Epidemiology, clinical characteristics, and outcome of candidemia in critically ill patients in Germany: a single-center retrospective 10-year analysis

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Abstract

Background: Despite advances in the management of bloodstream infections (BSI) caused by Candida spp., the mortality still remains high in critically ill patients. The worldwide epidemiology of yeast-related BSI is subject to changing species distribution and resistance patterns, challenging antifungal treatment strategies. The aim of this single-center study was to identify predictors of mortality after 28 and 180 days in a cohort of mixed surgical and medical critically ill patients with candidemia.

Methods: Patients, who had been treated for laboratory-confirmed BSI caused by Candida spp. in one of 12 intensive care units (ICU) at a University hospital between 2008 and 2017, were retrospectively identified. We retrieved data including clinical characteristics, Candida species distribution, and antifungal management from electronic health records to identify risk factors for mortality at 28 and 180 days using a Cox regression model.

Results: A total of 391 patients had blood cultures positive for Candida spp. (incidence 4.8/1000 ICU admissions). The mortality rate after 28 days was 47% (n = 185) and increased to 60% (n = 234) after 180 days. Age (HR 1.02 [95% CI 1.01–1.03]), a history of liver cirrhosis (HR 1.54 [95% CI 1.07–2.20]), septic shock (HR 2.41 [95% CI 1.73–3.37]), the Sepsis-related Organ Failure Assessment score (HR 1.12 [95% CI 1.07–1.17]), Candida score (HR 1.25 [95% CI 1.11–1.40]), and the length of ICU stay at culture positivity (HR 1.01 [95% CI 1.00–1.01]) were significant risk factors for death at 180 days. Patients, who had abdominal surgery (HR 0.66 [95% CI 0.48–0.91]) and patients, who received adequate (HR 0.36 [95% CI 0.24–0.52]) or non-adequate (HR 0.31 [95% CI 0.16–0.62]) antifungal treatment, had a reduced mortality risk compared to medical admission and no antifungal treatment, respectively.

Conclusions: The mortality of critically ill patients with Candida BSI is high and is mainly determined by disease severity, multiorgan dysfunction, and antifungal management rather than species distribution and susceptibility. Our results underline the importance of timely treatment of candidemia. However, controversies remain on the optimal definition of adequate antifungal management.

Keywords: Candidemia, Candida species, Critically ill patients, Intensive care unit, Antifungal agents, Fluconazole, Echinocandin, Bloodstream infection

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patients [1, 2]. Yeast-related BSI are usually healthcare-associated infections with a high mortality of up to 60% in critically ill patients [1, 3–5]. Importantly, BSI caused by Candida spp., central-line-associated BSI in particular, have been increasing over the past decades [6]. The international EPIC II study including more than 14,000 patients showed that Candida was the third most common cause of infection and was second in both North America and Western Europe [7]. Importantly, mortality was found to be substantially higher in patients with Candida BSI compared with patients suffering from Gram-positive or Gram-negative BSI [5, 7].

In the past years, a shift in Candida spp. towards non-albicans Candida spp. has been observed. The proportion of candidemia caused by non-albicans Candida spp. was 59.8% in an Italian multicenter survey [8]. An analysis from a North American prospective registry showed similar rates with 57.9% of non-albicans Candida spp. [9]. The shift in species distribution may reflect selection pressure induced by prior azole prescription [9–11].

Current recommendations on the management of invasive candidiasis in nonneutropenic patients suggest that adequate source control including catheter removal, should be performed early, if clinically feasible [12]. Although there is strong evidence that a delay in treatment negatively affects outcome, the optimal time point of intervention, such as central venous catheter (CVC) removal, is under debate [13, 14].

The aim of this retrospective study was to identify risk factors for mortality 28 and 180 days after Candida BSI. We hypothesized that survival would mainly be determined by appropriate antifungal treatment, such as adequate antifungal substance and timely source control, and yeast spp. Therefore, we analyzed clinical characteristics, antifungal management, and patterns of Candida spp. distribution in a mixed population of critically ill patients at 12 multidisciplinary intensive care units (ICUs) over a 10-year period.

**Methods**

**Ethical approval and study design**

This study was approved by the ethics committee at the Hamburg State Chamber of Physicians (registration no.: WF 012/13). The need for an informed consent was waived by the ethics committee, because data were retrieved from electronic health records. Critically ill patients with blood cultures positive for Candida spp. between October 2008 and July 2017 were included in the current analysis.

**Setting**

The University Medical Center Hamburg-Eppendorf is a tertiary care hospital with 1738 hospital beds that treated 98,356 in-patients in 2017. The number of critical care patients increased over time, from 5999 patients in 2008 to 8817 patients in 2017. The Department of Intensive Care Medicine includes 12 multidisciplinary ICUs with a total of 140 ICU beds. The Department of Intensive Care Medicine has units for the postoperative care following cardiac, neurosurgery, traumatologic, vascular or visceral surgery. Our department routinely treats patients following solid organ or allogeneic stem cell transplantations. Mixed patient populations, both medical and surgical, are being treated on each unit.

**Data collection**

The following demographic and clinical variables were collected from the electronic patient data management system (PDMS, ICM, Dräger, Lübeck, Germany): age, sex, body mass index, admission diagnosis, comorbidities, Candida spp., antifungal treatment; Simplified Acute Physiology Score II (SAPS II) and Sepsis-related Organ Failure Assessment (SOFA) score at time of culture positivity; septic shock; laboratory findings; CVC duration, number of CVCs per patient; length of ICU, and hospital stay.

In addition, the Candida score was calculated in all patients at the onset of clinical symptoms. The Candida score is a four-item clinical score and includes the components “severe sepsis”, “total parenteral nutrition”, “surgery”, and “multifocal Candida colonization” [15]. One point is added for each component resulting in a maximum score of 4. A score of 3 is considered an accurate discriminative value to select patients with Candida colonization requiring antifungal treatment [16, 17].

Survival data at 28 and 180 days after culture positivity were obtained from medical records or from telephone follow-up with the patient, next-of-kin or caregiver.

**Microbiological assays**

Aerobe and anaerobe blood cultures (BD Bactec Plus, BD, Heidelberg, Germany) were incubated in a Bactec instrument for up to 5 days. Bottles flagged positive were subjected to Gram-staining. Bottles showing growth of yeast and those that did not show visible microorganisms were streaked onto Columbia blood and Sabouraud agar plates (Oxoid, Basingstoke, UK). After incubation at 37°C for up to 48 h yeast were identified to the species level using whole cell mass spectrometry fingerprinting (Biotype, Bruker Daltonics, Bremen, Germany), microscopy, or biochemical profiling (Auxacolor, BioRad, Munich, Germany). All yeast isolates were subject to susceptibility testing using gradient strips. Susceptibility was interpreted according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).
Antifungal management
We categorized antifungal treatment into (a) empirical treatment; (b) treatment upon confirmation of BSI with Candida spp.; (c) antifungal medication resistant to the culprit Candida spp.; (d) delayed antifungal treatment (>24 h after culture positivity), and no antifungal treatment. Empirical antifungal treatment was administered to patients with risk factors for candidiasis and persistent fever despite antibacterial medication and/or a positive culture from non-sterile sites [12].

The initial treatment was considered adequate, if: (1) antifungal medication was administered empirically or within the first 24 h of culture positivity; (2) the isolated yeast was susceptible to the antifungal agent, and (3) source control, defined as CVC removal, was initiated within the first 48 h after blood culture positivity [18].

Statistical analysis
Continuous variables are expressed as median with 1st to 3rd quantile. Categorical variables are given as absolute and relative numbers. The distribution of data was visually interpreted using histograms. Variables were compared between groups (survivors vs. non-survivors and albicans vs. non-albicans) with the Wilcoxon–Mann–Whitney U test, the Chi-square test or the Fisher’s exact test as appropriate.

A multivariable Cox proportional hazards regression model was performed to identify variables associated with mortality at 28 days and 180 days. One episode of candidemia per patient was analyzed. Variables that were considered clinically relevant or that had been identified as predictors of mortality in the EUCANDICU trial were included as covariates [1]: age, SOFA score, septic shock, Candida spp. (albicans vs. non-albicans), Candida score, admission diagnosis (medical, abdominal surgery, surgery other than abdominal), liver cirrhosis, immunosuppression (including solid organ or stem cell transplantation, acquired immune deficiency syndrome, immunosuppressive medication), mean CVC duration at culture positivity, mechanical ventilation, length of ICU stay at culture positivity, antifungal treatment (adequate, non-adequate, none), echinocandin. The proportional hazards assumption and the linearity assumption for continuous variables in the Cox model were assessed based on Schoenfeld and marginal residuals.

Cochran–Armitage trend test was performed to assess a change in distribution patterns of Candida spp. during the study period. All given p-values are of descriptive nature and not adjusted for multiple testing.

Statistical analyses were performed using IBM® SPSS® Statistics 21 and R Version 3.5.1.

Results
Patient characteristics
For this retrospective study, we identified 391 patients with Candida BSI, who were treated in one of 12 ICUs. The first patient was enrolled on October 24th, 2008 and the last 180-day follow-up was on January 13th, 2018. During the study period from January 2008 until December 2017, 75,741 patients were admitted to our department with a crude mortality of 8.9%. Candida BSI was found in 391 patients (0.5%), accounting for an incidence of 4.8/1000 ICU admissions. For the flow of participants throughout the study, see Fig. 1.

Table 1 shows baseline demographic characteristics, comorbid conditions, admission diagnoses, and treatment-related variables for survivors and non-survivors at 180 days. The median age was 65.2 years (IQR: 56.0–73.7); 61.4% (n=240) patients were male. There were no significant differences in demographic characteristics between survivors and non-survivors. Patients who died had higher SAPS II, SOFA, and Candida scores, increased length of hospital and ICU stays. Non-survivors suffered more frequently from liver cirrhosis and septic shock, required extracorporeal organ support before and after Candida BSI more frequently, had higher mean CVC duration, and increased length of ICU and hospital stays. Selected patient characteristics throughout the study period are presented in Additional file 1. A list of referring specialties is provided in Additional file 2.

Candida species
Microbiological assays identified ten different Candida spp. in our study population (Additional file 3). The most frequent species was C. albicans (n=238, 60.9%), followed by C. glabrata (n=76, 19.4%), C. parapsilosis (n=26, 6.6%) and C. tropicalis (n=23, 5.9%). C. dubliniensis was identified in 13 patients (3.3%) and C. krusei in 7 patients (1.8%). C. lusitaniae and C. kefyr were detected in 3 patients (0.8%) each. Only one patient (0.3%) each was tested positive for C. norvegensis or C. guilliermondii. C. auris was not identified in any blood culture. Figure 2 shows the distribution of non-albicans and C. albicans throughout the study period from 2008 until 2017. The albicans/non-albicans ratio did not change over this time period (p=0.653). For details on species distribution, see Additional file 3.

Of note, the number of Candida albicans and non-albicans Candida spp. were similarly distributed between
2012 and 2015 (2012; 48.8%, 2013; 43.6%, 2014; 46.6%, 2015 48.0% non-albicans Candida spp.). By contrast, the proportion of non-albicans Candida spp. decreased in 2016 and 2017 (30.6% and 26.5%, respectively, Additional file 4).

**Antifungal management**

Two hundred ninety-six patients (75.7%) were accessible for antifungal treatment. In the remaining patients, 63 (16.1%) died and 32 (8.2%) had been transferred before microbiological results were obtained. Empirical antifungal medication was administered in 88/391 patients (22.5%), Table 2. The criteria for adequate antifungal treatment were fulfilled by 258/296 (87.5%) patients of those accessible for treatment (Fig. 3). Treatment was considered non-adequate in 7/296 (2.4%) patients for CVC removal more than 48 h after culture positivity with Candida spp. In another 35/296 (11.8%) patients, treatment was delayed or not susceptible for the BSI-causing Candida spp. (Fig. 3). The three most frequently used substances were fluconazole, anidulafungin, and caspofungin. For details on antifungal medication, see Table 2.

**Follow-up 28 and 180 days after Candida BSI**

The mortality after 28 days was 47.3% (n = 185) and increased to 59.8% (n = 234) after 180 days, counted from the first day of BSI with Candida spp. Higher age, SOFA and Candida scores, liver cirrhosis, septic shock,
Table 1 Baseline demographic and clinical characteristics, admission diagnosis, treatment-related variables and microbiological findings in critically ill patients with laboratory-confirmed bloodstream infection with *Candida* spp. Continuous variables are given as median (1st to 3rd quantile), categorical variables are given as n (%)

| Study participants n = 391 | Non-survivors n = 234 | Survivors n = 157 | Descriptive p-value (unadjusted) |
|---------------------------|-----------------------|-------------------|-------------------------------|
| **Demographics**          |                       |                   |                               |
| Age (years)               | 65 (56–74)            | 65 (57–73)        | 65 (53–74)                    | 0.614 |
| Male gender               | 240 (61)              | 151 (65)          | 89 (57)                       | 0.138 |
| **Comorbid conditions on admission** |                       |                   |                               |
| Coronary heart disease    | 100 (26)              | 63 (27)           | 37 (24)                       | 0.480 |
| Diabetes mellitus         | 99 (25)               | 62 (27)           | 37 (24)                       | 0.554 |
| COPD                      | 57 (15)               | 31 (13)           | 26 (17)                       | 0.383 |
| Liver cirrhosis           | 70 (18)               | 56 (24)           | 14 (9)                        | <0.001 |
| Chronic kidney disease    | 205 (52)              | 129 (55)          | 76 (48)                       | 0.216 |
| Hematologic malignancy    | 28 (7)                | 22 (9)            | 6 (4)                         | 0.045 |
| Solid tumor               | 139 (36)              | 82 (35)           | 57 (36)                       | 0.830 |
| Implantable cardiac devices | 32 (22)              | 21 (23)           | 11 (20)                       | 0.837 |
| Stem cell transplantation | 5 (1)                 | 4 (2)             | 1 (1)                         | 0.355 |
| Human immunodeficiency virus | 0 (0)              | 2 (1)             | 2 (1)                         | 0.245 |
| Solid organ transplantation | 22 (6)              | 13 (6)            | 9 (6)                         | 0.941 |
| **Admission diagnosis**   |                       |                   |                               |
| Medical                   | 175 (45)              | 116 (50)          | 59 (38)                       | 0.041 |
| Abdominal surgery         | 133 (34)              | 76 (33)           | 57 (36)                       |       |
| Surgery other than abdominal | 83 (21)              | 42 (18)           | 41 (26)                       |       |
| **ICU stay**              |                       |                   |                               |
| Arterial catheter         | 363 (93)              | 216 (92)          | 147 (94)                      | 0.619 |
| Mechanical ventilation    | 362 (93)              | 218 (93)          | 144 (92)                      | 0.594 |
| Red blood cell transfusion| 2 (0–7)               | 3 (0–9)           | 2 (0–6)                       | 0.056 |
| SAPS II score\(^b\)       | 44 (35–53)            | 48 (40–57)        | 36 (31–47)                    | <0.001 |
| SOFA score\(^b\)          | 8 (5–11)              | 10 (7–12)         | 6 (3–9)                       | <0.001 |
| Candida score\(^b\)       | 3 (2–4)               | 3 (2–4)           | 2 (1–4)                       | <0.001 |
| Sepsis                    | 287 (73)              | 198 (85)          | 89 (57)                       | <0.001 |
| Septic shock              | 151 (39)              | 128 (55)          | 23 (15)                       | <0.001 |
| Extracorporeal organ support before culture positivity | 182 (47)              | 129 (55)          | 53 (34)                       | <0.001 |
| After culture positivity  | 210 (54)              | 156 (68)          | 54 (34)                       | <0.001 |
| ICU length of stay (days) | 28 (15–51)            | 25 (13–48)        | 33 (21–54)                    | 0.003 |
| Before culture positivity | 12 (5–23)             | 12 (5–23)         | 13 (5–23)                     | 0.638 |
| Hospital length of stay (days) | 37 (22–66)         | 30 (16–58)        | 50 (33–72)                    | <0.001 |
| Before culture positivity | 15 (8–30)             | 16 (8–31)         | 14 (8–29)                     | 0.428 |
| **Inflammatory parameters at culture positivity** |                       |                   |                               |
| White blood cell count (10^9/l) | 13 (9–20)            | 14 (2–22)         | 12 (9–16)                     | 0.005 |
| Procalcitonin (µg/l)      | 2 (1–7)               | 3 (1–7)           | 2 (1–8)                       | 0.042 |
| C-reactive protein (mg/dl) | 124 (71–189)          | 129 (71–193)      | 121 (68–187)                  | 0.682 |
| Lactate (mmol/l)          | 2 (1–4)               | 3 (2–5)           | 2 (1–2)                       | <0.001 |
| **Central venous catheter (CVC)** |                       |                   |                               |
| Number of CVCs per patient| 5 (3–8)               | 5 (3–8)           | 5 (3–9)                       | 0.232 |
| CVC overall time in place (hours) | 726 (326–1432)       | 698 (306–1400)    | 772 (344–1443)                | 0.710 |
| Max. time in place per CVC (hours) | 242 (162–308)       | 230 (156–308)     | 257 (188–308)                 | 0.204 |
| Min. time in place per CVC (hours) | 43 (15–87)           | 38 (12–68)        | 61 (18–99)                    | 0.001 |
| Mean time in place per CVC (hours) | 141 (101–176)       | 135(94–168)       | 157 (109–190)                 | 0.009 |
CVC duration, and length of ICU stay were risk factors for mortality at 28 and 180 days in the multivariable Cox regression. Patients, who received adequate and non-adequate antifungal treatment for Candida BSI, and patients undergoing abdominal surgery had a higher probability of survival at 28 and 180 days. Echinocandins for antifungal treatment were associated with survival at 28, but not at 180 days. Details on the multivariable models are presented in Table 3 and Additional file 5.

Discussion

In this single-center retrospective study, including 391 critically ill patients with Candida BSI, we observed a high mortality 28 and 180 days after culture positivity. We identified higher age, a history of liver cirrhosis, high SOFA and Candida scores, increased length of ICU stay, and the presence of septic shock as risk factors for mortality after Candida BSI. Patients, who had abdominal surgery, and patients receiving any empirical antifungal agent had a reduced risk of mortality compared...
to medical admission type and no antifungal treatment, respectively. Throughout the study period of 10 years, we did not observe a significant change in the distribution pattern of yeast species and no multidrug-resistant C. auris was identified.

We found a mortality rate of 47% 28 days after diagnosis of C. BSI. Our results are in line with findings from previous studies. In one of the largest European multicenter trials on the epidemiology of ICU-acquired candidiasis, the 30-day mortality rate was 42% [1]. Similarly, a 30-day-mortality of 45% has been reported after candidemia in internal medicine wards [19]. The French Mycoses study group observed 50% survival in a mixed ICU population 30 days after candidemia [11], which is similar to the findings of a retrospective observation by Ghanem-Zoubi and colleagues [3]. An analysis from prospectively collected data in the French REA-RAISIN network showed a mortality rate of 52% among patients with ICU-acquired candidemia in 213 ICUs [20].

We found that adequate antifungal management, defined by the start of antifungal medication, susceptibility of C. spp., and time point of CVC removal, was a predictor of survival after 28 and 180 days. Interestingly, multivariable analysis showed that also non-adequate antifungal treatment including delayed administration of antifungal medication or resistant drugs was associated with an increased probability of survival. By contrast, adequate antifungal treatment does not seem to be superior with regard to survival after 28 or 180 days when compared to non-adequate antifungal management. Several factors may be accountable for the non-superiority of adequate antifungal treatment over non-adequate antifungal management. Several factors may be accountable for the non-superiority of adequate antifungal treatment over non-adequate antifungal management with regard to survival in our study population. First, there are no detailed uniform criteria for adequate antifungal treatment used throughout the study period between 2008 and 2017. The total number does not add up to 284 because of escalation/de-escalation of antifungal treatment.

Table 2: Antifungal treatment in critically ill patients with laboratory-confirmed bloodstream infection with C. spp. Continuous variables are given as median (1st to 3rd quantile), categorical variables are given as n (%)

| Antifungal strategy                                      | Study participants n = 391 | Non-survivors n = 234 | Survivors n = 157 | Descriptive p-value (unadjusted) |
|----------------------------------------------------------|-----------------------------|------------------------|-------------------|---------------------------------|
| Targeted b                                               | 174 (44.5%)                 | 96 (41.0%)             | 78 (49.7%)        | 0.128                           |
| Empirical c                                              | 88 (22.5%)                  | 53 (22.6%)             | 35 (22.3%)        | 0.278                           |
| Resistant d                                              | 8 (2.0%)                    | 3 (1.3%)               | 5 (3.2%)          | 0.948                           |
| Delayed e                                                | 14 (3.6%)                   | 8 (3.4%)               | 6 (3.8%)          | 0.886                           |
| None                                                     | 107 (27.4%)                 | 74 (31.6%)             | 33 (21.0%)        | 0.283                           |
| Treatment with echinocandin                              | 187 (47.8%)                 | 108 (46.2%)            | 79 (50.3%)        | 0.163                           |
| Empirical therapy                                        |                             |                        |                   | 0.435                           |
| Echinocandin                                             | 41 (10.5%)                  | 24 (10.3%)             | 17 (10.8%)        | 0.419                           |
| Azoles                                                   | 48 (12.3%)                  | 32 (13.7%)             | 16 (10.2%)        | 0.453                           |
| Amphotericin B                                           | 6 (1.5%)                    | 2 (0.9%)               | 4 (2.5%)          | 0.680                           |
| Duration of antifungal treatment (days)                  | 8 (0–17)                    | 5 (0–15)               | 11 (3–19)         | <0.001                          |
| Antifungals                                              |                             |                        |                   |                                 |
| Fluconazole                                              | 159 (40.7)                  | 83 (35.5)              | 76 (48.4)         |                                 |
| Anidulafungin                                            | 129 (33.0)                  | 75 (32.1)              | 54 (34.4)         |                                 |
| Caspofungin                                              | 66 (16.9)                   | 37 (15.8)              | 29 (18.5)         |                                 |
| Voriconazole                                             | 22 (5.6)                    | 18 (7.7)               | 4 (2.5)           |                                 |
| Amphotericin B                                           | 16 (4.1)                    | 8 (3.4)                | 8 (5.1)           |                                 |
| Posaconazole                                             | 1 (0.3)                     | 1 (0.4)                | 0 (0)             |                                 |
| Itraconazole                                             | 1 (0.3)                     | 1 (0.4)                | 0 (0)             |                                 |

* Wilcoxon–Mann–Whitney U test was performed for continuous variables and Fisher’s exact test for categorical variables. †Targeted treatment was initiated within 24 h of culture positivity. ‡Empirical treatment was administered in patients with risk factors for candidemia and persistent fever despite antibacterial medication or positive culture from non-sterile sites. Empirical treatment refers to antifungal medication that was effective according to antifungal susceptibility testing. §Resistant: antifungal treatment that was not effective against the detected C. species. ¶Delayed: antifungal treatment was started more than 24 h after culture positivity. ‡Antifungal substances used throughout the study period between 2008 and 2017. The total number does not add up to 284 because of escalation/de-escalation of antifungal treatment.
with mortality after candidemia has been reported by another retrospective trial. Three definitions of appropriate empiric treatment and their association with 30-day mortality were compared in a cohort of 302 critically ill patients [3]. Interestingly, statistical associations varied by definition, which underlines the impact of treatment criteria on outcome prediction.

Second, the susceptibility of *Candida* spp. to specific antifungal drugs may not necessarily correlate with outcome. Ghrenassia and colleagues observed that *Candida* susceptibility was not associated with survival after candidemia in immunocompromised patients [21]. Neither was the choice of antifungal agent in favor of echinocandins. As opposed to the treatment regimen in our study, antifungal prophylaxis was used by Ghrenassia et al. which may limit the comparability with our results.

Third, the fact that any empiric antifungal treatment was initiated, irrespective of susceptibility and time point, may mirror awareness and disease recognition of *Candida* BSI by the ICU team, which might explain the positive association with survival at 28 and 180 days.

We found an association between treatment with echinocandins and survival after 28 days. By contrast, mortality after 180 days was not influenced by echinocandins for antifungal management. There remains controversy on the impact of echinocandins on mortality [22–25]. Of note, other factors such as comorbid conditions, disease severity, and appropriate antifungal management including source control may be more relevant for survival after candidemia, which may explain the conflicting results [22]. We found a beneficial effect of echinocandins on short-term mortality after 28 days that did not sustain the 180-day follow-up. Long-term survival in critically ill patients may be determined by the underlying condition and disease severity rather than the type of initial antifungal medication.

Compared with medical patients, patients undergoing abdominal surgery had a lower risk of mortality at 28 and 180 days. Similar results have been reported from the Spanish CANDIPOP trial that found a lower mortality from candidemia in surgical wards compared with medical wards [26]. Better outcome in surgical patients might be attributable to lower disease severity, fewer immunosuppression, and organ failure [26].

Preexisting liver cirrhosis was associated with increased 28- and 180-day mortality in our study population, which confirms the results of previous studies [27]. Next to the SOFA score as an indicator of morbidity in critical care patients and the presence of septic shock, we found an association between the *Candida* score and reduced survival at 28 and 180 days [28]. All factors that were identified as predictors of poor outcome in our study population have been linked with increased mortality in ICU patients before [29–31]. Thus, our results confirm the importance of disease severity and multiorgan dysfunction for the prognosis after *Candida* BSI.
Candida albicans was the most frequently encountered yeast isolate in our study population, followed by Candida glabrata and Candida parapsilosis. Our findings are in line with data from the multicenter EUCANDICU trial reporting similar distribution patterns. There are conflicting results on a shift in Candida spp. towards non-albicans isolates. Several Italian studies report a decrease of Candida albicans and an increase of non-albicans Candida spp.\[32, 33\]. By contrast, two observational studies in French and Belgian ICUs did not observe a species shift and describe patterns similar to our results with a predominance of Candida albicans\[34, 35\]. We found a relatively stable Candida albicans/non-albicans ratio between 2012 and 2015. Interestingly, there was a substantial shift towards Candida albicans in the years 2016 and 2017. The decrease of non-albicans species in favor of Candida albicans might be attributable to episodic fluctuations that have been observed periodically\[35\]. Of note, Candida auris, a multidrug-resistant pathogen, which was first described in Japan in 2009\[36\], has been recently associated with outbreaks worldwide, including Europe, could not be detected in our study population\[37–40\].

Table 3 Probability of death 28 and 180 days after blood cultures were tested positive for Candida spp. 381 observations, 178 events (28 days), and 227 events (180 days) were included in the multivariable analysis

| Variable | Hazard ratio (95% CI) | 28 days | Hazard ratio (95% CI) | 180 days |
|----------|----------------------|---------|----------------------|----------|
| Age (per year increase) | 1.02 (1.00–1.03) | 1.02 (1.01–1.03) | 1.02 (1.01–1.03) | 1.01–1.03 |
| Liver cirrhosis (vs. none) | 1.61 (1.09–2.38) | 1.54 (1.07–2.20) | 1.07–2.20 | 1.07–2.20 |
| Immunosuppressiona (vs. none) | 0.97 (0.71–1.32) | 0.84 (0.63–1.11) | 0.63–1.11 | 0.63–1.11 |
| SOFA score (per point increase) | 1.14 (1.08–1.19) | 1.12 (1.07–1.17) | 1.07–1.17 | 1.07–1.17 |
| Septic shock | 2.60 (1.77–3.82) | 2.41 (1.73–3.37) | 1.73–3.37 | 1.73–3.37 |
| Admission diagnosis | | | | |
| Abdominal surgery vs. medical | 0.55 (0.38–0.81) | 0.66 (0.48–0.91) | 0.48–0.91 | 0.48–0.91 |
| Other surgery vs. medical | 0.79 (0.52–1.20) | 0.70 (0.48–1.03) | 0.48–1.03 | 0.48–1.03 |
| Abdominal surgery vs. other surgery | 1.43 (0.89–2.30) | 1.06 (0.71–1.60) | 0.71–1.60 | 0.71–1.60 |
| Days at ICU before Candida BSI (per day increase) | 1.01 (1.00–1.01) | 1.01 (1.00—1.01) | 1.00—1.01 | 1.00—1.01 |
| Mechanical ventilation (vs. none) | 0.95 (0.49–1.82) | 0.77 (0.44–1.34) | 0.44–1.34 | 0.44–1.34 |
| Extracorporeal organ support before Candida BSI (vs. none) | 1.23 (0.85–1.78) | 1.28 (0.93–1.76) | 0.93–1.76 | 0.93–1.76 |
| Mean CVC duration (per h increase) | 1.00 (1.00–1.00) | 1.00 (1.00–1.00) | 1.00–1.00 | 1.00–1.00 |
| Candida score (per point increase) | 1.21 (1.06–1.37) | 1.25 (1.11–1.40) | 1.11–1.40 | 1.11–1.40 |
| Candida species (albicans vs. non-albicans) | 1.14 (0.82–1.59) | 1.08 (0.80–1.44) | 0.80–1.44 | 0.80–1.44 |
| Treatment with echinocandins (vs. none or other antifungals) | 0.67 (0.45–0.99) | 0.79 (0.56–1.11) | 0.56–1.11 | 0.56–1.11 |
| Antifungal treatment: | | | | |
| Non-adequate vs. none | 0.23 (0.10–0.56) | 0.31 (0.16—0.62) | 0.16—0.62 | 0.16—0.62 |
| Adequate vs. none | 0.30 (0.20–0.45) | 0.36 (0.24–0.52) | 0.24–0.52 | 0.24–0.52 |
| Adequate vs. non-adequate | 0.78 (0.34–1.81) | 0.88 (0.47–1.65) | 0.47–1.65 | 0.47–1.65 |

SAPS II: Simplified Acute Physiology Score II at time of culture positivity. ICU: intensive care unit. BSI: bloodstream infection. CVC: central venous catheter. SOFA score: Sepsis-related organ failure assessment score. *Immunosuppression: stem cell transplantation, acquired immunodeficiency syndrome, solid organ transplantation, immunosuppressive medication. The criteria for adequate antifungal treatment were fulfilled, if (1) antifungal medication was administered within the first 24 h of culture positivity, (2) substance dosage was weight adjusted and in accordance with current recommendations, (3) the isolated yeast was susceptible to the antifungal agent, and (4) source control was initiated within the first 48 h after blood culture positivity.
variables that were omitted from our analyses may have biased the results of this study, which has to be considered when interpreting our findings.

Source control was defined as CVC removal in our study. We did not include other management strategies such as the removal of implanted devices, drainage of infected fluid collections or surgical debridement of infected solid tissue. We chose this definition, because we aimed to analyze the impact of measures that were immediately performed by the ICU team rather than surgical procedures.

One strength of our study is the long observation period of 10 years that allows the analysis of species distribution independently from seasonal fluctuations. Importantly, we obtained microbiological results from a mixed population of critically ill patients, including surgical and medical conditions, hematologic malignancy, solid and organ stem cell transplantation.

Most previous trials that assessed outcome after candidemia report short-term mortality rates after one month [1, 46], since the 30-day outcome is traditionally used as an endpoint in critical care trials [47]. We aimed to evaluate outcome beyond this time period and assessed long-term survival 180 days after diagnosis of Candida BSI in addition to 28-day mortality.

### Conclusion

Candida BSI is still a serious and life-threatening disease with very high morbidity and mortality in critically ill patients. Our study demonstrates that prompt antifungal treatment improves the likelihood of survival, regardless of yeast susceptibility and exact time point of administration. Patients with liver cirrhosis and high disease severity as expressed by the SAPS II and the Candida scores, and organ failure requiring extracorporeal support are at increased risk of death 28 and 180 days after culture positivity, whereas surgical patients seem to have more favorable outcome after Candida BSI. Species distribution remained relatively constant throughout a 10-year period with Candida albicans as the predominant yeast species. Our results underline the importance of rapid treatment of Candida BSI and point to the need for a uniform definition of adequate antifungal management.

### Supplementary information

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s13613-020-00755-8.

**Additional file 1.** a-d: Selected patient characteristics throughout the study period between 2008 and 2017. a) Age, b) Sepsis-related Organ Failure Assessment (SOFA) score, and c) Simplified Acute Physiology Score on the day of Candida BSI are given as median. d) Surgical admission in %.

**Additional file 2.** Referring/co-managing specialties divided by mortality after 180 days. Data are given as absolute and relative numbers. *Fisher’s exact test was performed for categorical variables.

**Additional file 3.** Distribution of Candida spp. in survivors (n = 157) and non-survivors (n = 234) at 180 days: BSI bloodstream infection.

**Additional file 4.** Distribution of C. albicans versus non-albicans Candida spp. between 2008 and 2017.

**Additional file 5.** Predictors of mortality 180 days after blood cultures positive for Candida spp. were obtained. Squared symbols indicate hazard ratios, error bars indicate 95% confidence intervals.

**Abbreviations**

BSI: Bloodstream Infections; CVC: Central venous catheter; ICU: Intensive care unit; SAPS II: Simplified Acute Physiology Score II; SOFA: Sepsis-related Organ Failure Assessment.

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None.

**Authors’ contributions**

MSch, MF and SK have made substantial contributions to conception and design of the study as well as to the acquisition, analysis and interpretation of data. TW, TD, AKO and SW have made substantial contributions to analysis and interpretation of data. MSch, MF, HR and SK have drafted the submitted article. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets generated and/or analyzed during the current study are not publicly available due to data protection of the patients, but are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

Study was approved by the local ethical committee.

**Consent for publication**

Is enclosed by each author.

**Competing interests**

The authors declare that they have no competing interests.

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