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Attributable mortality of candidemia at the University Hospital of Cologne from 01.07.1997-30.06.2001 before the introduction of echinocandins

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Eine Liste aller in Frage kommenden Fallpatienten wurde mir ohne meine Mitarbeit von Prof. Dr. med. Harald Seifert aus dem Institut für Mikrobiologie, Immunologie und Hygiene zur Verfügung gestellt. Eine Liste aller in Frage kommenden Kontrollpatienten wurde durch eine Datenbankabfrage von Roman Voskoboynik, Medizincontrolling der Uniklinik Köln, ohne meine Mitarbeit erstellt. Die Auswahl der geeigneten Fall- sowie Kontrollpatienten sowie das präzise matching wurde von mir selbst unter Beratung von Dr. med Philipp Köhler durchgeführt. Die für diese Arbeit verwendeten Krankengeschichten wurden von mir selbst im ECMM *Candida* Register – *Candi*Reg dokumentiert und ausgewertet. Die statistische Auswertung wurde von mir selbst, unter Beratung von Dr. Jon Salmanton-García, durchgeführt.

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CCI	Charlson Comorbidity Index
CVC	central venous catheter
ECMM	European Confederation of Medical Mycology
ESCMID	European Society of Clinical Mycology and Infectious Diseases
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
UHC	University Hospital of Cologne
USA	United States of America
US	United States
vs	versus

1. Summary

Invasive candidiasis includes mucocutaneous candidiasis and invasive *Candida* infections. The latter is divided into bloodstream infections with *Candida* species (candidemia) and deep-seated organ infections.

Candida species are among the four most common causes of nosocomial bloodstream infections in the United States of America (USA). Worldwide, the most common species causing candidemia are *Candida albicans*, *Candida glabrata, Candida tropicalis, Candida parapsilosis* and *Candida krusei.* Risk factors for candidemia are antibiotic treatment, glucocorticoids, parenteral nutrition, hemodialysis, presence of a central venous catheter (CVC), abdominal surgery, a compromised immune system and critical care treatment. Candidemia often occurs in critically ill patients, and it is associated with a high morbidity and mortality. Two studies performed in the USA in the 1980s and from 1997 to 2001 have analyzed the attributable mortality of candidemia. They have shown attributable mortality rates of 38% and 49%, respectively. Until now, only little data about the epidemiology, risk factors and mortality rates of candidemia during this time in Germany have been published. Without historical comparators, current studies and data published are difficult to evaluate and interpret. To overcome this obstacle, we performed a retrospective, matched case-control study including 57 patients with candidemia, hospitalized at the University Hospital of Cologne (UHC) between 1st of July 1997 and 30th of June 2001. To each case patient, a carefully selected control patient was matched.

In our study, the incidence of candidemia was 3.5 per 10,000 admissions. For cases and controls, we observed in-hospital mortality rates of 33.3% and 11.8%, and a 30-day mortality of 23.5% and 7.8%, respectively. Therefore, the attributable mortality rate of candidemia at the University Hospital of Cologne at the abovementioned time point was 21.5%, with a 30-day mortality of 15.7%.

Currently, due to higher incidence rates in a demographically changing society, the relevance of candidemia is increasing. A high awareness of the relevance of candidemia and a controlled disease management by adherence to current guidelines have an impact on the outcome of candidemia.

2. Zusammenfassung

Die invasive Candidose umfasst die mukokutane Candidose sowie invasive *Candida* Infektionen. Letztere werden unterteilt in Blutstrominfektionen mit *Candida* Spezies (Candidämie) und Organinfektionen.

Candida Spezies gehören in den Vereinigten Staaten von Amerika (USA) zu den vier häufigsten Ursachen für nosokomiale Infektionen der Blutbahn. Weltweit sind die häufigsten Spezies, die eine Candidämie verursachen, *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis und Candida krusei*. Risikofaktoren für eine Candidämie sind eine Antibiotikabehandlung, Glukokortikoide, parenterale Ernährung, Hämodialyse, das Vorhandensein eines zentralen Venenkatheters (ZVK), abdominale Operationen, ein geschwächtes Immunsystem und die Behandlung auf der Intensivstation. Eine Candidämie tritt häufig bei kritisch kranken Patienten auf und ist mit einer hohen Morbidität und Mortalität verbunden. In zwei Studien, die in den 1980er Jahren und von 1997 bis 2001 in den USA durchgeführt wurden, wurde die zuschreibbare Sterblichkeit von Candidämien untersucht. Sie zeigten zuschreibbare Sterblichkeitsraten von 38 % beziehungsweise 49 %. Über die Epidemiologie, die Risikofaktoren und die Sterblichkeitsraten der Candidämie in diesem Zeitraum in Deutschland sind bisher nur wenige Daten veröffentlicht worden. Ohne historische Vergleichsdaten sind aktuelle Studien und veröffentlichte Daten jedoch schwer zu bewerten und zu interpretieren. Um Vergleichsdaten zur Verfügung zu stellen, haben wir daher eine retrospektive, gematchte Fall-Kontroll-Studie durchgeführt, in die 57 Patienten mit Candidämie einbezogen wurden, die zwischen dem 1. Juli 1997 und dem 30. Juli 1997 in der Uniklinik Köln (UHC) hospitalisiert wurden. Jedem Fallpatienten wurde ein sorgfältig ausgewählter Kontrollpatient gegenübergestellt.

In unserer Studie lag die Inzidenz der Candidämie bei 3,5 pro 10.000 Einweisungen. Bei den Fällen und den Kontrollen wurden Sterblichkeitsraten von 33,3 % bzw. 11,8 % und eine 30-Tage-Sterblichkeit von 23,5 % bzw. 7,8 % festgestellt. Die zuschreibbare Sterblichkeitsrate der Candidämie am Universitätsklinikum Köln betrug somit zum oben genannten Zeitpunkt 21,5 % und die 30-Tage-Sterblichkeit betrug 15,7 %.

Gegenwärtig nimmt die Bedeutung der Candidämie aufgrund höherer Inzidenzraten in einer sich demografisch verändernden Gesellschaft zu. Ein hohes Bewusstsein für die Relevanz der Candidämie und ein kontrolliertes Krankheitsmanagement durch die Einhaltung aktueller Leitlinien haben einen Einfluss auf den Verlauf der Candidämie.

3. Introduction

3.1 Invasive Candidiasis

Invasive candidiasis is a broad term that includes mucocutaneous candidiasis and invasive *Candida* infections. The latter is divided into bloodstream infections with *Candida* species, defined as candidemia, and deep-seated organ infections.

Candida species are part of the normal skin and gut microbiota and can be detected on the mucosal surfaces of 50-70% of healthy humans. In cases of increased or abnormal colonization with *Candida* species in combination with a local defect of the mucocutaneous barriers or a compromised immune system, an asymptomatic colonization with *Candida* species can develop into invasive candidiasis. In the majority of *Candida* infections, the patient shows colonization with the respective *Candida* species [1, 2].

Mucocutaneous candidiasis can affect the respiratory system, the urogenital system causing urethritis, vaginal mycosis and balanitis, and the gastrointestinal system as *Candida* esophagitis.

Invasive *Candida* infections can occur in almost any organ, as deep-seated organ infection, or affect the blood, as candidemia. Deep-seated infections can remain localized or disseminate, leading to secondary bloodstream infections. Bloodstream infections with *Candida* species can likewise remain localized or lead to disseminated infections, involving liver, spleen, kidney, central nervous system, bones, jones, eyes, and the heart.

Candidemia is the most common manifestation of invasive *Candida* infections. Besides compromised mucocutaneous barriers, indwelling foreign bodies, like CVCs, can be the source of infection. *Candida* species colonizing the skin can colonize the catheter and form a biofilm, which leads to candidemia.

3.2 Candidemia

3.2.1. Incidence

Candida species are among the most common causes of nosocomial bloodstream infections. In 2011, a German study including data from 586 intensive care units (ICUs), observed *Candida albicans* as the fourth leading pathogen of CVC-associated bloodstream infections [3]. A study performed in 2004 in Switzerland reported *Candida* species as the seventh leading pathogen of nosocomial bloodstream infections [4]. In the United States (US), *Candida* species are among the four most common pathogens inducing nosocomial bloodstream infections [5-7].

The incidence of candidemia varies between countries and has increased over the last decades. Studies performed in Europe between 2000 and 2002 reported an incidence between 3.6 and 3.8 per 10,000 admissions [4, 8, 9]. Similar results have been described in a meta-analysis performed in 2019 considering 43,799 cases of candidemia in Europe between 2000 and 2019. The study observed an overall pooled incidence rate of 3.88/10,000 admissions [10]. More recently, a study performed at the UHC in 2020 reported a higher incidence of 6 per 10,000 admissions [11].
In the US between 2002 and 2004, incidence rates ranked between 4.6 and 7 per 10,000 admissions [12, 13].

3.2.2. Mortality

Candidemia poses a great challenge to treating physicians. This may be due to an increasing number of critically ill patients in a demographically changing society. Candidemia is associated to a high morbidity and mortality as well as a prolonged hospital stay [14-16]. A prospective cohort study performed in Germany in 2018, including 937 ICUs between 2006 and 2015, showed that *Candida albicans* and non-*albicans* species were under the four pathogens that showed the highest pathogen-related mortality [17].

In 1988, a monocentric, retrospective, case-control study performed by Wey et al. at the University of Iowa Hospitals and Clinics in the US analyzed the attributable mortality of candidemia [16]. They analyzed 88 patients with candidemia between July 1983 and December 1986. To each candidemia patient, a non-candidemia control patient was matched. Control patients were matched by underlying disease, age, major surgical procedure, date of admission and sex. Reported mortality rates were 57% for candidemia cases and 19% for control cases. Thus, an attributable mortality of 38% was observed [16].

In 2003, Gudlaugsson and colleagues reevaluated the attributable mortality of candidemia at the same university hospital, analyzing whether new treatment strategies, the introduction of fluconazole as the treatment of choice for candidemia [18] and the emergence of triazole-resistant species [12], influenced the attributable mortality. They performed a study of the same design, including 108 candidemia cases and 108 control patients between 1st of July 1997 and 30th of June 2001. They showed that the attributable mortality had not decreased but increased to 49% [15]. This was interpreted to be caused by a very high crude mortality rate of 61% in their study population, which was higher than other studies performed during a similar time period [15, 19, 20].

In 2020, Cornely et al. performed a similar matched case-control study in analogy to Wey et al. and Gudlaugsson et al. at the UHC in Germany. Their aim was to evaluate, whether the introduction of echinocandins as the gold standard of antifungal therapy had an influence on the attributable mortality of candidemia. They included 100 cases and controls between 2014 and 2017. The study showed a decrease of the attributable mortality to 26% [11]. A multinational study performed in 2022 by Hönigl et al. analyzed 632 candidemia cases in 20 European countries. They described an overall mortality of 46% and in 37% of those cases, the investigators attributed death to candidemia [21].

3.2.3. Risk factors

Well-established risk factors for candidemia are long-term antibiotic treatment, systemically administered glucocorticoids, parenteral nutrition, hemodialysis, excessive granulocytopenia, presence of CVC and abdominal surgery. Immunocompromised patients and patients in ICU are particularly vulnerable [6, 22, 23]. In 2020, a prospective, multicenter, matched case–control study analyzed risk factors separately in both ICU and non-ICU settings. Independent risk factors for patients in ICU settings were total parenteral nutrition, acute kidney injury, heart disease, prior septic shock and administration of aminoglycoside antibiotics. Risk factors for non-ICU patients were total parenteral nutrition, presence of CVC and administration of glycopeptides and nitroimidazoles [24]. Considering cases of candidemia caused by non-*albicans* species, immunosuppressive therapy is an independent risk factor in comparison to candidemia caused by *Candida albicans* [25]. The study performed by Hönigl et al in 2022 observed the older age of patients, ICU admission and candidemia caused by rarer *Candida* species as independent risk factors for candidemia [21].

3.2.4. Species distribution

The most common species of Candidemia is *Candida albicans*, followed by *Candida glabrata, Candida tropicalis, Candida parapsilosis* and *Candida krusei*. The ARTEMIS DISK Global Antifungal Surveillance Study analyzed more than 140,000 yeast isolates from 39 countries from June 1997 to the end of 2003. *Candida albicans* was the most common cause of candidemia with 66.2% of all *Candida* species [26]. However, over the last decades, a shift towards the ‚non-*albicans*‘ species was documented [10, 27]. The “ARTEMIS DISK Global Antifungal Surveillance Study” described a decrease of 10-11% of *Candida albicans* isolation over the 6.5-year period whereas the isolation of *Candida tropicalis* and *Candida parapsilosis* increased 2.9% and 3.1%, respectively [26]. A study performed in Europe, including 399 isolates from 17 European countries between 2018 and 2022, likewise described a decrease of the population of *Candida albicans* of 6.9 - 9.3% and an increase of the population of

Candida glabrata of 8.5 - 8.7% compared to studies including patients in 1997-1999 and 2006-2008 [28]. In patients with hematological malignancies, *Candida parapsilosis* and *Candida tropicalis* were detected more frequently than *Candida albicans* [29]. *Candia glabrata* was described more frequently in elderly patients, patients with preliminary usage of fluconazole as well as broad-spectrum antibiotics, presence of CVC, parenteral nutrition or treatment in ICU [30].

The multidrug-resistant *Candia auris* species first emerged in Japan in 2009 and continued to spread globally [31, 32]. Unlike other *Candida* species, which are in most cases part of the normal skin and gut microbiota and thereby can lead to candidiasis, *Candida auris* is transmitted person-to-person and mostly occurs in outbreaks [33]. Since *Candida auris* is phenotypically similar to other *Candida* species, *Candida auris* is often misidentified by commercially available phenotypic platforms for yeast identification [34]. Therefore, the prevalence of *Candida auris* infections is unknown. It has been described in over 40 countries [35] and is associated with a high mortality and limited treatment options [36].

3.2.5. Therapy

The first guidelines published by the Infectious Diseases Society of America (IDSA) in 2000 recommended either amphotericin B deoxycholate or fluconazole as treatment of choice for candidemia. In case of severe infections, flucytosine should be combined. Lipid formations of amphotericin B were second-line therapy and recommended for patients who were intolerant of or refractory to therapy with conventional amphotericin B. In stable patients, fluconazole should be preferentially used whereas in critical, amphotericin B was preferred due to its broader spectrum. *Candida glabrata and Candida krusei* should both have been treated with amphotericin B. Due to the fact that many isolates of *Candida lusitaniae* were resistant to amphotericin B, it was suggested to be treated by fluconazole. Intravascular catheters should be removed, if feasible. Step-down approaches with the switch from amphotericin B to fluconazole (oral or intravenous) for completion of treatment were also described. Treatment duration was defined as 14 days after the first negative follow-up blood culture. Susceptibility testing should be performed, if available. Since *Candida* endophthalmitis can lead to sight-threatening lesions, retinal examination was recommended for every patient with candidemia [18].

Today, the latest guidelines published by the IDSA, and the European Society of Clinical Mycology and Infectious Diseases (ESCMID) recommend echinocandins as the gold standard for systemic antifungal therapy [37, 38]. No change in treatment duration was recommended (14 days) [39]. Susceptibility testing is performed for each *Candida* species isolated from a blood culture. In the case of azol-sensitive species, echinocandin treatment can be switched

to oral fluconazole. This procedure requires a stable patient and is usually applied if the patient is discharged before the completion of treatment. Since *Candida parapsilosis* is resistant to echinocandins, the latest guidelines recommend fluconazole as the first-line therapy of choice [40]. However, the number of fluconazole resistant isolates in different countries has been increasing over the last years. A study analyzing isolates of *Candida* collected in 39 countries between 2006 and 2016 described a fluconazole resistance rate of 3.9% [41].

Central venous catheters, which are often the source of infection, should be removed as soon as possible, if feasible [42]. In case of persistent bloodstream infection, echocardiography and fundoscopy should be performed to detect complications like endocarditis and endophthalmitis.

In case of a positive blood culture for any kind of *Candida* species, intravenous therapy should be started immediately. Any delay of therapy increases mortality. Studies showed that a delay of treatment from 24h to 48h leads to an increase of mortality from 23.7% to 36.4% [43].
In critically ill patients with high-risk factors for invasive candidiasis and no other source for fever and symptoms, empiric treatment may be considered with the beginning of the first symptoms [44]. In all other cases, targeted therapy is recommended, which is initiated at the time the preliminary test result for identification of a yeast is communicated to the treating physician.

3.2.6. Guidelines and EQUAL Candida score

Candida species can lead to a broad spectrum of infections. Diagnostic and therapeutic options therefore are complex and consistently developing. To summarize the most current knowledge and guide the decision-making of treating physicians, guidelines were established and regularly revised.
The first practice guidelines for the treatment of candidiasis were established by the IDSA and published in 2000 [18]. Guideline updates were published by the IDSA in 2004 [38], 2009 [45] and 2016 [46].
In 2012, the European Fungal Infection Study Group (EFISG) of the ESCMID developed a guideline to face the multitude of provided evidence regarding the management of *Candida* diseases in non-neutropenic adult patients and to facilitate evidence-based decision-making [37].
Still, in the everyday routine of the treating physicians, compliance with these guidelines is difficult. The reason might be their complexity as well as lack of familiarity. In order to summarize the strongest recommendations published by the IDSA in 2016 and the ESCMID in 2012 and to provide a tool enabling measurement of guideline adherence, the European

Confederation of Medical Mycology (ECMM) QUALity of Clinical Candidemia Management score (EQUAL score) was developed. It includes factors regarding diagnostic procedures (initial blood culture, species identification, susceptibility testing, echocardiography, and ophthalmoscopy), treatment strategies (echinocandin treatment, step down to fluconazole depending on susceptibility results, treatment for 14 days after first negative follow-up blood culture, removal of the central venous catheter) and follow up procedures (performance of follow up blood cultures). Adherence to each aspect is rated with 1-3 points and a total of 19 points for patients without CVC and 22 for patients with CVC can be scored. The score aims to provide a tool for (self-) evaluation of guideline adherence and *Candida* treatment [47].

3.3 ECMM Candida Registry – CandiReg

ECMM Candida Registry CandiReg (A Global Invasive Candidiasis Registry) is a register, in which patients with candidemia, invasive candidiasis and hepatosplenic candidiasis can be included (ClinicalTrials.gov Identifier: NCT03450005). It is accessible through www.clinicalsurveys.net. Clinicsurveys.net is a platform at which physicians can enter data into different databases and perform studies. *ECMM Candida Registry CandiReg* is approved by the local Institutional Review Board and Ethics Committee of the University of Cologne (Identifier 17-485). It gathers the following items: epidemiologic data (incidence, global and local tendencies, patients at risk, resistance of species, attributable mortality, and costs), information about the clinical course (diagnostic procedures, therapy concepts), information about isolates and antifungal resistance and recommendations regarding the management of *Candida* infections. The collected data of case and control patients are compared by using the *ECMM Candida Registry CandiReg.*

3.4 Aims of this Dissertation

1. To perform a matched case control study, analyzing patients with candidemia and matched controls between 1st July 1997 and 30th June 2001 treated at the University Hospital of Cologne
2. To collect and compare data about epidemiologic and demographic characteristics, risk factors for candidemia and the outcome for both case and control patients
3. To analyze the treatment management of candidemia regarding guideline adherence
4. To compare our data to previously published findings

4. Publication

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Attributable mortality of candidemia at a German tertiary hospital from 1997 to 2001 before the introduction of echinocandins

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Abstract

Objectives: The relevance of candidemia has increased over the last decades due to higher incidence rates in an ageing society. Studies on amphotericin B and fluconazole have shown high attributable mortality rates of 38% and 49% in the United States. Incidence rates and locational factors might have an impact on the mortality rates at the University Hospital of Cologne (UHC), Germany.

Methods: We performed a matched case-control study including 57 patients with candidemia, hospitalised at the UHC between 1 July 1997 and 30 June 2001. Controls were matched by age, sex, admission date, treatment on intensive care unit (ICU), number of days at risk, underlying diseases, surgical procedures and the Charlson Comorbidity Index.

Results: The incidence of candidemia was 3.5 per 10 000 admissions. For cases and controls, we observed in-hospital-mortality rates of 33.3% and 11.8%, and a 30-day mortality of 23.5% and 7.8% respectively. The attributable mortality rate to candidemia was 21.5%, and at 30 days, it was 15.7%. Underlying conditions were more frequent in cases than in controls, especially central venous catheter (80% vs 33%, $P < .001$), chronic cardiovascular disease (39.2% vs 25.5%, $P = .138$), treatment on ICU (31.4% vs 13.7%, $P = .033$) and chronic liver disease (21.6% vs 0%, $P < .001$).

Conclusions: The attributable mortality of candidemia at the UHC between 1997 and 2001 was lower compared to studies performed in the United States with a similar design. Contributing factors might be lower incidence rates and less comorbidities in our study.

KEYWORDS
Candida, fluconazole, invasive candidiasis, liposomal amphotericin B, mortality

1 | INTRODUCTION

Candidemia often results in a prolonged hospital stay and high morbidity and mortality.[1-3] *Candida* spp. are one of the most common causes of nosocomial bloodstream infections (BSI). A study performed in 2011 in Germany, including data from 586 intensive care units (ICUs), observed *Candida albicans* as the fourth lead- ing pathogen of central venous catheter (CVC) associated BSI.[4] In 2004, *Candida* spp. ranked seventh of the pathogens of nosocomial BSI in Switzerland.[5] Studies performed in the United States (US) reported that *Candida* spp. are among the four most common pathogens causing nosocomial BSI.[6-8] Well-established risk factors for candidemia are prior and prolonged antibiotic treatment, parenteral nutrition, haemodialysis, presence of CVC, prolonged hospitalisation and abdominal surgery. Immunocompromised patients and patients on ICU are at high risk for candidemia.[7,9,10] In 1988, a monocentric, retrospective, case-control study performed in Virginia, US, by Wey et al observed an attributable mortality of candidemia of 38%.[3] Gudlaugsson et al re-analysed the situation at the same institution from 1997 to 2001 addressing the question if new treatment strategies, the introduction of fluconazole as treatment of choice for candidemia[11] and emergence of triazole-resistant species[12] influence the attributable mortal- ity. In this second study, an increase of the attributable mortality to 49% was reported.[2] In 2020, a similar study was performed at the University Hospital of Cologne (UHC), Germany, analysing the attributable mortality of candidemia after the introduction of echinocandins. Cornely et al observed a significantly lower attributable mortality of 26%.[13]

Until now, little data on epidemiology, risk factors and mortality rates of candidemia have been published in Germany at the turn of the millennium. To study medical progress and to analyse trends and developments, historical comparators are needed. We therefore performed a retrospective, matched case-control study analysing the attributable mortality of candidemia at the UHC from 1997 to 2001.

2 | PATIENTS AND METHODS

We performed a retrospective, monocentric, case-control study analysing all hospitalised patients with nosocomial candidemia at the UHC, between 1 July 1997 and 30 June 2001. The UHC is a ter- tiary care teaching hospital, which had an average annual number of 44 863 admissions during that period. Nosocomial candidemia was defined as at least one positive blood culture for any *Candida* species occurring >24 hours after admission. Control patients were matched to candidemia cases, which did not have a sign of invasive *Candida* infection.

To ascertain the best matching to a control patient, we used a stepwise procedure. In the first step, we used SAP databases (SAP Graphical User Interface (SAP GUI) 750 for Windows, SAP SE) to generate a list of possible control patients matched by age ±6 years (children: age ±1 year), sex, admission ±18 months, treatment on ICU ±14 days, days at risk and underlying disease. In a second step, we took surgical procedures and the Charlson Comorbidity Index (CCI) into consideration.[14] During the matching process, YB and PK were blinded to the outcome of each matched patient chosen by the predefined algorithm.

For reasons of comparability, we defined the day of candidemia diagnosis as day d0. This was the day at which a preliminary identification of a yeast was communicated to the treating physician, which triggered antifungal therapy and further measures (eg removal of indwelling central lines). The timespan from the initial identification of a yeast in blood culture to the subsequent identification to species level was zero to five days. For controls, d0 was defined as the last day of the timespan t0 after admission, which was equivalent to the timespan t0 between admission and first positive blood culture of case patients. If no suitable control patient matched by days at risk could be identified, the patient with the longest time of hospitalisation was chosen. In those cases, d0 was defined as the last day of hospitalisation for non-survivors and patients lost to follow-up, whereas for survivors the definition of d0 did not differ from other control patients and occurred beyond the date of discharge.

For both case and control patients, epidemiologic and demographic characteristics were documented. We captured data of the underlying disease, Charlson Comorbidity Index, and risk factors for candidemia. ICU stay and indwelling CVC were only considered as a risk factor if they were present at least two days before d0. Both groups were compared by time of hospitalisation before and after d0, the latter, respectively, for survivors and non-survivors. We calculated Day 30 and in-hospital mortality and defined mor- tality attributable to candidemia as the difference between the in-hospital mortality of cases and controls. For candidemia cases, we captured *Candida* species distribution, microbiological findings, susceptibility testing, outcome by species and treatment strate- gies. The dosage of antifungal drugs was stratified according to the maintenance dose, which was administered for the majority of treatment days.

Adherence to guidelines of the Infectious Diseases Society of America (IDSA) published in 2000[11] was analysed considering diagnostic procedures (initial blood culture, species identification, susceptibility testing, echocardiography and ophthalmoscopy), treatment strategies (treatment for 14 days after first negative follow-up blood culture, removal of central venous catheter) and follow-up blood cultures. If case patients were discharged with ongoing antifungal therapy, treatment duration was presumed to be at least for 14 days after first negative follow-up blood culture.

Data were accessed through microfilmed and paper health records and entered into the electronic case report form FungiScope® *Candi*Reg accessible through www.clinicalsurveys.net.[15] *Candi*Reg is approved by the local Institutional Review Board and Ethics Committee of the University of Cologne (Identifier 17-485) and registered at www.clinicaltrials.gov (NCT03450005). All data collected were transferred to IBM SPSS statistics v27 (IBM Corp. Released 2020; IBM SPSS Statistics for Windows, Version 27.0) and

TABLE 1 Baseline characteristics of candidemia and control cases

	Candidemia (n = 51)	Control (n = 51)	*P*-value
Demography			
Sex (Female), n (%)	22 (43%)	22 (43%)	1.000[a]
Age in years, median (IQR)	55 (42-61)	55 (44-64)	.763[b]
CCI, median (IQR)	3 (2-5)	3 (2-5)	.777[b]
Risk factors, n (%)			
Haematological disease	24 (47%)	28 (54%)	.428[c]
HIV/AIDS	3 (6%)	3 (6%)	1.000[c]
Major surgery	17 (33%)	17 (33%)	1.000[c]
Alcoholism	4 (8%)	3 (6%)	1.000[c]
Chronic cardiovascular disease	20 (39%)	13 (25%)	.138[c]
Chronic liver disease	11 (22%)	0 (0%)	<.001[c]
Chronic pulmonary disease	2 (4%)	3 (6%)	1.000[c]
Chronic renal disease	3 (6%)	1 (2%)	.617[c]
Diabetes mellitus	7 (14%)	3 (6%)	.318[c]
Rheumatic/Autoimmune disease	3 (6%)	4 (8%)	1.000[c]
Obesity, BMI >30 kg/m^2	3 (6%)	1 (2%)	.617[c]
Underweight, BMI <18.5 kg/m^2	6 (12%)	4 (8%)	.741[c]
CVC[d]	41 (80%)	17 (33%)	<.001[a]
ICU[d]	16 31%)	7 (14%)	.033[a]
Mechanical ventilation	11 (22%)	6 (12%)	.184[a]
Other risk factors[e]	7 (14%)	1 (2%)	.060[c]
No risk factors	0 (0%)	2 (4%)	.495[c]
Length of stay in days, median (IQR)			
Before day 0	20 (12-37)	20 (12-28)	.639[b]
After day 0	17 (9-48)	12 (1-22)	.003[b]
After day 0 (survivors)	23.5 (10.5-48)	6 (1-19.5)	<.001[b]
After day 0 (non-survivors)	13 (6.5-52)	23 (13.75-46.5)	.319[b]
Days on ICU	23.5 (10.25-39.5)	15 (7-38)	.570[b]

Note: Excluded from this table due to low numbers of exposed patients: solid organ transplantation, trauma, intravenous drug abuse and other disorder requiring immunosuppression.

Abbreviations: BMI, body mass index; CCI, Carlson comorbidity index; CVC, central venous catheter; HIV/AIDS, human immunodeficiency virus infection / acquired immunodeficiency syndrome; ICU, intensive care unit; IQR, interquartile range.

[a]Calculated using *chi-square* test.

[b]Calculated using Mann-Whitney U test.

[c]Calculated using Fisher's exact test.

[d]At least 2 days before d0.

[e]For example prosthetic valve/foreign body.

subsequently analysed. Susceptibility testing was performed by use of VITEK® 2 Fungal Susceptibility Cards (bioMérieux, Nürtingen, Germany) for fluconazole, itraconazole, voriconazole and amphotericin B.

Categorical variables are presented with frequencies and percentages, while continuous variables with median and interquartile range (IQR). We performed chi-square test and Fisher's exact test for categorical and Mann-Whitney U test for continuous variables. A two-tailed *P*-value <.05 was considered as statistically significant.

3 | RESULTS

3.1 | Incidence

During the observation period, 62 patients hospitalised at the UHC developed candidemia, resulting in an incidence of 3.5 per 10 000 admissions. For five patients, only incomplete data sets could be retrieved, so that they were excluded from the analysis. Hence, 57 patients were enrolled. For 51 candidemia patients, a suitable control patient was matched.

3.2 | Baseline characteristics

Characteristics serving as matching criteria such as sex, median age, CCI and major surgery were similar across both groups (P = n.s.; Table 1). In eight cases, no suitable control patient matched by days at risk was identified. In these cases, we matched the patient with the longest time of hospitalisation. Discrepancies were 4 days in four cases and 9, 12, 14 and 31 days in one case, each. Established risk factors for candidemia were more frequently observed in cases than in controls, especially chronic cardiovascular disease (39.2% vs 25.5%, P =.138), chronic liver disease (21.6% vs 0%, P <.001), chronic renal disease (5.9% vs 2%, P =.617), diabetes mellitus (13.7% vs 5.9%, P =.318) and obesity (5.9% vs 2%, P =.617). Treatment on ICU at least 2 days before d0 and mechanical ventilation (MV) was observed more often in cases than in controls (ICU: 31.4% vs 13.7%, P =.033; MV: 21.6% vs 11.8%, P =.184). Treatment duration on ICU likewise was longer for cases than for controls (median 23.5 days vs 15 days, P =.570). CVCs present at least two days before d0 were observed in 80% of cases and 33% of controls (P <.001; Table 1).

3.3 | Duration of hospitalisation

Overall median time until discharge was longer for cases (17 [IQR 9-48]) than for controls (12 [IQR 1-22], P =.003). Median time until discharge of surviving case and control patients was 23.5 (IQR 10.5-48) and 6 days (IQR 1-19.5, P >.001) respectively. However, for the deceased, median time until discharge was shorter for cases than for controls with 13 (IQR 6.3-52, P =.319) days and 23 (IQR 13.75-46.5) days respectively (Table 1).

3.4 | Species distribution and antifungal susceptibility

C albicans was the most frequent species identified (37/57 patients, 65%), followed by *C glabrata* and *C tropicalis* in 7/57 patients (12%) and 5/57 patients (9%) respectively. *C krusei*, *C lusitaniae*, *C parapsilosis* and *C pseudotropicalis* were diagnosed in one patient (1.8%) each. Three patients (5%) with *C albicans* infection had mixed infections with a second fungal pathogen (*C krusei, C guilliermondii and C glabrata)* (Table 2).

Susceptibility results were available for only seven isolates at the time of hospitalisation. At a later stage, 55 isolates were retrospectively tested in 2007.[16] All analysed *C albicans* isolates (39) were susceptible to amphotericin B and fluconazole. All *C glabrata* isolates (8) were susceptible to amphotericin B, but not susceptible to fluconazole (1 resistant, 7 intermediate). Five *C tropicalis* isolates have been analysed, all of them were susceptible to Amphotericin B, four were susceptible to fluconazole and one showed an intermedi- ate susceptibility to fluconazole. *C krusei* (2 isolates) was susceptible to amphotericin B but resistant to fluconazole, and *C. parapsilosis* (1 isolate) was susceptible to both amphotericin B and fluconazole. Table 3 shows the baseline characteristics of candidemia patients stratified by the underlying species.

3.5 | Treatment

Antifungal therapy was administered to 51 of 57 patients (89.5%) for a median of 16 days (IQR 11-29). Fluconazole was the most frequently used drug (47/57, 82.5%). Amphotericin B deoxycholate was used in 13 patients (13/57, 22.8%). Voriconazole was adminis- tered to one patient (1/57, 1.8%) and one patient (1/57, 1.8%) participated in a double-blind randomised controlled study comparing caspofungin to liposomal amphotericin B. A total of 10/57 patients (17.5%) received two or more antifungal agents (numbers above are superadditive).

Considering the substance which was administered for the majority of days, fluconazole was used in 40 (40/51, 78.4%) patients, amphotericin B deoxycholate was used in 10 (10/51, 19.6%) patients and voriconazole in one (1/51, 1.9%) patient. The dose of fluconazole was 800mg in 7.5% (3/40), 400mg in 47.5% (19/40), 200mg in 22.5% (9/40) and 100mg in 2.5% (1/40). Three patients were children and

TABLE 2 Species distribution

Candida infections (n = 57)			
***Candida* species**	**Patients (n)**	**Survivors n (%)**	**Non-Survivors n (%)**
Candida albicans[a]	37	21 (57%)	16 (43%)
Candida glabrata	7	7 (100%)	0 (0%)
Candida tropicalis	5	2 (40%)	3 (60%)
Candida krusei	1	1 (100%)	0 (0%)
Candida lusitianiae	1	1 (100%)	0 (0%)
Candida parapsilosis	1	1 (100%)	0 (0%)
Candida pseudotropicalis	1	0 (0%)	1 (100%)
Candida NOS[b]	4	2 (50%)	2 (50%)
Total	54	34 (63%)	20 (37%)

[a]Three patients had a mixed infection of two *Candida* species: *Candida albicans* + *Candida glabrata*, *Candida albicans* + *Candida guilliermondii* and *Candida albicans* + *Candida krusei*.
[b]Not otherwise specified.

TABLE 3 Baseline characteristics of candidemia patients stratified by the underlying species

	Candida albicans		*Candida glabrata*		*Candida tropicalis*		*Candida guilliermondii*		*Candida krusei*		*Candida lusitaniae*		*Candida parapsilosis*		*Candida pseudotropicalis*		*Candida* spp.	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex																		
Female	18	48.6%	1	12.5%	2	40.0%	1	100.0%	1	50.0%	0	0.0%	0	0.0%	0	0.0%	3	75.0%
Male	19	51.4%	7	87.5%	3	60.0%	0	0.0%	1	50.0%	1	100.0%	1	100.0%	1	100.0%	1	25.0%
Age	55 (37-62)		56 (48.5-67)		55 (40-57)		55 (55-55)		48.5 (33-64)		51 (51-51)		47 (47-47)		31 (31-31)		62 (32.5-67)	
Charlson Comorbidity Index	4 (2-5)		4.5 (3-6)		3 (2-3)		3 (3-3)		3.5 (3-4)		5 (5-5)		0 (0-0)		3 (3-3)		3.5 (2.5-4.5)	
Underlying conditions																		
Hem./Onc. disease	17	45.9%	3	37.5%	2	40.0%	1	100.0%	2	100.0%	0	0.0%	0	0.0%	1	100.0%	2	50.0%
HIV/AIDS	1	2.7%	2	25.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Major surgery	11	29.7%	2	25.0%	1	20.0%	1	100.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%	2	50.0%
Alcoholism	2	5.4%	1	12.5%	0	0.0%	0	0.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%	0	0.0%
Chr. cardiovascular disease	12	32.4%	4	50.0%	2	40.0%	1	100.0%	0	0.0%	1	100.0%	1	100.0%	0	0.0%	2	50.0%
Chr. liver disease	5	13.5%	3	37.5%	2	40.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	25.0%
Chr. pulmonary disease	1	2.7%	2	25.0%	1	20.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Chr. renal disease	3	8.1%	0	0.0%	1	20.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Diabetes mellitus	4	10.8%	1	12.5%	1	20.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	100.0%	1	25.0%
Rheumatic diseases Autoimmune disorder	3	8.1%	1	12.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Obesity (BMI >30)	2	5.4%	0	0.0%	0	0.0%	0	0.0%	1	50.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Underweight (BMI <18.5)	4	10.8%	1	12.5%	2	40.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	25.0%
CVC	33	89.2%	8	100.0%	5	100.0%	1	100.0%	2	100.0%	1	100.0%	1	100.0%	1	100.0%	4	100.0%
ICU stay	23	62.2%	1	12.5%	4	80.0%	1	100.0%	1	50.0%	1	100.0%	0	0.0%	0	0.0%	3	75.0%
MV	15	40.5%	1	12.5%	3	60.0%	1	100.0%	0	0.0%	1	100.0%	0	0.0%	0	0.0%	2	50.0%
Trauma	2	5.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
IV drug abuse	0	0.0%	1	12.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other risk factors*	4	10.8%	2	25.0%	1	20.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Note: Three patients had a mixed infection of two *Candida* species: *Candida albicans* +Candida *glabrata*, *Candida albicans* +Candida *guilliermondii* and *Candida albicans* +Candida *krusei*

Abbreviations: BMI, body mass index; CCI, Carlson comorbidity index; Chr, chronic; CVC, central venous catheter; Hem./Onc., haematology/oncology; HIV/AIDS, human immunodeficiency virus infection / acquired immunodeficiency syndrome; ICU, intensive care unit; iv, intravenous; MV, mechanical ventilation.

**Candida albicans*: aortic aneurysm +aortal prothesis, Tenckhoff catheter, Ventriculo-peritoneal stunt, and vascular stent (n = 1, each). *Candida glabrata*: cardiac pacemaker and jejunal tube (n = 1, each). *Candida tropicalis*: aortic prothesis (n = 1).

TABLE 4 Antifungal therapy

Antifungal therapy, n (%)	
Amphotericin B	13 (22.8%)
Amphotericin B deoxycholate	12 (21.1%)
Liposomal Amphotericin B	1 (1.8%)
Triazoles	48 (84.2%)
Fluconazole	47 (82.5%)
Voriconazole	1 (1.8%)
Study medication	1 (1.8%)
Study medication (MK 0991 vs placebo or liposomal Amphotericin B vs Placebo – empiric treatment)	1 (1.8%)
Length of treatment in days, median (IQR)	16 (11-29)
Treatment sequence, n (%)	
Single monotherapy	41 (71.9%)
Single therapy sequential	7 (12.3%)
Single +combined therapy	2 (3.5%)
Combined therapy	1 (1.8%)
No antifungal therapy[a]	3 (5.3%)
Unknown	3 (5.3%)
Treatment strategies, n (%)	
Antifungal treatment	22 (38.6%)
Antifungal treatment + CVC removal	29 (50.9%)
CVC removal	1 (1.8%)
No treatment[b]	2 (3.5%)
Unknown	3 (5.3%)

[a]Two of them died.
[b]Due to death.

were dosed according to bodyweight. In five cases (12.5%), the fluconazole dose remained unknown. Dosage chosen for amphotericin B deoxycholate was 0.5-1 mg/kg bodyweight per day and 200 mg twice daily for voriconazole.

Monotherapy was applied to 48 case patients (84%) of which 7 (12.3%) received two antifungals sequentially. Combination antifungal therapy was used in three patients (5.3%). CVC removal combined with antifungal medication was a treatment strategy used in 29 patients (50.9%) whereas 22 patients (38.6%) kept their catheter and received antifungals. In three cases (5.3%), patients did not re- ceive any antifungal medication, two (3.5%) of them due to changed therapy goals to palliative care and death of the patient and one (1.8%) was treated with CVC removal only. In three cases (5.3%), no information regarding treatment could be retrieved due to incomplete data on archived files (Table 4).

3.6 | Guideline adherence

Diagnostic procedures were provided to more survivors than to non-survivors, in particular susceptibility testing (17.1% vs 4.5%, P =.404) and ophthalmoscopy (28.6% vs 0%, P =.005). 45.7% of survivors were treated for 14 days after first negative follow-up blood culture whereas only 13.6% of non-survivors were treated in the same manner (P =.003). CVCs were removed in 72.4% of survivors and 64.7% of non-survivors (P = n.s.), and follow-up blood cultures were performed in 82.8% and 63.6% of surviving and non-surviving patients (P =.003; Table 5).

3.7 | Mortality

During our study period, we observed an in-hospital mortality of 33.3% for candidemia cases (17/51) and 11.8% for control patients (6/51). Day 30 mortality rates for cases and controls were 23.5% (12/51) and 7.8% (4/51) respectively. The attributable mortality of candidemia therefore was 21.5%. Attributable Day 30 mortality was 15.7%. In case of a fluconazole-resistant *Candida* isolate causing the bloodstream infection, the overall mortality was 27.3% (3/11). Figures 1 and 2 provide Kaplan-Meier analysis of patients and controls (Figure 1) and survival according to *Candida* species (Figure 2).

4 | DISCUSSION

We performed a retrospective, single-centre, matched-pair study analysing the attributable mortality in patients with nosocomial candidemia from 1997 to 2001.

Our study observed a lower attributable mortality than studies previously performed in Iowa during the same period (21.5% vs 49%) and from 1983 to 1986 (38%).[2,3] Overall mortality in candidemia patients was significantly lower in our study (33% vs 61%) whereas mortality in control patients was similar (11.8% vs 12%).[2]

Our prior single-centre study showed higher case / control in-hospital-mortality rates in comparison with our more recent study (cases 33.3% vs 43%, controls 11.8% vs 17%; attributable mortality 21.5% vs 26%).[13] Furthermore, comorbidity rates and overall candidemia incidence were lower in our study (3.5/10 000 admissions vs 6/10 000 admissions).[13] Higher morbidity and mortality rates in more recent publications could be explained by the demographically changing society.[1] A retrospective analysis including all episodes of candidemia from 2004 to 2015 in Belgium observed a significant increase of the incidence of candidemia over the study period.[17]

A Swiss study, including all national university hospitals, described an incidence of 3.6 episodes per 10 000 hospital admissions in 2000, which is in accordance with the incidence of 3.5 per 10 000 admissions observed in our study.[5] Similar results have been published in French and Italian studies.[18,19] A Slovenian study including all candidemia cases between 2001 and 2012 in two hospitals described an incidence of 3.2 per 10 000 admissions.[20]

Comorbidity rates reported by Gudlaugsson et al were higher compared to our study (CCI median for cases and controls 3.3 and 3.4 vs 3.0 and 3.0) as was the incidence of candidemia (5.2/10 000

TABLE 5 Guideline adherence in surviving and non-surviving candidemia patients

Procedure	Survivors (n = 35)	Non-Survivors (n = 22)	*P*-value
Diagnostic			
Initial blood culture	100%	100%	1.000[a]
Species identification	100%	100%	1.000[a]
Susceptibility testing	17.1% (6/35)	4.5% (1/22)	.404[b]
Echocardiography	31.4% (11/35)	27.3% (6/22)	.738[a]
Ophthalmoscopy	28.6% (10/35)	0% (0/22)	.005[b]
Treatment			
Treatment for 14 days after fist negative follow-up	45.7% (16/35)	13.6% (3/22)	.020[b]
CVC removal			
All	96.6% (28/29)	82.4% (14/17)	.825[b]
<24 h from diagnosis	55.2% (16/29)	41.2% (7/17)	
>24 h and <72 h from diagnosis	17.2% (5/29)	23.5% (4/17)	
>72 h from diagnosis	24.1% (7/29)	17.6% (3/17)	
Patient died or unknown	3.4% (1/29)	17.6 (3/17)[c]	
Follow-up blood culture			
On at least one different day	11.4% (4/35)	13.6% (3/22)	.207[b]
Until proven negative	71.4% (25/35)	50% (11/22)	
No follow-up blood culture or unknown	17.1% (6/35)	36.4% (8/22)[d]	

Abbreviation: CVC, Central venous catheter.

[a]*Chi-square* test was performed.

[b]Fisher's exact test was performed.

[c]One of them died.

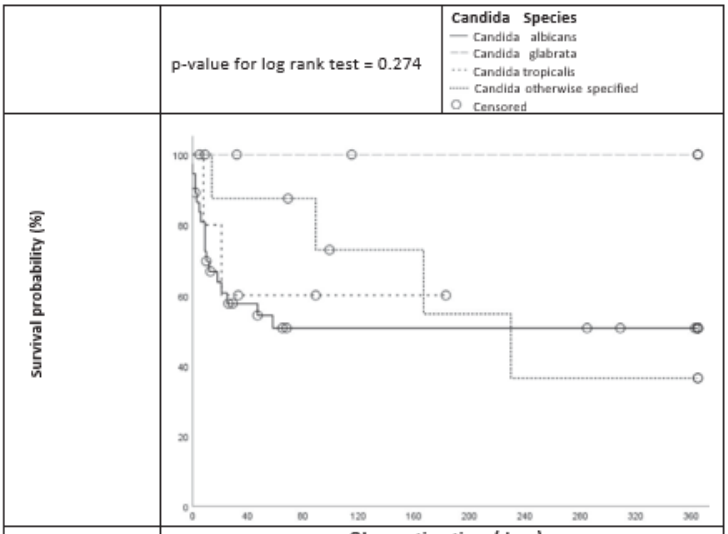
[d]Five of them died.

admissions vs 3.5/10 000 admissions).[2] This is in accordance with studies performed in Europe and the United States, which reported a higher incidence of candidemia in the United States compared to European countries. Between 2002 and 2004, the incidence of candidemia in the United States was between 4.6 and 7 per 10 000.[7,12]

Amphotericin B deoxycholate and fluconazole were the treatment of choice for candidemia between 1997 and 2001.[11] Our study shows a lower share of amphotericin B treatment with a rate of 22% vs 65% for amphotericin B monotherapy and 28% vs 40% for amphotericin B plus fluconazole compared to the studies performed by Gudlaugsson et al.[2]

Mortality rates observed in our study are similar to a multicentre, prospective, observational study of 427 consecutive patients with candidemia, performed in 1995 in the United States which observed a crude mortality of 34%.[21] A large study analysing patients with nosocomial BSI between 1995 and 2002 in the United States reported a crude mortality rate of candidemia of 39.2%.[7] A study analysing candidemia in five centres in Scotland and Wales in 2008 described an overall mortality of 40.4%.[22] Median age at the onset of candidemia was 55 years in our analysis. Case patients hospitalised in Iowa, US, during the same time period were in average 9 years younger with a median of 45.8 years. Median age of candidemia patients in our more recent study was 62 years.[2,13] We observed a similar species distribution as previously published by Gudlaugsson et al and Cornely et al (*C albicans* 65% vs 63% vs 57%, *C glabrata* 12% vs 17% vs 17%, *C tropicalis* 9% vs 9% vs 9%, *C parapsilosis* 2% vs 12% vs 9%).[2,13]

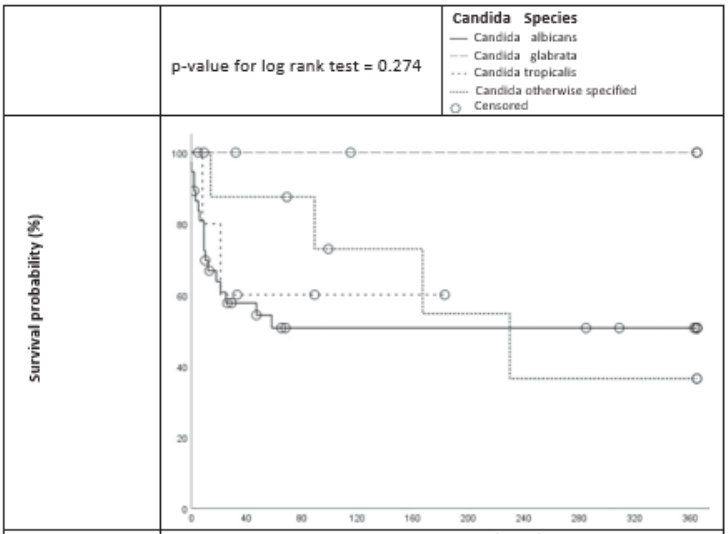
CVCs at least two days before Day 0 were present in 80% of cases (41/51) and only 33% of controls (17/51), illustrating the high impact of the presence of CVC on development and outcome of candidemia. A prospective multicentre case-control study including 118 cases and 236 controls pointed out that CVCs are one of the major risk factors for development of candidemia.[23] A study performed in 1995 in Texas, US, including 206 patients with candidemia, showed that removal of all intravascular lines was associated with a reduction in the subsequent mean duration of candidemia from 5.6 ± 0.8 to 2.6 ± 0.5 days (P <.001).[24] In our study, mortality rates of the patients with CVC removal within 72h vs >72h were 34% (11/32) vs 30% (3/10) respectively. CVCs were removed in 72% of survivors and 65% of non-survivors within 72h. Need of intensive care medicine is one of the major risk fac- tors for the development of candidemia. A retrospective study collecting data from 1256 ICUs in 76 countries in 2011 reported a candidemia incidence of 69/10 000 ICU patients.[25] A Belgian study observed a 10-fold higher incidence of candidemia in ICUs



Number of patients at risk										
Candida albicans	36	17	12	12	12	12	12	12	10	10
Candida glabrata	6	4	4	3	3	3	3	3	3	3
Candida tropicalis	4	2	2	1	1	0	0	0	0	0
Candida NOS[a]	7	7	6	4	4	3	2	2	2	2

[a] Not otherwise specified

FIGURE 1 Survival of patients with and without candidemia (Kaplan-Meier analysis for 365 days)



Number of patients at risk										
Candida albicans	36	17	12	12	12	12	12	12	10	10
Candida glabrata	6	4	4	3	3	3	3	3	3	3
Candida tropicalis	4	2	2	1	1	0	0	0	0	0
Candida NOS[a]	7	7	6	4	4	3	2	2	2	2

[a] Not otherwise specified

FIGURE 2 Survival of patients by Candida species (Kaplan-Meier analysis for 365 days)

compared to normal wards (7.22 vs 0.69 episodes per 10 000 patient days respectively) between 2004 and 2015.[17] In our study, more case than control patients were hospitalised on ICU at least two days before d0 (31.4% vs 13.7%) and were treated on ICU for a longer time period (median 23.5 days vs 15 days). 21.6% of cases and 11.8% of controls needed mechanical ventilation. The first clinical practice guideline was published by the IDSA in 2000, one year before the end of our observation period.[11] The lacking or not yet well-established guidelines might be the reason for a less consistent treatment management in our study. During the time of our observational period, susceptibility testing at the UHC had not yet been implemented as a standard of care; therefore, only 7 of 57 isolates were tested.

Our study is limited by several factors. These include the retrospective study design, selection bias and a small study population. Due to incomplete data sets and hindered legibility of microfilmed files, relevant information was incomplete or not available in eight cases: five of them had to be excluded from our study, and in three cases, we could not retrieve any informa- tion about antifungal treatment or management of central lines. However, these three patients were not excluded from our study. We tried to eliminate confounding effects by performing a precise matching process. Due to enhanced knowledge about risk factors, matching procedure was more accurate compared to Gudlaugsson et al: treatment on ICU became one of the main selection criteria. However, out of 57 case patients, only 51 could be matched to suitable control patient. Treatment on ICU at least two days before Day 0 was a risk factor present in 29.4% of cases but only 13.7% of controls. Still, to every case patient treated on ICU on Day 0, a control patient with admission on ICU within 14 dayswas matched. In eight cases, patients could not be matched by length of time at risk until Day 0. In these cases, time of risk wasshorter for control patients.

Our study showed that crude and attributable mortality rates of candidemia at the UHC before the introduction of echinocandins were slightly lower than after their introduction. Thus, despite a higher efficiency of available antifungals, the attributable mortality did not decrease. Due to a higher morbidity of patients in a demographically changing society, the incidence of candidemia increased over the last decade. In our study, we observed a significantly lower attributable mortality compared to the study performed in Iowa, US, in the same time period. This might be driven by a lower comorbidity rate in case patients and a lower incidence of candidemia in our study. Furthermore, the preferential usage of amphotericin B over triazoles in the study population of Gudlaugsson et al might be a contributing factor. In several studies, amphotericin B deoxycholate is shown to be as effective but more toxic than fluconazole,[26-28] although these studies could not identify a difference in survival. The combination of ampho- tericin B with fluconazole is as effective as fluconazole alone but more toxic.[29]

An improved disease management, including aspects recommended by the IDSA Guideline from 2000 like follow-up blood cultures, treatment for 14 days after first negative follow-up blood culture and removal of CVCs,[11] might also improve morbidity rates. Improved diagnostic and prophylactic procedures as well as a better disease management by adherence to current guidelines contribute to a better outcome of candidemia.

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AUTHOR CONTRIBUTIONS

Yael Blankenheim: Data curation (lead); Formal analysis (lead); Investigation (lead); Writing – original draft (lead); Writing – review & editing (lead). **Jon Salmanton-García:** Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (supporting); Writing – review & editing (supporting). **Harald Seifert:** Investigation (supporting); Writing – original draft (supporting); Writing – review & editing (supporting). **Oliver A. Cornely:** Conceptualization (lead); Formal analysis (supporting); Methodology (lead); Writing – original draft (equal); Writing – review & editing (equal). **Philipp Koehler:** Conceptualization (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Writing – original draft (lead); Writing – review & editing (lead).

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted in the author's guideline page, have been adhered to.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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5. Discussion

We performed a single-center, retrospective, matched case-control study analyzing the attributable mortality of patients with nosocomial candidemia from 1997 to 2001.

We observed an overall candidemia incidence rate of 3.5 per 10,000 admissions at the University Hospital of Cologne. This is lower compared to the recent study by Cornely et al., which described an incidence of 6 per 10,000 admissions [11]. The results obtained by the presented study are comparable to a French study performed in 2002, which described an incidence of 3.8 episodes per 10,000 hospital admissions [8]. A Swiss study, which included all national university hospitals, reported an incidence of 3.6 per 10,000 hospital admissions in 2000. [4]. Similar results have been published in an Italian study in 2002, describing an incidence of 3.8 per 10,000 admissions [9]. The incidence of candidemia in our study was lower compared to the incidence reported by Gudlaugsson et al. (3.5/10,000 admissions versus 5.2/10,000 admissions) [15]. Studies performed in Europe and the US likewise described a lower incidence of candidemia in European countries compared to the US. An incidence of 4.6 – 7 per 10,000 admissions was presented by Studies performed between 2002 and 2004 in the US [12, 13].

The attributable mortality of candidemia in our study was lower than in studies performed in Iowa analyzing the same time period (21.5% vs 49%) and the time from 1983 to 1986 (38%) [15, 16]. The overall mortality of candidemia patients was significantly lower (33% vs 61%) whereas the mortality of control patients in our study was similar (11.8% vs 12%) [15].

This might be explained by a higher incidence rate of candidemia as well as the higher comorbidity rates of case patients observed in the study performed in Iowa at the same time period compared to our study.

In-hospital mortality rates for cases and controls reported in the current study are lower than in the single-center study previously published at the UHC. Mortality rates were 33.3% vs 43% for cases and 11.8% vs 17% for controls. The attributable mortality of candidemia therefore was 21.5% vs 26% [11].

Between 1995 and 2002, a large study performed in the US analyzed the crude mortality rate of patients with candidemia. They described a crude mortality rate of 39.2% [13]. A prospective, observational, multicenter study including 427 cases of candidemia in the US in 1995 reported a crude mortality of 34%, which is similar to this study [48].

In our study, the median age at the onset of candidemia was 55 years. Compared to the study performed in Iowa, which described a median of 45.8 years, patients in our study were on average 9 years older. In the more recent study from Cologne, the median age at the onset of Candidemia was 62 years, which is 7 years older than between 1997 and 2001 [11, 15]. The older age of patients in the more recent study could be explained by the higher life expectancy and the later onset of disease in a demographically changing society. A study performed in

Germany between 2002 and 2018 showed an increase in life expectancy: at the age of 50, healthy life expectancy increased by 1.92 and 2.53 years respectively for women and men during the study period [49].

Gudlaugsson et al describe higher comorbidity rates compared to our study. Especially pulmonary, cardiovascular, and endocrine diseases were diagnosed more often. Rates for cases and controls were 19% and 23% vs 2% and 4% for COPD, 12% and 15% vs 4% and 2% for congestive heart failure and 23% and 19% vs 14% and 6% for diabetes, respectively [15]. In the more recent study performed by Cornely et al, rates for internal diseases were higher than in our study (pulmonary diseases: 25% and 16% vs 4% and 6%, renal diseases: 35% and 32% vs 6% and 2%, diabetes mellitus: 25% and 22% vs 14% and 6%) [11]. Higher morbidity and mortality rates in more recent publications could be explained by the demographically changing society [14]. The presence of CVCs is one of the major risk factors for the development of candidemia. This was shown by a prospective multicenter case-control study including 118 cases and 236 controls [50]. In our study, the high impact of the presence of CVCs on the development of candidemia was observed: CVCs at least two days before day 0 were present in 80% of cases (41/51) and only 33% of controls (17/51). Furthermore, a study performed in 1995 in Texas, US, including 206 patients with candidemia, showed that removal of all intravascular lines was associated with a reduction in the subsequent mean duration of candidemia from 5.6 ± 0.8 days to 2.6 ± 0.5 days [51]. Another prospective multicenter observational study performed in 1995, including 427 consecutive patients with candidemia showed a significantly higher mortality in patients in whom CVCs were not removed (41% vs 21%) [48]. However, this correlation could not be observed in our study.

The mortality rate observed in our study was 34% (11/32) for patients with CVC removal within 72h, whereas for patients with CVC removal after 72h the mortality rate was 30% (3/10). CVCs were removed in 72% of survivors and 65% of non-survivors within 72h. Another major risk factor for the development of candidemia is the need for critical care treatment. In our study, 31.4% of case patients but only 13.7% of control patients were hospitalized in ICU at least two days before d0 and were treated in ICU for a longer time period (median 23.5 days vs 15 days). A total of 21.6% of cases and 11.8% of controls needed mechanical ventilation. A study performed in 2011 collected data from 1,256 ICUs in 76 countries. They described an incidence of 69/10,000 ICU patients [52]. A prospective multicenter point prevalence study including 1,265 ICUs from 75 countries in 2009, showed that the infection rate for candidemia increased from 32% to 70% for patients whose pre-study ICU stay was 1 day vs >7 days [53].

Patients included in the more recently performed study were treated more frequently in ICU than in our study (70% of cases and 64% of controls vs 31% of cases and 14% of controls) [11].

The species distribution described in our study was similar to our more recent study and the study performed at the same time period in Iowa (*Candida albicans* 65% vs 57% vs 63%, *Candia glabrata* 12% vs 17% vs 17%, *Candida tropicalis* 9% vs 9% vs 9%, *Candida parapsilosis* 2% vs 9% vs 12%) [11, 15]. In the timespan between our study and the more recently performed study, we observed a shift towards the non-*albicans* species: the incidence of *Candida albicans* has decreased from 65% to 57% whereas the incidence of the non-*albicans* species has increased (*Candida glabrata* from 12% to 17%, *Candida parapsilosis* from 2% to 9%). During the time of our observational period, susceptibility testing at the UHC had not yet been implemented as a standard of care. At the time of hospitalization, only 7 of 57 (12.2%) isolates were tested. In the more recently performed study, susceptibility results were performed for every isolate (100%) [11].

According to the initial guidelines published by the IDSA in 2000, Amphotericin B deoxycholate and fluconazole were the treatment of choice for candidemia between 1997 and 2001 [18]. In stable patients, fluconazole was the treatment of choice whereas in critically ill patients, amphotericin B was preferred. In the study performed by Gudlaugsson et al, amphotericin B was administered more frequently than in our study with a rate of 65% vs 22% for amphotericin B single and 40% vs 28% for amphotericin B in combination with fluconazole.

In our study, 71% of candidemia patients were treated with single therapy. Switching to another or combination therapy was observed in 17.6% of cases. In the more recently performed study by Cornely et al., switching to another or combination therapy was performed in 54% whereas single therapy was administered to only 45% of candidemia patients [11].

Today, echinocandins are the treatment of choice, recommended by current clinical practice guidelines [37, 54]. Studies have shown their higher efficiency over triazoles [55, 56]. Still, attributable mortality in our hospital did not decrease after echinocandins became the gold standard of antifungal therapy [11].

Candidemia management, including the performance of ophthalmoscopy and echocardiography, treatment for 14 days after the first negative follow-up blood culture, removal of indwelling central catheters and follow-up blood cultures, were performed more consistently in the study of Cornely and colleges than in our study. Especially ophthalmoscopy and treatment for 14 days after the first negative blood culture was performed more often (ophthalmoscopy for survivors and non-survivors in the study of Cornely et al. versus our study: 46% and 44% vs 28% and 0%, treatment for 14 days: 47% and 37% vs 37% and 14%) [11].

The first clinical practice guidelines were published by the IDSA in 2000, one year before the end of our observation period. The lack of or not yet well-established guidelines might be the reason for a less consistent treatment management in our study. [18]

Our study has certain limitations. These include a heterogeneous patient population, selection bias, a small study population and a retrospective study design. We performed a precise

matching process and hereby tried to eliminate confounding effects. Due to enhanced knowledge about risk factors, the matching process was adjusted and therefore more accurate compared to Gudlaugsson et al.: treatment in ICU became one of the main selection criteria. However, this reduced the chances of finding a suitable matching partner: out of 57 case patients, only 51 could be matched to a suitable control patient. Furthermore, not to every case patient with treatment in ICU at least two days before day 0, a suitable control patient with treatment in ICU at least two days before day 0 could be matched. This risk factor was present in 29.4% of cases but only in 13.7% of controls. Still, in those cases, a control patient with admission to ICU within 14 days was matched. In eight cases, patients could not be matched by length of time at risk until day 0. In these cases, the time of risk was shorter for control patients. Some microfilmed files were defective or incomplete. Therefore, five case patients had to be excluded from our study. In three cases, information about antifungal treatment or management of central lines was not available. However, these cases were not excluded from our study.

5.1 Conclusions

The relevance of candidemia has increased over the last decades. Cornely et al. observed higher incidence rates of candidemia. and higher comorbidity rates compared to our study. This could be explained by the higher morbidity of patients in an aging society. In analogy to an increasing incidence of candidemia, the attributable mortality of candidemia slightly increased over the last ten years. Our study showed that before the introduction of echinocandins, the crude and attributable mortality rates of candidemia at the UHC were slightly lower than after their introduction. Thus, despite the echinocandins may have higher efficiency, the attributable mortality did not decrease after their introduction.

Compared to the study performed in Iowa, US, during the same time, we observed lower comorbidity rates and a lower incidence of candidemia in case patients. In accordance with this, the attributable mortality of candidemia was significantly lower in our study. Furthermore, the higher usage of amphotericin B over triazoles in the study population analyzed in Iowa, US, might have an influencing factor. Studies have shown that amphotericin B is more toxic than fluconazole whereas their efficiency is equal [20, 57, 58]. The combination of amphotericin B with fluconazole is as effective as fluconazole alone but more toxic [59]. However, an influence on the mortality of patients was not described in these studies. A difference in the treatment management of candidemia, including the recommendations of the Guideline from 2000, might also have an impact on morbidity rates. Since these data were not collected by Gudlaugsson et al., a comparison regarding this factor is not possible.

Although the mortality rate in our study was lower than in the studies by Gudlaugsson et al. and Cornely et al., candidemia was still associated with a high attributable mortality and its

relevance is undisputed. Increasing the popularity of current guidelines among treating physicians and strict adherence to their recommendations could have a positive impact on the mortality and outcome of candidemia.

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7. Preliminary Publications

7.1 Poster presentation

Poster Presentation at Trends in Medical Mycology (TIMM) Congress, 8th – 10th October 2021:

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Attributable mortality of candidemia at a German tertiary hospital from 1997 to 2001 before the introduction of echinocandins

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Introduction

The relevance of candidemia has increased over the last decades due to higher incidence rates in an aging society. It often results in a prolonged hospital stay and high morbidity and mortality. Studies performed in the United States (US) reported that Candida species are among the four most common pathogens causing nosocomial bloodstream infections. Well-established risk factors for candidemia are antibiotic treatment, parenteral nutrition, hemodialysis, presence of central venous catheter (CVC) and abdominal surgery. Immunocompromised patients and patients on intensive care unit (ICU) are at high risk for candidemia. Studies on amphotericin B and fluconazole have shown high attributable mortality rates of 38% and 49% in the US. Incidence rates and locational factors might have an impact on the mortality rates at the University Hospital of Cologne (UHC), Germany.

Methods

We performed a matched case-control study including 57 patients with candidemia, hospitalized at the UHC between 1st of July 1997 and 30th of June 2001. Controls were matched by age, sex, admission date, treatment on ICU, number of days at risk, underlying diseases, surgical procedures, and the Charlson Comorbidity Index (CCI). For both cases and control patients we captured epidemiologic and demographic characteristics, data of the underlying disease, secondary diagnosis, CCI, and risk factors for candidemia such as malignancy, diabetes, liver cirrhosis, chronic cardiovascular disease, chronic lung disease, treatment on ICU, mayor surgery, mechanical ventilation, and presence of CVCs. We calculated day 30 and in-hospital-mortality and defined mortality attributable to candidemia as the difference between the in-hospital-mortality of cases and controls. For candidemia cases, we captured Candida species distribution, microbiological findings, susceptibility testing, outcome by species and treatment strategies. Furthermore, adherence to guidelines of the Infectious Diseases Society of America published in 2000 was analyzed considering diagnostic procedures (initial blood culture, species identification, susceptibility testing, echocardiography and ophthalmoscopy), treatment strategies (treatment for 14 days after first negative follow up blood culture, removal of CVCs) and follow up blood cultures.

	Candidemia (n=51)	Control (n=51)	p-value
Demography			
Sex (Female), n (%)	22 (43%)	22 (43%)	1.000[a]
Age in years, median (IQR)	55 (42-61)	55 (44-64)	0.763[b]
CCI, median (IQR)	3 (2-5)	3 (2-5)	0.777[b]
Risk factors, n (%)			
Haematological disease	24 (47%)	28 (54%)	0.428[c]
HIV/AIDS	3 (6%)	3 (6%)	1.000[c]
Major surgery	17 (33%)	17 (33%)	1.000[c]
Alcoholism	4 (8%)	3 (6%)	1.000[c]
Chronic cardiovascular disease	20 (39%)	13 (25%)	0.138[c]
Chronic liver disease	11 (22%)	0 (0%)	<0.001[c]
Chronic pulmonary disease	2 (4%)	3 (6%)	1.000[c]
Chronic renal disease	3 (6%)	1 (2%)	0.617[c]
Diabetes mellitus	7 (14%)	3 (6%)	0.318[c]
Rheumatic/Autoimmune disease	3 (6%)	4 (8%)	1.000[c]
Obesity, BMI >30 kg/m²	3 (6%)	1 (2%)	0.617[c]
Underweight, BMI <18.5 kg/m²	6 (12%)	4 (8%)	0.741[c]
CVC[d]	41 (80%)	17 (33%)	<0.001[a]
ICU[d]	16 31%)	7 (14%)	0.033[a]
Mechanical ventilation	11 (22%)	6 (12%)	0.184[a]
Other risk factors[e]	7 (14%)	1 (2%)	0.060[c]
No risk factors	0 (0%)	2 (4%)	0.495[c]

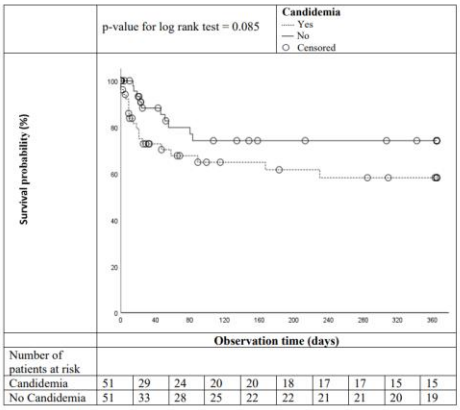
Table 1. Baseline characteristics of candidemia and control cases

n=number. %=percent, BMI, body mass index; CCI, Carlson comorbidity index; CVC, central venous catheter; HIV/AIDS, human immunodeficiency virus infection / acquired immunodeficiency syndrome; ICU, intensive care unit; IQR, interquartile range.
[a] calculated using χ^2 test. [b] calculated using Mann-Whitney U test.
[c] calculated using Fisher's exact test. [d] at least 2 days before d0.
[e] e.g. prosthetic valve / foreign body

Procedure	Survivors (n= 35)	Non-Survivors (n=22)	p value
Diagnostic			
Initial blood culture	100%	100%	1.000[a]
Species identification	100%	100%	1.000[a]
Susceptibility testing	17.1% (6/35)	4.5% (1/22)	0.404[b]
Echocardiography	31.4% (11/35)	27.3% (6/22)	0.738[a]
Ophthalmoscopy	28.6% (10/35)	0% (0/22)	0.005[b]
Treatment			
Treatment for 14 days after fist negative follow up	45.7% (16/35)	13.6% (3/22)	0.020[b]
CVC removal			
All	96.6% (28/29)	82.4% (14/17)	
<24 h from diagnosis	55.2% (16/29)	41.2% (7/17)	
>24 h and <72 h from diagnosis	17.2% (5/29)	23.5% (4/17)	0.825[b]
>72 h from diagnosis	24.1% (7/29)	17.6% (3/17)	
Patient died or unknown	3.4% (1/29)	17.6 (3/17)[c]	
Follow up blood culture			
On at least one different day	11.4% (4/35)	13.6% (3/22)	
Until proven negative	71.4% (25/35)	50% (11/22)	0.207[b]
No follow up blood culture or unknown	17.1% (6/35)	36.4% (8/22)[d]	

Table 2. Guideline adherence in surviving and non-surviving candidemia patients

n=number. %=percent. CVC, Central venous catheter. [a] χ^2 test was performed.
[b] Fisher's exact test was performed. [c] one of them died. [d] five of them died



Number of patients at risk										
Candidemia	51	29	24	20	20	18	17	17	15	15
No Candidemia	51	33	28	25	22	22	21	21	20	19

Figure 1. Survival of patients with and without candidemia (Kaplan-Meier analysis for 365 days)

Results

The incidence of candidemia was 3.5 per 10,000 admissions. For cases and controls, we observed in-hospital-mortality rates of 33.3% and 11.8%, and a 30-day mortality of 23.5% and 7.8%, respectively. The attributable mortality rate to candidemia was 21.5%, and at 30-days it was 15.7%. Established risk factors for candidemia were more frequently observed in cases than in controls, especially chronic liver disease (21.6% vs 0%, p<0.001), chronic cardiovascular disease (39.2% vs. 25.5%, p=0.138) and diabetes mellitus (13.7% vs 5.9%, p=0.318). Treatment on ICU at least 2 days before d0 and mechanical ventilation (MV) was observed more often in cases than in controls (ICU: 31.4% vs. 13.7%, p=0.033; MV: 21.6% vs. 11.8%, p=0.184). CVCs present at least two days before d0 were observed in 80% of cases and 33% of controls (p<0.001) (Table 1). Antifungal therapy was administered to 51 of 57 patients (89%) for a median of 16 days (IQR 11-29). Fluconazole was the most frequently used drug (47/57 patients, 82.5%), followed by Amphotericin B deoxycholate (13/57 patients, 22.8%). Diagnostic procedures were provided to more survivors than to non-survivors, in particular susceptibility testing (17.1% vs. 4.5%, p=0.404) and ophthalmoscopy (28.6% vs 0%, p=0.005). 37.1% of survivors were treated for 14 days after first negative follow-up blood culture whereas only 13.6% of non-survivors were treated in the same manner (p=0.003). CVCs were removed in 72.4% of survivors and 64.7% of non-survivors (p=n.s.) and follow-up blood cultures were performed in 82.8% and 63.6% of surviving and non-surviving patients (p=0.003) (Table 2).

Conclusion

Our study showed that crude and attributable mortality rates of candidemia at the UHC between 1st of July 1997 and 30th of June 2001 before the introduction of echinocandins were slightly lower than after their introduction in 2020. Thus, despite a higher efficiency of available antifungals, the attributable mortality did not decrease. Due to a higher morbidity of patients in a demographically changing society, the incidence of candidemia increased over the last decade. In our study we observed a significantly lower attributable mortality compared to the study performed in Iowa, US, in the same time period. This might be driven by a lower comorbidity rate in case patients and a lower incidence of candidemia in our study. Improved diagnostic and prophylactic procedures as well as a better disease management by adherence to current guidelines contribute to a better outcome of candidemia.

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