (n= 61)	**Other Candidas** (n= 46)	**SMD**
Hospital mortality (yes)	52 (48.6%)	30 (49.2%)	22 (47.8%)	0.027
Age (Years)	61 [43 to 71]	59 [41 to 69]	64 [48 to 73]	0.301
Gender (Female)	34 (31.8)	23 (37.7%)	11 (24.4%)	0.302
More than one positive sample for invasive candidiasis (yes)	26 (24.3%)	13 (21.3%)	13 (28.3%)	0.161
Invasive candidiasis diagnosis from blood culture (yes)	83 (77.6%)	49 (80.3%)	34 (73.9%)	0.153
Previous hospital admission (yes)	61 (57.0%)	32 (52.5%)	29 (63.0%)	0.216
Previous ICU admission (yes)	33 (30.8%)	19 (31.1%)	14 (30.4%)	0.015
Apache II score	22 (5)	21 (6)	22 (6)	0.174
CKD (yes)	15 (14.0%)	8 (13.1%)	7 (15.2%)	0.060
Diabetes (yes)	27 (25.2%)	14 (23.0%)	13 (28.3%)	0.122
COPD (yes)	16 (15.0%)	4 (6.6%)	12 (26.1%)	0.548
Immunodeficiency (yes)	11 (10.3%)	9 (14.8%)	2 (4.3%)	0.360
Cancer (yes)	19 (17.8%)	10 (16.4%)	9 (19.6%)	0.083
Liver cirrhosis (yes)	7 (6.5%)	4 (6.6%)	3 (6.5%)	0.001
CVC > 48 hours (yes)	103 (96.3%)	59 (96.7%)	44 (95.7%)	0.056
Total parenteral nutrition	89 (83.2%)	50 (82.0%)	39 (84.8%)	0.076
Abdominal surgery (yes)	38 (35.5%)	21 (34.4%)	17 (37.0%)	0.053
CVVHDF (yes)	27 (25.2%)	10 (16.4%)	17 (37.0%)	0.478
ECMO (yes)	15 (14.0%)	9 (14.8%)	6 (13.0%)	0.049
Multifocal colonization	98 (91.6%)	57 (93.4%)	41 (89.1%)	0.153
MV > 48 hours (yes)	97 (90.7%)	55 (90.2%)	42 (91.3%)	0.039
Candida score				0.342
0	4 (3.7%)	2 (3.3%)	2 (4.3%)	
1	11 (10.3%)	8 (13.1%)	3 (6.5%)	
2	22 (20.6%)	13 (21.3%)	9 (19.6%)	
3	22 (20.6%)	14 (23.0%)	8 (17.4%)	
4	32 (29.9%)	17 (27.9%)	15 (32.6%)	
5	16 (15.0%)	7 (11.5%)	9 (19.6%)	
Antifungal treatment before invasive candidiasis diagnosis (yes)	38 (36.2%)	21 (35.6%)	17 (37.0%)	0.028
Septic shock (yes)	77 (72.0%)	46 (75.4%)	31 (67.4%)	0.178
Targeted antifungal treatment (yes)	96 (89.7%)	44 (72.1%)	38 (82.6%)	0.252
More than one antifungal drug (yes)	83 (77.6%)	18 (29.5%)	12 (26.1%)	0.076
Pulmonary complication during ICU stay (yes)	34 (31.8%)	55 (90.2%)	41 (89.1%)	0.034
Hemodynamic complication during ICU stay (yes)	55 (51.4%)	43 (70.5%)	40 (87.0%)	0.411
GI complication during ICU stay (yes)	49 (45.8%)	19 (31.1%)	15 (32.6%)	0.031
Kidney complication during ICU stay (yes)	96 (89.7%)	31 (50.8%)	24 (52.2%)	0.027
Neurological complication during ICU stay (yes)	83 (77.6%)	26 (42.6%)	23 (50.0%)	0.148

Data are reported as mead (SD) or median [25th to 75th percentile] or n (%). SMD, standardized mean difference; ICU, Intensive Care Unit, CKD, chronic Kidney disease; COPD, chronic Obstructive Pulmonary disease; CVC, central venous catheter; CVVHDF, continuous veno–venous hemodiafiltration; ECMO, extra–corporeal membrane oxygenation; MV, mechanical ventilation; GI, gastrointestinal.

Table 2. Effect estimate of *Candida Auris* vs. other type of *Candida spp.*–related invasive fungal disease on hospital mortality.

Type of fitted model	**OR [95%CI]**	**P value**
CBPS weighted estimate	1.12 [0.46 to 2.75]	0.999
Generalized boosted estimate	1.06 [0.49 to 2.28]	0.999
Elastic net feature selection estimate	0.89 [0.34 to 2.21]	0.999
PS matched cohort estimate	1.10 [0.33 to 3.74]	0.999

CBPS, Covariate balancing propensity score; PS, propensity score; OR, Odds Ratio; CI, Confidence Interval

Second, we minimized confounders' influence with a robust methodology providing precise estimation and confounders control. Third, we implemented several sensitivity analyses to further test estimates' precision and variance and propensity score specification. We also focused on the in-hospital period to reduce loss to follow–up and assess the maximum risk period for death in IC.

Remarkably, although *C.auris* has been described as a particularly virulent species, we did not find any association between hospital mortality and *C.auris* vs. non-auris–related IC neither in the logistic nor survival analysis. Indeed, we did not observe higher attributable mortality to *C.auris* compared to *non–Auris* spp. and found a *C.auris*–related IC mortality rate similar to previously published series [6, 14] suggesting that the *C.auris* danger derives from its ease to spread and colonize rather than a greater intrinsic virulence.

The IC incidence has increased by 50% over the last decade worldwide. It ranges between 2.4·10-5 and 15·10-5 patients depending on the geographical and clinical setting [15–17]. Overall mortality in patients with IC has not improved despite significant progress in antifungal treatment options and source control [18–20]. We observed global and attributable mortality consistent with published data. However, attributable mortality ranges from 5% to 49% [21–24], and the overall crude mortality rate ranges between 20 and 60% [25, 26], depending on the chosen control group and the underlying comorbidities. This ongoing controversy regarding attributable mortality to IC. might be related to the definition of attributable mortality, which depends on the underlying disease severity and the time from hospital admission to IC diagnosis. In our population, IC attributable mortality was defined as per the attending physician's criteria and *Candida spp*. isolation in sterile fluids cultures. Therefore, mortality rates might differ from series focused on candidaemia exclusively and those without distinction in crude and attributable mortality. This is because of bloodstream infections with *Candida spp*. usually occur in patients with severe comorbidities who also have several risk factors associated with adverse outcomes.

We observed similar mortality risk factors to those previously reported in other IC series without *C.auris* isolation [27] and candidaemia–only cases [21]. We found that septic shock, acute kidney injury, renal replacement therapy, and higher APACHE scores are mortality predictors in patients with IC. The progression from IC to septic shock has also been identified as a risk factor for mortality in previous data with overall mortality rates ranging from 60 to 90% [28–30].

Mortality rates and risk factors could be related to the specific clinical characteristics of the studied population. For instance, an Australian multicenter trial carried out mainly in oncologic critically ill patients [24] showed a seven–day and 30-day overall mortality of 21% and 31%, respectively, with a candidaemia attributable mortality of 13% as per the treating physician's criteria. Our sample was drawn from a SICU population with a high percentage of polytrauma patients or patients who underwent cardiac or abdominal surgery and invasive procedures like extracorporeal membrane oxygenation (ECMO). Indeed, cardiac surgery with cardiopulmonary bypass times greater than 120 minutes had an eight times higher probability of developing candidaemia [31]. The use of intravascular devices, renal replacement therapy, urinary catheterization, invasive mechanical ventilation, and parenteral nutrition are more prevalent and consistent risk factors for IC throughout the literature in SICU patients than in medical ICU patients [32]. Furthermore, enteric barrier breakdown related to abdominal surgery occurs frequently in SICU patients, even in the absence of neutropenia.

The treatment with one or two antifungal drugs and therapy with -azole vs. echinocandin was not a predictor of mortality, although most of the patients were treated with echinocandin and a high proportion of them were under antifungal treatment before IC diagnosis. A previous trial reported that mortality was not different in patients treated with fluconazole vs. echinocandin as initial therapy [24]. Early initiation of appropriate antifungal therapy is mandatory to improve survival [29]. Consequently, antifungal drugs are often pre-emptively or empirically administered in high-risk patients, especially in complicated abdominal surgery [33]. The resulting overuse of antifungal drugs might lead to the emergence of *Candida spp* resistance to azoles or echinocandins [34,35].

In the present study, non-Albicans spp.–related IC was predominant in the *non–Auris* cohort and polytrauma and postoperative cardiac patients were the most frequently affected patients in our series. The proportion of candidemia due to *C. albicans* has decreased in recent years regardless of the clinical setting and non-albicans *Candida spp*. the increase reflects a global trend [18,36]. In our data, we observed a high incidence of *C.auris* (57%) due to the outbreak setting, followed by incidence

by *C. parapsilosis* (13,1%) and albicans (10,3%). *C. albicans* was the most frequently isolated species in the last Spanish multicenter study, followed closely by *C. parapsilosis*, glabrata, and tropicalis, unlike other European or American studies where it continues to be the second isolated species [36].

Some limitations must be acknowledged. The retrospective design cannot guarantee that unrecognized confounders can play a role in the association with mortality. Also, the generalizability of results may be done with caution due to the studied population's clinical specificity such as the underlying surgical condition and particular *Candida spp*. epidemiology. The used variable selection method effectively achieves a good predictive set of variables; nevertheless, refitting the models with no penalty to estimate confidence intervals for the selected variables is still a matter of debate [37]. While our data identified septic shock as a mortality risk factor, data regarding concomitant bacterial infection were not collected, and further analyses including this feature would be useful.

In conclusion, in a surgical critically ill population, mortality in patients with invasive candidiasis remains high. *C.auris* etiology was not associated with increased hospital mortality or decreased survival time compared to *non–Auris*–related invasive fungal disease. The development of septic shock with hemodynamic, respiratory, and renal compromise are the main risk factors for mortality.

DECLARATIONS

International Clinical Trials Registry (ICTR): this study was registered at clinicaltrials.gov (NCT04484376).

Financial Disclosure and Conflicts of Interest: Authors declare no conflict of interest.

Funding: None.

Availability of data and material: Data available on request to corresponding author.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Forsberg K, Woodworth K, Walters M, Berkow EL, Jackson B, Chiller T, et al. Candida auris: The recent emergence of a multidrug-resistant fungal pathogen. Med Mycol. 2019;57(1):1-12.
2. de Cássia Orlandi Sardi J, Silva DR, Soares Mendes-Giannini MJ, Rosalen PL. Candida auris: Epidemiology, risk factors, virulence, resistance, and therapeutic options. Microb Pathog. 2018;125:116-121.
3. Eyre DW, Sheppard AE, Madder H, Moir I, Moroney R, Quan TP, et al. A Candida auris Outbreak and Its Control in an Intensive Care Setting. N Engl J Med. 2018;379(14):1322-1331.
4. Xie GH, Fang XM, Fang Q, Wu XM, Jin YH, Wang JL, et al. Impact of invasive fungal infection on outcomes of severe sepsis: a multicenter matched cohort study in critically ill surgical patients. Crit Care. 2008;12(1):R5.
5. Garcia-Bustos V, Salavert M, Ruiz-Gaitán AC, Cabañero-Navalon MD, Sigona-Giangreco IA, Pemán J. A clinical predictive model of candidaemia by Candida auris in previously colonized critically ill patients. Clin Microbiol Infect. 2020;26(11):1507-1513.
6. Chakrabarti A, Sood P, Rudramurthy SM, Chen S, Kaur H, Capoor M, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med. 2015;41(2):285-295.
7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810.
8. Imai K, Ratkovic M. Covariate balancing propensity score. J R Stat Soc Ser B Stat Methodol. 2014;76:243-263.
9. Lutchen KR, Jackson AC, Reliability of parameter estimates from models applied to respiratory impedance data. J Appl Physiol 1987;62(2):403–413.
10. Zou H, Hastie T. Erratum: Regularization and variable selection via the elastic net. J R Stat Soc Ser B Stat Methodol 2005;67(2):301–320.
11. Franklin JM, Eddings W, Austin PC, Stuart EA, Schneeweiss S. Comparing the performance of propensity score methods in healthcare database studies with rare outcomes. Stat Med. 2017;36(12):1946-1963.
12. Setodji CM, McCaffrey DF, Burgette LF, Almirall D, Griffin BA. The Right Tool for the Job: Choosing Between Covariate-balancing and Generalized Boosted Model Propensity Scores. Epidemiology. 2017;28(6):802-811.
13. Schuster T, Lowe WK, Platt RW. Propensity score model overfitting led to inflated variance of estimated odds ratios. J Clin Epidemiol 2016;80:97-106.
14. Ruiz-Gaitán A, Martínez H, Moret AM, Calabuig E, Tasias M, Alastruey-Izquierdo A, et al. Detection and treatment of Candida auris in an outbreak situation: risk factors for developing colonization and candidemia by this new species in critically ill patients. Expert Rev Anti Infect Ther. 2019;17(4):295-305.
15. Lortholary O, Renaudat C, Sitbon K, Madec Y, Denoeud-Ndam L, Wolff M, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002-2010). Intensive Care Med. 2014;40(9):1303-1312.
16. Lamoth F, Lockhart SR, Berkow EL, Calandra T. Changes in the epidemiological landscape of invasive candidiasis. J Antimicrob Chemother. 2018;73(suppl_1):i4-i13.

17. Cleveland AA, Farley MM, Harrison LH, Stein B, Hollick R, Lockhart SR, 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(10):1352-1361.

18. Rajendran R, Sherry L, Deshpande A, Johnson EM, Hanson MF, Williams C, et al. A Prospective Surveillance Study of Candidaemia: Epidemiology, Risk Factors, Antifungal Treatment and Outcome in Hospitalized Patients. Front Microbiol. 2016;7:915.

19. Chen S, Slavin M, Nguyen Q, Marriott D, Playford EG, Ellis D, et al. Active Surveillance of Candidemia, Australia. 2006;12(10):1508-1516.

20. Li D, Xia R, Zhang Q, Bai C, Li Z, Zhang P. Evaluation of candidemia in epidemiology and risk factors among cancer patients in a cancer center of China: an 8-year case-control study. BMC Infect Dis. 2017;17(1):536.

21. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Effects of nosocomial candidemia on outcomes of critically Ill patients. Am J Med 2002;113(6):480-485.

22. González de Molina FJ, León C, Ruiz-Santana S, Saavedra P. Assessment of candidemia-attributable mortality in critically ill patients using propensity score matching analysis. Crit Care 2012;16:R105.

23. Falagas ME, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. Eur J Clin Microbiol Infect Dis. 2006;57(7):419-425.

24. Keighley C, Chen SC, Marriott D, Pope A, Chapman B, Kennedy K, et al. Candidaemia and a risk predictive model for overall mortality: a prospective multicentre study. BMC Infect Dis. 2019;19(1):445.

25. Mohr A, Simon M, Joha T, Hanses F, Salzberger B, Hitzenbichler F. Epidemiology of candidemia and impact of infectious disease consultation on survival and care. Infection. 2020;48(2):275-284.

26. Jia X, Li C, Cao J, Wu X, Zhang L. Clinical characteristics and predictors of mortality in patients with candidemia: a six-year retrospective study. Eur J Clin Microbiol Infect Dis. 2018;37(9):1717-1724.

27. Poissy J, Damonti L, Bignon A, Khanna N, Von Kietzell M, Boggian K, et al. Risk factors for candidemia: a prospective matched case-control study. Crit Care. 2020;24(1):109.

28. Guzman JA, Tchokonte R, Sobel JD. Septic Shock Due to Candidemia: Outcomes and Predictors of Shock Development. J Clin Med Res. 2011;3(2):65-71.

29. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis. 2012;54(12):1739-1746.

30. Bassetti M, Righi E, Ansaldi F, Merelli M, Trucchi C, De Pascale G, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med. 2014;40(6):839-845.

31. Michalopoulos AS, Geroulanos S, Mentzelopoulos SD. Determinants of Candidemia and Candidemia-Related Death in Cardiothoracic ICU Patients. Chest 2003;124(6):2244-2255.

32. Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis. 2001;33(2):177-186.

33. Playford EG, Eggimann P, Calandra T. Antifungals in the ICU. Curr Opin Infect Dis. 2008; 21(6):610-619.

34. Shields RK, Nguyen MH, Clancy CJ. Clinical perspectives on echinocandin resistance among Candida species. Curr Opin Infect Dis. 2015; 28(6):514-522.

35. Pemán J, Cantón E, Linares-Sicilia MJ, Roselló EM, Borrell N, Ruiz-Pérez-de-Pipaon MT, et al. Epidemiology and antifungal susceptibility of bloodstream fungal isolates in pediatric patients: a Spanish multicenter prospective survey. J Clin Microbiol. 2011;49(12):4158-4163.

36. Pemán J, Salavert M. Epidemiología general de la enfermedad fúngica invasora. Enferm Infecc Microbiol Clin. 2012;30(2):90-98.

37. Lee JD, Sun DL, Sun Y, Taylor JE. Exact post-selection inference, with application to the lasso. Ann Stat. 2016;44(3):907-927.