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Attributable mortality of candidemia – Results from the ECMM *Candida* III multinational European Observational Cohort Study

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SUMMARY

Introduction: Despite antifungal advancements, candidaemia still has a high mortality rate of up to 40%. The ECMM *Candida* III study in Europe investigated the changing epidemiology and outcomes of candidaemia for better understanding and management of these infections.
Methods: In this observational cohort study, participating hospitals enrolled the first ten consecutive adults with blood culture-proven candidemia. Collected data included patient demographics, risk factors, hospital stay duration (follow-up of 90 days), diagnostic procedures, causative *Candida* spp., management details, and outcome. Controls were included in a 1:1 fashion from the same hospitals. The matching process ensured similarity in age (10-year range), primary underlying disease, hospitalization in intensive care versus non-ICU ward, and major surgery within 2 weeks before candidemia between cases and controls. Overall and attributable mortality were described, and a survival probability for cases and controls was performed.
Results: One hundred seventy-one pairs consisting of patients with candidemia and matched controls from 28 institutions were included. In those with candidemia, overall mortality was 40.4%. Attributable mortality was 18.1% overall but differed between causative *Candida* species (7.7% for *Candida albicans*, 23.7% for *Candida glabrata/Nakaseomyces glabratus*, 7.7% for *Candida parapsilosis* and 63.6% for *Candida tropicalis*). Regarding risk factors, the presence of a central venous catheter, total parenteral nutrition and acute or chronic renal disease were significantly more common in cases versus controls. Duration of hospitalization, and especially that of ICU stay, was significantly longer in candidemia cases (20 (IQR 10–33) vs 15 days (IQR 7–28); p = 0.004).
Conclusions: Although overall and attributable mortality in this subgroup analysis of matched case/control pairs remains high, the attributable mortality appears to have decreased in comparison to historical cohorts. This decrease may be driven by improved prognosis of *Candida albicans* and *Candida parapsilosis* candidemia; whereas candidemia due to other *Candida* spp. exhibits a much higher attributable mortality.
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Introduction

Candida species remain important pathogens causing blood stream infections, prolonged hospital stays and increased health care costs.[1] Despite development of several antifungal compounds within the last decades, mortality still remains high – merely unchanged with up to 40% for critically ill patients treated on intensive care units (ICU).[2]

Candida species epidemiology seems to have changed over the last decades with a higher rate of clinically relevant non-*albicans* *Candida* species with reduced susceptibility or even resistance to fluconazole and partially also to echinocandins.[3,4] Globally, *Candida auris* has emerged as a new multi-resistant species with a propensity for outbreaks, especially in ICUs.[5]

A historical landmark study reporting attributable mortality for candidemia performed in the 1980s reported an attributable mortality of 38%.[6] A subsequent study at the same hospital even resulted in an increased attributable mortality rate of 49%.[7] Retrospectively analyzed data from a German tertiary care hospital between 1997 and 2001 observed 21.5%. [8] Recent data from the same institution showed an increase to 27%.[9]

With the aim of improving the knowledge regarding candidemia in Europe, the European Confederation of Medical Mycology (ECMM)

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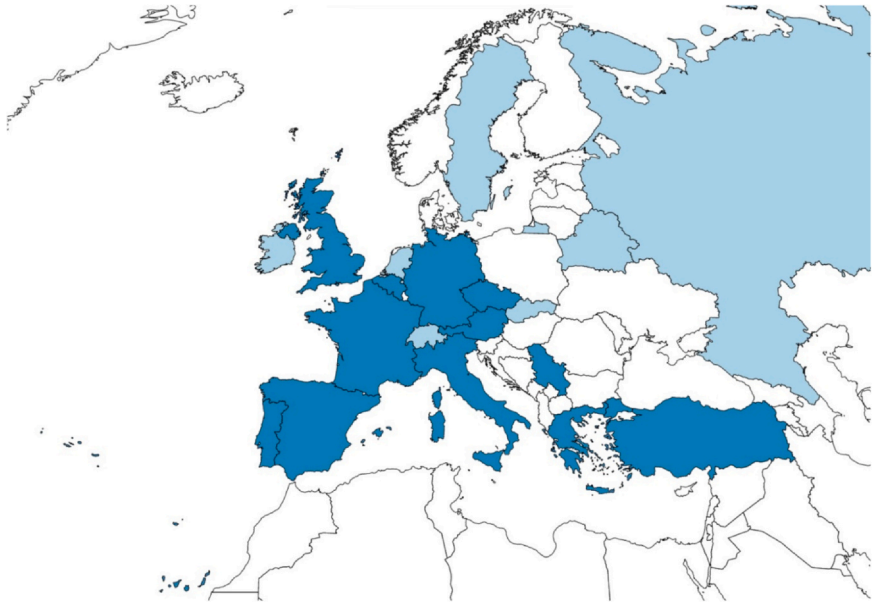


Fig. 1. Participating European countries. Dark blue represents countries that are part of both the ECMM *Candida* III study and the case-control analysis: the analysis included documented cases and controls from the following countries: United Kingdom (n = 37 case-control pairs), Turkey (n = 34 case-control pairs), Germany (n = 29 case-control pairs), Serbia (n = 13 case-control pairs), Czech Republic (n = 10, case-control pairs), Austria, Italy and Portugal (n = 8 case-control pairs each), Belgium, France, and Greece (n = 7, case-control pairs each), and Spain (n = 3 case-control pairs). Light blue represents countries involved in the ECMM *Candida* III study but not in the case-control analysis: Belarus, Ireland, Netherlands, Russia, Slovakia, Sweden, and Switzerland.

designed and conducted the ECMM *Candida* III study after prior ECMM surveillance studies from 1997 to 1999[10] and from 2006 to 2008.[11] The objectives were to study epidemiology, adherence to guideline recommendations and associated outcome of candidemia across Europe.[12–14] To increase knowledge about risk factors and attributable mortality, the ECMM *Candida* III study, in contrast to prior ECMM surveillance studies,[10,11] also included a matched control group.

The objective of this subgroup analysis was to assess attributable mortality of candidemia overall and in *albicans* and non-*albicans* candidemia specifically.

Methods

In this European multicentre observational case-control study, participating tertiary care hospitals enrolled the first ten consecutive adults (≥ 18 years old) with blood culture-proven candidemia after July 1, 2018, until the end of June 2019 according to ESCMID criteria, and matched to controls without candidemia.[15] This inclusion strategy of the parent study was chosen to accurately depict candidemia epidemiology across Europe and to avoid overrepresentation of specific regions or hospitals as well as selection or observer bias. Previously published reports from ECMM *Candida* III, network described elsewhere,[16] have focused on the full cohort of candidemia cases (n = 634), and specifically the impact of adherence to clinical guideline recommendations, via EQUAL *Candida* Score card use,[12] analysis and susceptibility testing of isolates that were centrally collected,[14] and impact of antifungal therapy on duration of hospitalization.[13] While previous analyses have focused exclusively on the cases with candidemia, this is the first analysis reporting results of cases with candidemia compared to the matched controls enrolled in the same study. Ethical standards were adhered to, with ethical approval obtained at the University of Cologne (Cologne, Germany; EK 17–485) for the ECMM *Candida* Registry (Fungiscope *Candida*) for retrospective data entry and analysis. Each hospital obtained local institutional review board confirmation or approval as appropriate based on local regulations. To ensure a comprehensive representation of candidemia epidemiology, eligible hospitals per country were determined based on population size, as described before.[12–14]

Cases of candidemia and controls were all diagnosed/hospitalized within the observation period, i.e., between July 1, 2018, and June 31, 2019. Data collection was performed between July 1, 2018, and March 31, 2022, with participating centers entering data into the ECMM *Candida* Registry[16] (Fungiscope *Candida*; NCT01731353) via an online platform provided by EFS Fall 2022 (TIVIAN, Cologne, Germany). Collected data included anonymized patient demographics, risk factors (which were predominantly derived from clinical assessments conducted by the respective participants), hospital stay duration (maximum follow-up of 90 days), diagnostic procedures, causative *Candida* spp., management details, and clinical outcomes.

In cases, the day of diagnosis, or day 0, was defined as the day when the first positive blood culture for *Candida* species was communicated to the attending physician, prompting the initiation of systemic treatment if not already commenced. For cases with a fatal outcome before the positive blood culture result became available, the day of culture positivity was defined as the day of diagnosis. In controls, day 0 was defined as a day between the admission of the control patient and the day the case patient had a positive blood culture for *Candida* spp. Additionally, the respective ECMM Quality of Clinical Candidaemia Management (EQUAL *Candida*) was determined. EQUAL is a scoring system that aggregates and weights the recommendations according to their strength derived from current guidelines and is used to quantify guideline adherence in patients with fungal infections.[17] Pathogens have been named following international consensus recommendations.[18]

We determined the following matching criteria as essential: age within a 10-year range, ICU stay with and without mechanical ventilation versus in-hospital stay in a non-ICU ward at day 0, primary underlying disease, and major surgical procedures within 2 weeks before day 0; all case-control pairs that did not match for those factors were excluded. By meticulously matching cases and controls based on these criteria, the study aimed to minimize potential confounding factors and provide valuable insights into the association between guideline adherence, defined as healthcare providers' compliance with established clinical recommendations

and their strength to ensure patients receive optimal care based on current evidence, and outcomes in candidemia cases across Europe (Fig. 1). Categorical variables were presented as frequency and percentages; continuous variables were described using summary statistics such as medians, interquartile ranges, and ranges. Variables were compared between cases and their respective controls with the McNemar test or the Wilcoxon signed-rank test, respectively. We performed sensitivity analyses in order to determine whether factors not included in the matching criteria could play a role in patient mortality. We utilized a univariable Cox regression model, where variables that had significantly different proportions in the observations were included. Variables with a p-value ≤0.1 in the univariable analysis were selected for multivariable analysis following validation of their clinical significance. The multivariable Cox regression model was developed using the Wald backward method, employing backward elimination with the Wald test for variable selection. We established exclusion criteria a priori, based on a predetermined statistical significance threshold (p-value ≤ 0.05), to retain variables significantly contributing to the model. The study assessed survival probability rates between cases with candidemia and matched controls using the log-rank test visually depicted through Kaplan-Meier plots, illustrating the probability of survival over time for each group. We defined the attributable mortality as excess mortality due to candidemia, which was calculated by [crude mortality of candidemia cases] minus [crude mortality of matched controls]. We assessed the risk ratio for death by dividing the crude mortality rate for the cases by that for the controls for the overall study population and for matched pairs with cases due to *Candida albicans*, *Candida glabrata/Nakaseomyces glabratus*, *Candida parapsilosis*, and *Candida tropicalis*, other *Candida* spp., and multiple *Candida* spp. separately. Throughout this process, endeavors were undertaken to minimize the occurrence of data missing entirely at random by reaching out to contributors to address any outstanding queries. This validation procedure played a pivotal role in upholding the dependability and authenticity of the collected data. In instances where the time variable had missing data among valid cases, those patients were also excluded from the analysis, as in previous analysis within ECMM *Candida* III.[12] However, sensitivity analyses were conducted for this variable using the following series mean method. If outcome on mortality analysis days was unknown, patient was set as dead. Statistical significance in performed comparisons was set at $p < 0.05$. The statistical analysis was performed using SPSS v27 (SPSS, IBM Corp, Chicago, IL, United States).

Results

A total of 171 pairs of patients with candidemia and matched controls were included into the analysis (Fig. 2). Baseline patient characteristics are presented in Table 1, and causative *Candida* spp. and treatment characteristics in patients with candidemia are displayed in Table 2 and Supplementary table 1.

Case-control analysis

Cancer was reported in 43.9% (95% CI 34.5–55.0%) of cases as an underlying condition at the time of diagnosis, and 40.4% (95% CI 31.4–51.1%) required ICU treatment (Table 1). Non-candidemia controls had overall similar underlying conditions, with differences regarding acute or chronic renal disease, which was more common among candidemia cases (n = 45, 26.3%, 95% CI 19.2–35.2%) than non-candidemia controls (n = 30, 17.5%, 95% CI 11.8–25.0%, p = 0.02). Furthermore, the use of total parenteral nutrition (TPN) was more prevalent in candidemia cases (n = 47, 27.5%, 95% CI 20.2–36.6%) than non-candidemia controls (n = 27, 15.8%, 95% CI 10.4–23.0%), p < 0.001 (Table 1). Candidemia cases experienced an extended median hospital stay of 20 days (IQR 10–33) after diagnosis, which was significantly longer compared to non-candidemia controls with a median stay of 15 days (IQR 7–28; p = 0.004) after day 0 (matched for duration of hospitalization at the time of diagnosis in candidemia cases). Regarding duration of ICU stay after diagnosis, candidemia cases stayed for a median of 13 days (IQR 6–27) and non-candidemia controls for 10 days (IQR 5–21; p < 0.001) (Table 1).

A significant disparity in the overall mortality rate was evident between the two groups. Overall, candidemia cases had a notably higher mortality rate of 40.4% (n = 69/171 patients, 95% CI 31.4–51.1%) compared to a lower mortality rate of 22.2% (n = 38/171 patients, 95% CI 15.7–30.5%) in non-candidemia controls, p < 0.001. This results in an attributable mortality of 18.2%. Overall survival probability was significantly higher (p < 0.001) in non-candidemia controls as compared to candidemia cases (Table 1, Fig. 3).

In sensitivity analyses aimed at assessing the mortality impact of risk factors that significantly differed between candidemia cases and their respective controls, it was observed that higher mortality was associated with infection by specific *Candida* species, notably *Candida glabrata/Nakaseomyces glabratus*, *Candida parapsilosis*, and *Candida tropicalis*. Conversely, low albumin levels and total parenteral nutrition did not demonstrate an impact on mortality in their respective multivariable Cox regression models, whereas the Charlson comorbidity index did (Table 2).

Attributable mortality depending on causative Candida spp

With regard to identified *Candida* species distribution, *Candida albicans* was most prevalent in 78 cases (45.6%, 95% CI 36.1–56.9%), followed by *Candida glabrata/Nakaseomyces glabratus* with 38 cases (22.2%, 95% CI 15.7–30.5%), *Candida parapsilosis* with 26 cases (15.2%, 95% CI 10.0–22.3%), and *Candida tropicalis* with 11 cases (6.4%, 95% CI 3.2–11.5%). *Candida auris* was observed in a single case, who died. The highest species-dependent attributable mortality was observed for *Candida tropicalis* with 63.6%, followed by *Candida glabrata/Nakaseomyces glabratus* with 23.7%. *Candida parapsilosis* and *Candida albicans* with 7.7% each, respectively (Table 3). Species dependent survival probability is displayed by Kaplan Meier curves in Fig. 3.

Analysis of treatment strategies and characteristics of survivors vs.non-survivor of candidemia

An analysis of treatment strategies indicated that 16 (9.4%, 95% CI 5.3–15.2%) cases did not receive antifungal treatment, primarily consisting of patients deceased at the time of diagnosis (n = 10/16, 62.5%). The predominant treatment strategy was antifungal therapy and CVC removal in 85 cases (49.7%, 95% CI 39.7–61.5%). Seventy cases (40.9%, 95% CI 31.9–51.7%) received antifungal therapy alone. In terms of antifungal administration, echinocandins (118 cases, 69.0%, 95% CI 57.1–82.6%) or fluconazole (78 cases, 45.6%, 95% CI 36.1–56.9%) were the most frequently used. (Table 3). Evaluation of the EQUAL Score revealed notable differences between survivors and non-survivors also for the reported subset of cases. The proportion of achieved EQUAL Score points relative to achievable points was higher among surviving patients, with 79% (IQR 59%–89%) achievable points, compared to non-survivors, with 73% (IQR 59%–82%) achievable points; however, this difference was not statistically significant, p = 0.067 (Supplementary table 1).

Discussion

We report results of a subgroup analysis from a pan-European multicentre, observational study of candidemia,[12–14] investigating the attributable mortality and risk factors of candidemia in a matched case-control design. This analysis of 171 candidemia cases and matched controls reveals key findings. Patients with previous chronic liver disease and ICU admission were at an increased risk of

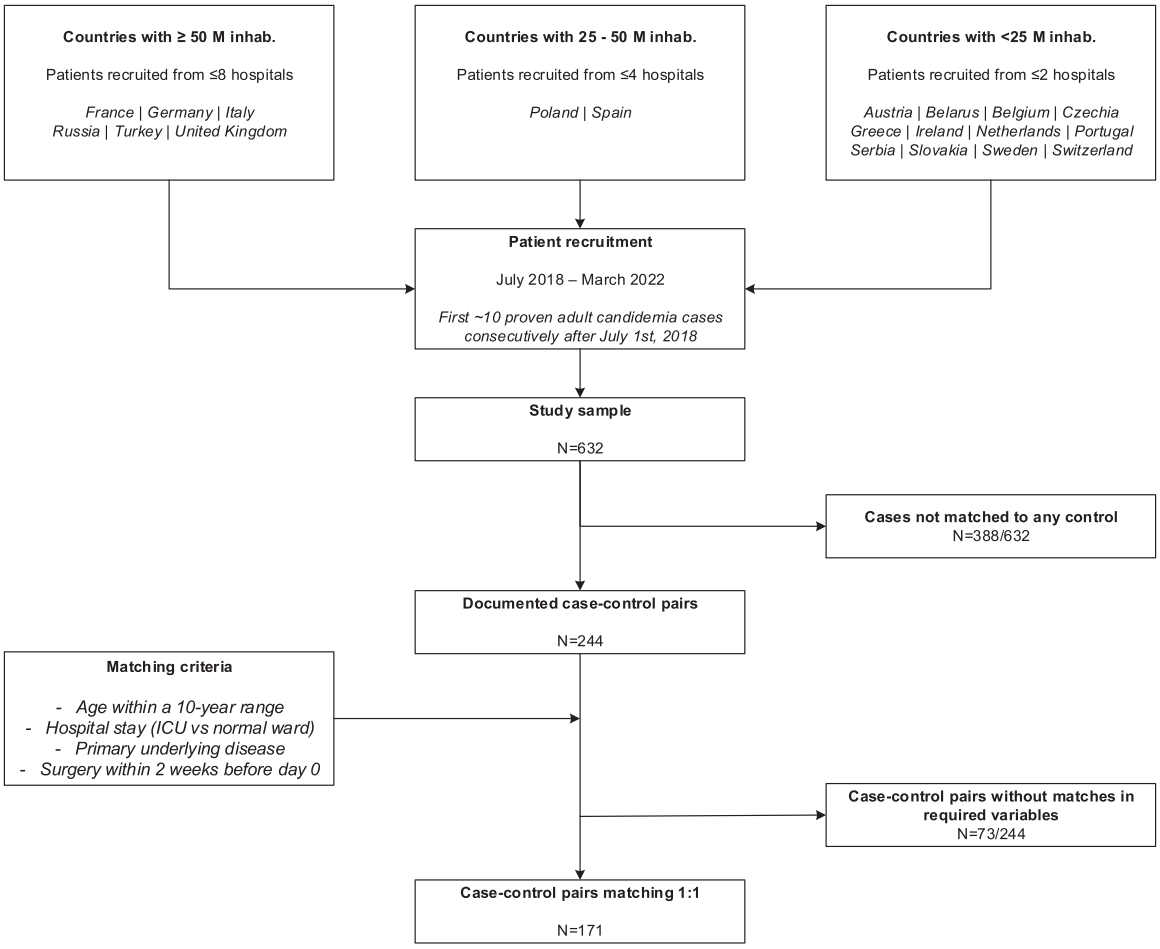


Fig. 2. CONSORT diagram on study enrollment.

mortality. Additionally, candidemia patients, often with cancer and requiring ICU treatment, had a longer hospital stay compared to non-candidemia controls, despite not being significantly different in our sample. The overall mortality rate was significantly higher in candidemia cases (40.4%) with an attributable mortality of 18.2%. *Candida tropicalis* exhibited the highest species-dependent mortality of 63.6%. Echinocandins and fluconazole were commonly used. The EQUAL Score indicated differences in treatment effectiveness between survivors and non-survivors.

We observed a crude overall mortality of 40.4% and an attributable mortality of 18.2% for candidemia, irrespective of the underlying species. Alarmingly, 9.4% of the candidemia cases were diagnosed only post-mortem and were never treated. These missed cases contributed significantly to the attributable mortality. Historic studies until 2001 from France, Germany and the United States have showed attributable mortality rates between 22% and 49%.[6,8,19,20] These studies were performed during a time when candidemia was treated predominantly with amphotericin B deoxycholate and fluconazole, which nowadays are not first-line therapies of choice. In fact, when reviewing studies involving patients treated in recent times, when echinocandins were the primary treatment, it becomes evident that the attributable mortality rate due to *Candida* spp. has decreased to levels ranging from 18 to 35%, [9,21,22] much similar to the ECMM *Candida* III results. [12] In parallel, one could hypothesize that newer antifungals and improved diagnostic techniques have played a role in this observed improvement. Moreover, our findings underscore the potential necessity of assessing candidemia-related mortality on a species-specific basis rather than collectively. This approach is warranted, given that discrepancies in mortality between cases and controls may vary significantly depending on the causative *Candida* species. Recent studies have already triggered a discussion on the role of candidemia in elevating mortality rates.[23]

The trend of improving attributable overall mortality has been previously identified.[9,24] The total reduction of attributable mortality seems multifactorial; however, in our dataset, it may be driven by the source control, the frequent use of echinocandins, lack of resistance for most detected *Candida* spp., and improved care by a consultant from an infection specialist (e.g., infectious diseases or clinical microbiologist) compared to historic studies.[3,25] However, we found a lower attributable mortality to *Candida albicans* and *Candida parapsilosis* in comparison to other candidemia cases, which has not been previously demonstrated in such a large cohort. This observation is concerning, as a shift in *Candida* epidemiology to an increase of non-*albicans* species with increased resistance rates is ongoing globally.[2,14,26,27,4,28] In previous studies on candidemia during the last two decades, the proportion of *Candida glabrata/Nakaseomyces glabratus* isolates was between 8% and 26%, for *Candida parapsilosis* between 7 to 19%, and for *Candida tropicalis* between 5% and 9%, all of which comparable to our cohort,[26-28] but these studies did not, however, assess attributable mortality per individual *Candida* species. While mortality related to *Candida tropicalis* was the highest in our sample, this cannot solely be attributed to antifungal resistance as previous analyses of the ECMM *Candida* III initiative delineated that resistance to fluconazole is less prevalent for *Candida tropicalis* (4%) as compared to other species.[14] Only one case (0.6%) of *Candida auris*-driven candidaemia was observed in a patient who died. Still, this might vary depending on the diagnostic and treatment capacities of the respective handling institution.[29–32]

Table 1
Patient characteristics of candidemia cases and matched controls.

	Overall		Cases		Controls		p value
	n	%	n	%	n	%	
Sex							0.549
Female	157	45.9	80	46.8	77	45.0	
Male	185	54.1	91	53.2	94	55.0	
Age, *median (IQR) [range]*	65 (54-76) [19–97]		65 (54-74) [19–93]		66 (55-77) [19–97]		0.184
18-29 years old	11	3.2	5	2.9	6	3.5	
30-39 years old	25	7.3	11	6.4	14	8.2	
40-49 years old	26	8.2	16	9.4	12	7	
50-59 years old	55	16.1	29	17	26	15.2	
60-69 years old	91	26.6	45	26.3	46	26.9	
70-79 years old	75	21.9	38	22.2	37	21.6	
80-89 years old	46	13.5	20	11.7	26	15.2	
90-99 years old	11	3.2	7	4.1	4	2.3	
Underlying conditions at diagnosis							
CCI, *median (IQR) [range]*	5 (3-8) [0–18]		5 (3-8) [0–18]		5 (3-7) [0–13]		0.083
CVC	234	68.4	136	79.5	98	57.3	< 0.001[a]
Urinary catheter	150	43.9	84	49.1	66	38.6	0.005[a]
Low albumin level	136	39.8	77	45.0	59	34.5	0.005[a]
Cancer	144	42.1	75	43.9	69	40.4	0.210
Solid tumor	106	62.0	55	16.1	51	29.8	0.992
Acute leukemia	20	5.8	11	3.2	9	2.6	
Chronic leukemia	5	1.5	2	0.6	3	0.9	
Lymphoma	5	1.5	3	0.9	2	0.6	
Multiple myeloma	5	1.5	3	0.9	2	0.6	
Myelodysplastic syndrome	2	0.6	1	0.3	1	0.3	
Other	2	0.6	1	0.3	1	0.3	
Treatment in ICU	138	40.4	69	40.4	69	40.4	1.000
Major surgery	90	26.3	48	28.1	42	24.6	0.307
Total parenteral nutrition	74	21.6	47	27.5	27	15.8	< 0.001[a]
Acute or chronic renal disease	75	21.9	45	26.3	30	17.5	0.020[a]
Diabetes mellitus	76	22.2	39	22.8	37	21.6	0.860
Chronic cardiovascular disease	82	24.0	36	21.1	46	26.9	0.154
Obesity (BMI > 30)	50	14.6	28	16.4	22	12.9	0.392
Chronic pulmonary disease	40	11.7	23	13.5	17	9.9	0.286
Chronic liver disease	33	9.6	19	11.1	14	8.2	0.267
Alcoholism	17	5.0	8	4.7	9	5.3	1.000
ECMO	10	2.9	7	4.1	3	1.8	0.125
Solid organ transplantation[b]	10	2.9	6	3.5	4	2.3	0.687
Trauma	13	3.8	5	2.9	8	4.7	0.375
Rheumatic diseases/Autoimmune disorder	10	2.9	5	2.9	5	2.9	1.000
IV drug abuse	7	2.0	4	2.3	3	1.8	1.000
Viral pneumonia[c]	7	2.0	4	2.3	3	1.8	1.000
HIV/AIDS	5	1.5	3	1.8	2	1.2	1.000
Burn	6	1.8	3	1.8	3	1.8	1.000
Duration of hospital stay							
Before diagnosis	16 (9-29) [1-222]		17 (10-30) [1-222]		16 (9-27) [1-161]		0.193
After diagnosis	17 (8-31) [1-216]		20 (10-33) [1-169]		15 (7-28) [1-216]		0.004[a]
ICU after diagnosis	12 (6-23) [1-182]		13 (6-27) [1-126]		10 (5-21) [1-182]		< 0.001[a]
Mortality							
Day 30	81	23.7	58	33.9	23	13.5	< 0.001[a]
Day 60	89	26.0	62	36.3	27	15.8	< 0.001[a]
Day 90	91	26.6	64	37.4	27	15.8	< 0.001[a]
Last day of follow-up	107	31.3	69	40.4	38	22.2	< 0.001[a]

BMI, body mass index; CCI, Charlson comorbidity index; CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ICU, intensive care unit; IQR, interquartile range

[a] Difference statistically significant.

[b] Solid organ transplantations were distributed as follows: among cases, there were 3 liver transplantations, and 1 each of heart, kidney, and liver + lung; among controls, there was 1 each of heart, kidney, liver + lung, and lung.

[c] All viral pneumonias were due to influenza viruses.

The full ECMM *Candida* III dataset (including cases of candidemia that did not have matched controls) also confirmed indwelling CVCs, TPN, and acute or chronic renal disease as risk factors in a higher share in candidemia patients. This indicates that the presence of these factors poses a major risk on patients to develop candidemia.[12] It appears that cumulative risk factors lead to a higher probability of developing candidemia, as described previously, [33,34] so as in the current results, where the Charlson comorbidity index has been described as an explanatory variable for increased mortality, adjusted by pathogenic species.

We found a significant increase in duration of hospital stay and ICU stay in patients with candidemia with a median of 20 days in cases vs 15 days for controls and a median of 13 vs. 10 days, respectively. This observation has been described previously, [35,36] but is of increasing importance for health-economic aspects such as extended in-hospital stay for completion of intravenous

Table 2
Post-hoc sensitivity analyses performed on baseline risk factors potentially impacting on mortality of patients at risk.

	Univariable analysis				Multivariable analysis 1				Multivariable 2			
	p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI	
Underlying conditions at diagnosis												
Charlson comorbidity index	< 0.001	1.170	1.103	1.241	-	-	-	-	< 0.001	1.149	1.084	1.218
Total parenteral nutrition	0.378	1.227	0.779	1.931	-	-	-	-	-	-	-	-
Low albumin level	0.008	1.706	1.149	2.531	0.058	1.482	0.986	2.227	-	-	-	-
Pathogen												
Control	-	-	-	-	-	-	-	-	-	-	-	-
Candida albicans	0.079	1.615	0.947	2.757	0.101	1.565	0.917	2.673	0.101	1.565	0.917	2.670
Candida glabrata	0.026	2.019	1.088	3.745	0.040	1.913	1.029	3.556	0.042	1.896	1.022	3.518
Candida parapsilosis	0.021	2.251	1.130	4.486	0.023	2.231	1.119	4.447	0.064	1.929	0.962	3.869
Candida tropicalis	< 0.001	4.289	1.969	9.341	< 0.001	3.935	1.798	8.613	0.001	3.642	1.666	7.960
Other *Candida* spp.	< 0.001	3.964	1.819	8.635	0.003	3.306	1.487	7.348	0.002	3.467	1.571	7.650
Mixed *Candida* spp.	0.495	1.646	0.393	6.886	0.558	1.534	0.366	6.430	0.503	1.631	0.389	6.830

CI, confidence interval; HR, hazard ratio; spp., species

echinocandin therapy.[12] This impacts healthcare resources when ambulatory treatment is available. [37] In a comprehensive literature review, hospitalization costs were identified as a main cost driver for the treatment of patients with candidemia and invasive candidiasis in Western European countries ranging from $10,216 to $37,715. [38] Mean treatment costs for one day of treatment in an ICU range from €1334 (Eastern Europe) to €2197 (Southern Europe); thus, a reduction in ICU days suggests a substantial potential to save costs. [39] An analysis of treatment costs of a comparable population of candidemia and invasive candidiasis in an

Table 3
Species distribution and antifungal treatment in cases with candidemia.

	Overall		Survival	Non-survival			p value
	n	%	n	%	n	%	
***Candida* spp.**							
Candida albicans	78	45.6	53	67.9	25	32.1	0.077
Candida glabrata/Nakaseomyces glabratus	38	22.2	23	60.5	15	39.5	
Candida parapsilosis	26	15.2	15	57.7	11	42.3	
Candida tropicalis	11	6.4	3	27.3	8	72.7	
Candida krusei/Pichia kudriavzevii	3	1.8	2	66.7	1	33.3	
Candida dubliniensis	2	1.2	1	50.0	1	50.0	
Candida kefyr/Kluyveromyces marxianus	2	1.2	0	0.0	2	100.0	
Candida albicans + Candida glabrata/Nakaseomyces glabratus	1	0.6	1	100.0	0	0.0	
Candida albicans + Candida inconspicua/norvergensis/Pichia norvegensis	1	0.6	1	100.0	0	0.0	
Candida albicans + Candida lusitaniae/Clavispora lusitaniae + Candida parapsilosis	1	0.6	1	100.0	0	0.0	
Candida auris	1	0.6	0	0.0	1	100.0	
Candida dubliniensis + Candida glabrata/Nakaseomyces glabratus	1	0.6	0	0.0	1	100.0	
Candida guillermondii/famata/Meyerozyma guilliermondii/Debaryomyces hansenii	1	0.6	0	0.0	1	100.0	
Candida guilliermondii/Meyerozyma guilliermondii	1	0.6	0	0.0	1	100.0	
Candida krusei/Pichia kudriavzevii + Candida lusitaniae	1	0.6	0	0.0	1	100.0	
Candida lusitaniae/Clavispora lusitaniae	1	0.6	0	0.0	1	100.0	
Candida pelliculosa/Wickerhamomyces anomalus	1	0.6	1	100.0	0	0.0	
Candida rugosa/Diutina rugosa	1	0.6	1	100.0	0	0.0	
Antifungal treatment							
Overall strategies							0.179
Antifungal therapy	70	40.9	46	65.7	24	34.3	
Antifungal therapy + CVC removal	85	49.7	50	58.8	35	41.2	
CVC removal	4	2.3	2	50.0	2	50.0	
No treatment[a]	16	7.0	4	33.3	12	66.7	
Antifungal treatment days	16 (12-21) [1-107]		17 (14-24) [1-107]	13 (6-21) [1–81]			< 0.001*
Administered antifungals							
Amphotericin B	18	10.5	9	50.0	9	50.0	0.449
Amphotericin B liposomal	18	10.5	9	50.0	9	50.0	0.449
Echinocandins	118	69.0	72	61.0	46	39.0	0.616
Anidulafungin	44	25.7	24	54.5	20	45.5	0.477
Caspofungin	74	43.3	50	67.6	24	32.4	0.084
Micafungin	8	4.7	1	12.5	7	87.5	0.008*
Triazoles	82	48.0	59	72.0	23	28.0	0.002*
Fluconazole	78	45.6	57	73.1	21	26.9	0.002*
Posaconazole	1	0.6	1	100.0	0	0.0	1.000
Voriconazole	8	4.7	4	50.0	4	50.0	0.716
Flucytosine	2	1.2	1	50.0	1	50.0	1.000

CVC, central venous catheter; spp., species
Stratified data for *Candida albicans*, *Candida glabrata/Nakaseomyces glabratus*, *Candida parapsilosis*, and *Candida tropicalis* are depicted in Supplementary table 2.
*Statistically significant difference.
[a] Ten patients received post-mortem diagnosis. Among the six patients who did not receive antifungal therapy but were alive at the time of diagnosis, two patients subsequently passed away, while four patients survived.

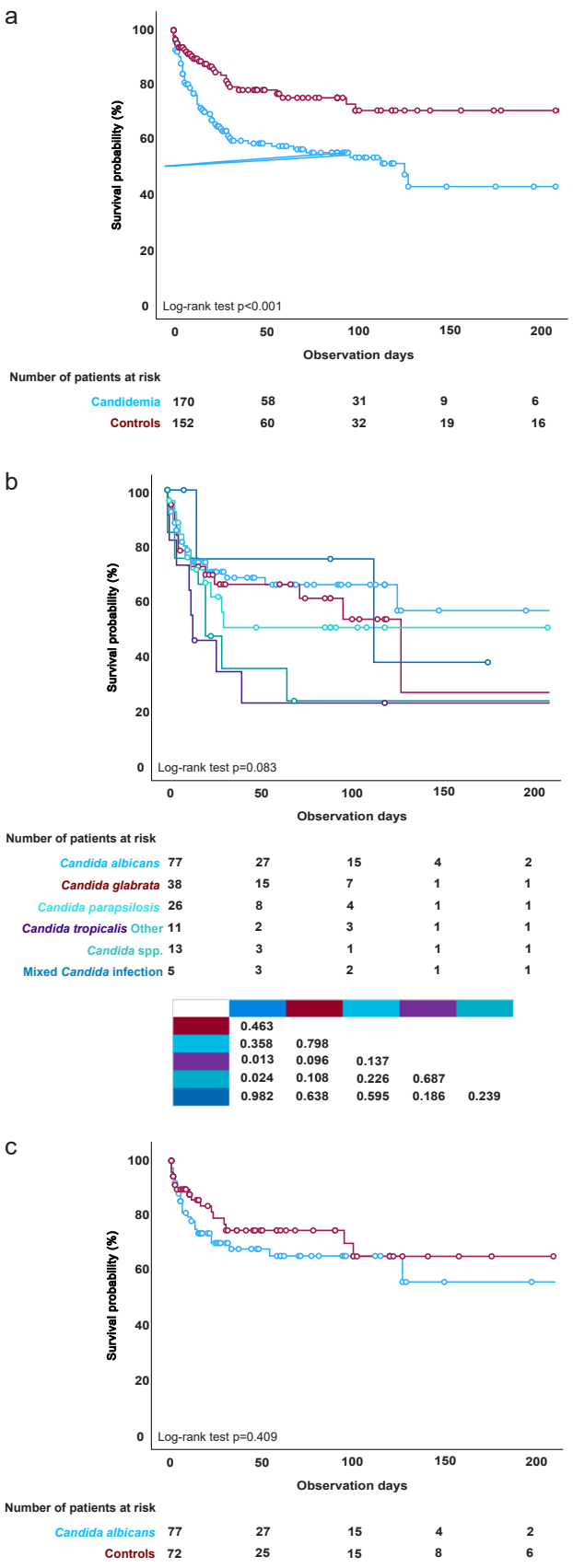
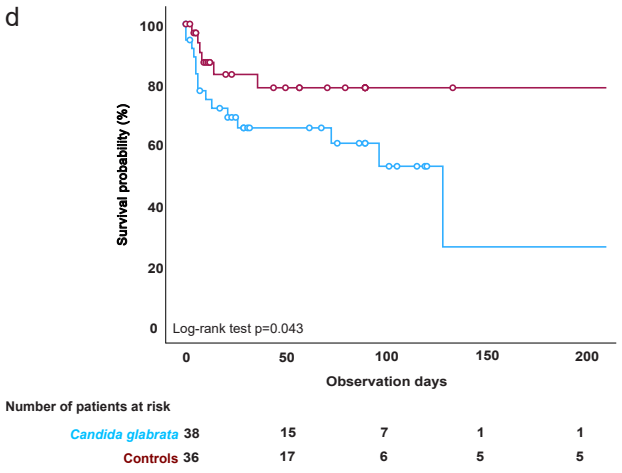


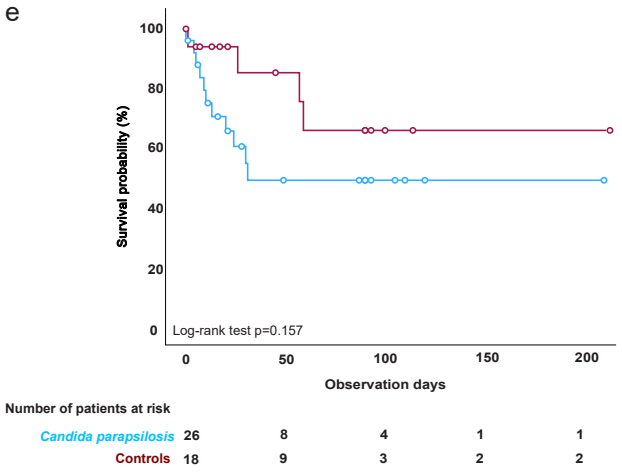
Fig. 3. Kaplan Meier survival curves for candidemia patients versus control patients. a) Survival probability in candidemia versus control patients. Sensitivity analysis is provided in Supplementary figure 1a. b) Candidemia survival probability according to species. Sensitivity analysis is provided in Supplementary figure 1b. c) Survival probability in *Candida albicans* candidemia and matched controls. Sensitivity analysis is provided in Supplementary figure 1c. d) Survival probability in *Candida glabrata/ Nakaseomyces glabratus* candidemia and matched controls. Sensitivity analysis is provided in Supplementary figure 1d. e) Survival probability in *Candida parapsilosis* candidemia and matched controls. Sensitivity analysis is provided in Supplementary figure 1e. f) Survival probability in *Candida tropicalis* candidemia and matched controls. Sensitivity analysis is provided in Supplementary figure 1f.

oncology department in Germany identified a median cost savings potential of €7175 if ICU treatment was reduced by five days. [40] Furthermore, hospital infection control to prevent nosocomial candidemia as well as antifungal stewardship may support the decrease in length of hospital stay associated with candidemia. [41]

Despite its large size (28 institutions in 12 European countries), this analysis has limitations. The patient population was heterogeneous, and not all requested data were available for all patients and controls. Besides, it is worth mentioning that the definitions of the respective underlying conditions were primarily based on clinical determination by participant researchers, potentially introducing variability and subjectivity. A matching process was performed, but each patient still exhibits an individual risk profile, and disease progression is highly variable. Considering the impact on mortality demonstrated both in our results and in the literature, it may be beneficial for future initiatives to include additional matching variables such as albumin levels or TPN. [12,42] In the protocol of the ECMM *Candida* III study, no predefined diagnostic strategies or treatment protocols were required, as this observational study aimed to assess the real-life situation in Europe, potentially affecting the ability to make an early diagnosis and thereby affecting clinical outcomes. Furthermore, to accurately ascertain changes in attributable mortality in candidemia over time, additional studies conducted in similar environments are warranted. Additionally, the reduced sample size constrains the capacity for drawing robust inferences and making definitive recommendations based on the current findings. Therefore, further analyses with larger sample sizes are both desired and recommended. Unfortunately, specific data regarding the potential role of antibiotics, particularly carbapenems, or on the complications experienced in the development of candidemia or antifungal treatment administration was not available. Simultaneously, the data analyzed in this study pertain to well-equipped tertiary care facilities with an elevated interest in fungal infections. Clinical management capacity and attributable mortality rates may differ in various types of institutions, such as community hospitals, based on the accessibility to either diagnostic or treatment tools.[29–31,43,44] Still, establishing close collaborations between institutions of varying specialization levels could mitigate this limitation.

Overall, the mortality rate in candidemia was 40.4% and thereby higher than in control cases resulting in a risk ratio for death among candidemia cases compared to controls of 1.8. Attributable mortality reported in our analysis has decreased in comparison to historical cohorts. However, we find an unchanged situation in non-*albicans* candidemia, which must concern clinicians. A changing *Candida* epidemiology poses a substantial threat to patient outcome.





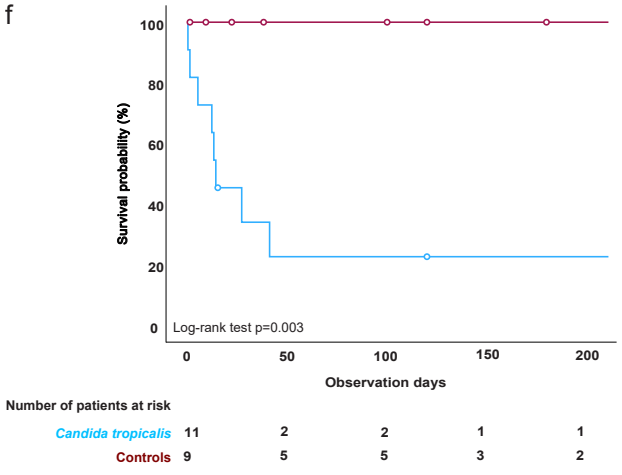


Fig. 3. (*continued*)

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Author contributions

PK, MH, OAC, JSG, MCA, J-PG, SA-A, and TB made substantial contributions to the study concept and design. PK, MH, OAC, and JSG accessed and verified all data. PK and JSG made substantial contributions to the statistical analysis and interpretation of data. JSG, PK, JS, JSG, MH and OAC drafted the manuscript. All authors made substantial contributions to the acquisition of data for the work, and critically reviewed the manuscript and gave the final approval for publication. PK, JSG, MH and OAC full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data Availability

Case-level deidentified participant data and data dictionary will be available from the corresponding author (hoeniglmartin@gmail.com or oliver.cornely@uk-koeln.de) on request from the time of publication, after approval of study proposals by the ECMM Candida III steering committee, confirming that planned analyses will not overlap with other planned sub analyses of the dataset.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: The authors do not declare conflicts of interest related to the submitted manuscript. The funder of the study (Scynexis) had no role in study design, data analysis, interpretation, or writing of the report. All authors had full access to the data and had final responsibility for the decision to submit for publication.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106229.

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