Guideline adherence and survival of patients with candidaemia in Europe: results from the ECMM *Candida* III multinational European observational cohort study

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Summary

Background The European Confederation of Medical Mycology (ECMM) collected data on epidemiology, risk factors, treatment, and outcomes of patients with culture-proven candidaemia across Europe to assess how adherence to guideline recommendations is associated with outcomes.

Methods In this observational cohort study, 64 participating hospitals located in 20 European countries, with the number of eligible hospitals per country determined by population size, included the first ten consecutive adults with culture-proven candidaemia after July 1, 2018, and entered data into the ECMM *Candida* Registry (FungiScope *Candi*Reg). We assessed ECMM Quality of Clinical Candidaemia Management (EQUAL *Candida*) scores reflecting adherence to recommendations of the European Society of Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of America guidelines.

Findings 632 patients with candidaemia were included from 64 institutions. Overall 90-day mortality was 43% (265/617), and increasing age, intensive care unit admission, point increases in the Charlson comorbidity index score, and *Candida tropicalis* as causative pathogen were independent baseline predictors of mortality in Cox regression analysis. EQUAL *Candida* score remained an independent predictor of mortality in the multivariable Cox regression analyses after adjusting for the baseline predictors, even after restricting the analysis to patients who survived for more than 7 days after diagnosis (adjusted hazard ratio 1·08 [95% CI 1·04–1·11; p<0·0001] in patients with a central venous catheter and 1·09 [1·05–1·13; p<0·0001] in those without one, per one score point decrease). Median duration of hospital stay was 15 days (IQR 4–30) after diagnosis of candidaemia and was extended specifically for completion of parenteral therapy in 100 (16%) of 621 patients. Initial echinocandin treatment was associated with lower overall mortality and longer duration of hospital stay among survivors than treatment with other antifungals.

Interpretation Although overall mortality in patients with candidaemia was high, our study indicates that adherence to clinical guideline recommendations, reflected by higher EQUAL *Candida* scores, might increase survival. New antifungals, with similar activity as current echinocandins but with longer half-lives or oral bioavailability, are needed to reduce duration of hospital stay.

Funding Scynexis.

Introduction

Invasive candidiasis including candidaemia remains the most frequent invasive fungal infection in the hospital setting, affecting male and female patients alike,[1] with around 700 000 cases of invasive candidiasis occurring globally per year,[2] 7·07 episodes per 1000 intensive care unit (ICU) admissions in Europe,[3] and an estimated overall pooled annual incidence rate of 3·88 per 100 000 population in Europe.[4] Known risk factors for developing invasive candidiasis in the ICU include (abdominal) surgery; total parenteral nutrition; renal replacement therapy; central venous catheter (CVC); broad spectrum antibiotics; diabetes; neutropenia; solid organ transplantation; clinically significant liver, respiratory, or cardiovascular disease; and intravenous drug use.[5–7]

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Research in context

Evidence before this study

Despite advances in management including improved central venous catheter management, candidaemia remains associated with high mortality. International guidelines for the diagnosis and management of candidaemia were created by the European Society for Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of America, with the ultimate goal of improving patient outcomes and survival, but whether these improvements actually occur (eg, also for first-line treatment with echinocandins) has not been comprehensively assessed. In 2018, the European Confederation of Medical Mycology (ECMM) introduced the EQUAL *Candida* score (ie, an ECMM score to measure quality of clinical candidaemia management), allowing for quantification of guideline adherence as a surrogate marker for the quality of diagnostic and therapeutic management. Although the score was predictive of mortality in subgroups of people with candidaemia in a few, small, single-centre studies, we did not find larger multicentre assessments on whether the score and individual guideline recommendations (ie, score variables) were separately associated with clinical outcomes. We searched PubMed for articles published in English between Jan 1, 2012, and Sept 1, 2022. Search terms included "(Candida* OR candidemia*) AND (EQUAL OR guideline OR recommendations OR guidance)". We also searched the reference lists of all relevant publications for additional reports and included those we deemed appropriate.

Added value of this study

This study collected data on epidemiology, risk factors, treatment, and outcomes of patients with culture-proven candidaemia from 64 institutions in 20 European countries to assess how adherence to guideline recommendations correlates with outcomes. Patient enrolment per country and number of participating centres were stratified by population size. Overall 90-day mortality was 43%. Increasing age, intensive care unit (ICU) admission, point increases in the Charlson comorbidity index score, and *Candida tropicalis* as causative pathogen were independent baseline predictors of mortality in Cox regression analyses. Lower EQUAL *Candida* scores, reflecting less adherence to guideline recommendations, were an independent predictor of mortality in the multivariable Cox regression analyses after adjusting for all significant baseline predictors: for a one score point decrease, adjusted hazard ratios were 1·08 (95% CI 1·04–1·11; p<0·0001) in patients with a central venous catheter and 1·09 (1·05–1·13; p<0·0001) in patients without a central venous catheter. Not-performing or not-completing each diagnostic or therapeutic measure (including initial echinocandin treatment) was associated with increased mortality compared with mortality in the overall cohort, emphasising the importance of every single guideline recommendation in the successful management of candidaemia. Initial echinocandin treatment was associated with longer duration of hospital stay among survivors.

Implications of all the available evidence

Although across Europe 90-day mortality in adults with candidaemia remains high at 43%, adherence to clinical guideline recommendations might increase survival. Notably, more controversial guideline recommendations, such as performance of ophthalmoscopy or echocardiography, are also associated with increased survival. Treatment with echinocandins might not only be associated with increased overall survival but also longer duration of hospital stay, causing extended hospitalisation solely for completing parenteral therapy in one of seven patients with candidaemia, due to the fact that no oral alternatives to azoles are available. This limitation could be overcome by new antifungals with oral bioavailability (eg, ibrexafungerp) or longer half-lives (eg, rezafungin), which could allow for earlier discharge and outpatient therapy.

Despite advances in management, including first-line treatment with echinocandins and improved CVC management, invasive candidiasis remains associated with high mortality.[8] Of approximately 79 cases occurring in Europe per day, an estimated 29 (37%) patients are expected to have a fatal outcome at day 30 after diagnosis.[4] Predictors of mortality due to candidaemia include increasing age, primary source (ie, unrelated to CVC), and sepsis or septic shock.[9] By contrast, early adequate antifungal treatment is efficacious,[9] as is consultation by an infectious diseases specialist (hazard ratio [HR] 0·81 [95% CI 0·73–0·91]; p<0·0001) after propensity score weighting.[10]

International guidelines for the diagnosis and management of candidaemia were created with the ultimate goal of improving patient outcomes and survival, but whether these improvements actually occur has been rarely assessed. In 2018, the European Confederation of Medical Mycology (ECMM) introduced the EQUAL scores (ie, ECMM scores to measure quality of disease management), allowing for quantification of guideline adherence as a surrogate marker for the quality of diagnostic and therapeutic management; the EQUAL *Candida* score was the first score published.[11] The score was derived from recommendations of the two most prominent guidelines for candidaemia, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline,[12] and the Infectious Diseases Society of America (IDSA) guideline.[13]

In single-centre studies in the past 5 years, the EQUAL *Candida* score[11] predicted mortality in CVC-associated candidaemia in general,[14] and candidaemia caused by *Candida tropicalis*;[15] however, larger multicentre assessments have not been done yet.

Therefore, the ECMM[16] has designed and completed the *Candida* III study—its third pan-European multicentre *Candida* study from 1997 to 2022,[17,18] to collect data on epidemiology, risk factors, treatment, and outcomes of patients with culture-proven candidaemia across Europe. The objective of the study was to assess how adherence to guideline recommendations for managing candidaemia is associated with outcomes. In this Article, we report the findings obtained from the *Candida* III study.

Methods

Study design and participating centres

For this European multicentre observational cohort study, each participating hospital included the first ten consecutive adults with blood culture-proven candidaemia after July 1, 2018. Candidaemia was defined according to ESCMID criteria.[19] The primary objective was to assess how adherence to guideline recommendations is associated with outcomes. Secondary objectives included the assessment of epidemiology, risk factors, treatment, and outcomes of patients with candidaemia across Europe.

To give a complete picture of the epidemiology of candidaemia in Europe, the target number of eligible hospitals per country was determined by population size. As guidance, up to a maximum of eight hospitals were invited to contribute for each of the six ECMM countries with populations of 50 million or more (ie, France, Germany, Italy, Russia, Türkiye, and the UK); up to a maximum of four hospitals for each ECMM country with populations of 25 million or more and less than 50 million (ie, Poland and Spain); and up to two hospitals for each of the remaining 19 ECMM countries with populations less than 25 million (ie, Austria, Belarus, Belgium, Czechia, Croatia, Denmark, Estonia, Greece, Ireland, the Netherlands, Norway, Portugal, Romania, Hungary, Serbia, Slovakia, Slovenia, Sweden, and Switzerland). However, hospitals in seven countries (Croatia, Denmark, Estonia, Norway, Poland, Romania, and Hungary), although eligible, did not participate in the study. Hospitals were recruited by ECMM council representatives of each participating country, or via the COVID-19 in Hematological Malignancies (EPICOVIDEHA)[20] and FungiScope[21] networks and among the ECMM Global Guidelines contributor and fellow groups.[16]

Between July 1, 2018, and March 31, 2022, participating centres entered data into the ECMM *Candida* Registry (FungiScope *Candi*Reg; NCT01731353), which was described previously.[21,22] The registry was accessible through an online platform provided by EFS Fall 2018 (Questback, Cologne, Germany). Data included patient demographics, risk factors, and characteristics; duration of hospital stay (maximum duration of follow-up 90 days); diagnostic procedures; causative *Candida* spp; treatment characteristics, including antifungal treatment and whether hospital stay was extended only for completion of parenteral antifungal treatment; and clinical outcomes.

The study was done in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. For the ECMM *Candida* Registry, retrospective data entry, and data analysis, a central ethical approval was obtained at the University of Cologne (Cologne, Germany; EK 17-485), indicating that, generally, neither informed consent nor institutional review board approval individual to each participating hospital would be required. However, each participating hospital was required to obtain local institutional review board confirmation or approval as deemed necessary by local regulations or authorities.

Statistical analysis

We did all statistical analyses using IBM SPSS Statistics 25 and R, version 4.3.1. We used descriptive statistics for the analysis of most variables, including distribution of *Candida* spp and extended hospital stay for parenteral antifungal treatment. We assessed EQUAL *Candida* scores[11] reflecting adherence to recommendations of ESCMID and IDSA guidelines for patients for whom data were available, whereas we excluded patients and did not calculate the corresponding EQUAL *Candida* scores when case data were not given for one or more score variables. We presented data as frequencies, percentages, or median (IQR) values, as appropriate. We tested categorical data using χ^2, or Fisher's exact test if one of the observed frequencies in the two-by-two contingency table was less than five. We summarised continuous variables using median (IQR) values and we compared groups with Student's *t* test (two groups) or ANOVA (three or more groups) when data were normally distributed, or with Mann-Whitney test (two groups) or Kruskall-Wallis test (three or more groups) when data were not normally distributed. Two-sided p values less than 0·05 were used as the cutoff for statistical significance.

Further analyses on EQUAL *Candida* scores were restricted to patients with candidaemia with follow-up data of 7 days or more after diagnosis, to exclude patients in whom earlier mortality or loss to follow-up might have precluded treating physicians from implementing measures recommended in the guidelines, and thereby potentially biasing our results towards lower scores in non-survivors. The ratio scores—that is, the actual EQUAL *Candida* scores divided by the maximum achievable EQUAL *Candida* score (19 for patients without CVC and 22 for those with CVC)—were used to calculate a proportion of the maximum achievable points for each patient and compared between survivors and non-survivors. For these EQUAL *Candida* score proportions, we plotted a receiver operating characteristic (ROC) curve and calculated area under the curve (AUC) values. We determined optimal cutoff using the Youden index.

To investigate the association of baseline risk factors with survival, univariable and multivariable Cox

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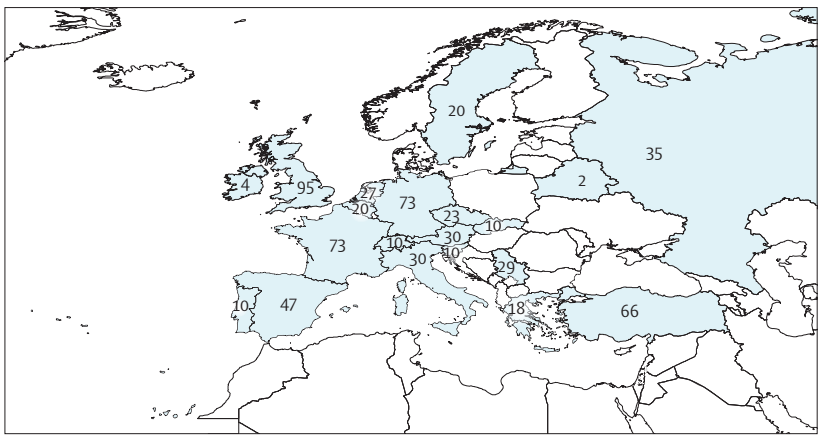

Figure 1: **Participating European countries and associated number of included cases**

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proportional hazard models (non-overlapping and non-mutually exclusive variables with p<0·1 included) were estimated for patients without missing data on duration of follow-up, with duration of follow-up capped at day 180. Causative *Candida* spp was the only variable that differed between the multivariable models; *C tropicalis* was included as a variable in one of these models, whereas, for the second model, emerging *Candida* spp that have been previously defined[23] (ie, *C kefyr*, *C guilliermondii*, *C lusitaniae*, *C dubliniensis*, *C famata*, *C inconspicua*, *C rugosa*, and *C norvegensis*) were grouped together with *C auris* into the variable *C auris* and other emerging *Candida* spp. The proportional hazard assumption was evaluated by fitting an interaction between a variable of interest and linear follow-up time. We used the Akaike information criterion to compare the relative quality of multivariable Cox models for baseline risk factors.

We then used a multivariable Cox proportional hazards model to measure the relative hazard for death between different EQUAL *Candida* scores when adjusting for significant baseline prognostic factors in patients who survived for more than 7 days and who had data on duration of follow-up available. Lastly, we estimated multivariable Cox models for each variable of the EQUAL *Candida* score adjusted for significant baseline risk factors.

The proportional hazard assumption was tested with the Schoenfeld residuals test for the overall model and individual covariates. The resultant model and all other Cox models did not violate the proportional hazard assumption for individual covariates or the global model. Because candidaemia diagnosis was the starting point for follow-up and the primary effect of interest (EQUAL *Candida* score), and because all other covariates were established at baseline, immortal time bias was not considered.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

632 patients with candidaemia were included from 64 institutions in 20 European countries (figure 1; appendix pp 10–11). The study flow is depicted in figure 2. Patients' demographic and clinical characteristics, risk factors, treatment, and outcomes, as well as distribution of *Candida* spp in the overall study cohort, in the survivors group, and in the non-survivors group, are separately detailed in the appendix (pp 12–15). The majority of patients (368/632 [58%]) were male and the median age was 65 years (IQR 53–73). Underlying haematological or oncological malignancy (247/632 [39%]), ICU admission (234/632 [37%]), and recent major surgery (164/632 [26%]) were the most common risk factors for candidaemia. Candidaemia was classified as catheter-related bloodstream infection in 130 (21%) of 632 patients. 224 (35%) of 632 patients underwent echocardiography, with cardiac involvement reported in 25 (11%) of 224 patients examined. 169 (27%) of 632 patients received an eye examination (ophthalmoscopy), with ocular involvement reported in 19 (11%) of 169 patients examined. Overall mortality was 46% (286/617; for 15 patients, survival status was unknown); in 77 (37%) of 209 patients who died, investigators attributed death to candidaemia (for the remaining 77 patients, investigators indicated death as unknown or left the field empty); 30-day mortality was 38% (232/617), 90-day mortality 43% (265/617), and 180-day mortality 45% (278/617). Median duration of hospital stay was 15 days (IQR 4–30) after the diagnosis of candidaemia. 502 (81%) of 620 patients with available data received treatment consultation by an infectious diseases or microbiology expert and echinocandins were the first-line antifungal treatment in 353 (56%) of 632 patients. Among survivors, initial echinocandin treatment was associated with longer duration of hospital stay (median 24 days [IQR 15–40]) than initial treatment with other antifungals, such as azoles (16 days [7–33]; p<0·0001). In patients in whom candidaemia was treated for at least 14 days (n=306), 239 (78%) survived, compared with 67 (66%) of 102 patients who were treated for less than 14 days, but who survived beyond day 14 after diagnosis (p=0·01). Hospital stay was extended specifically for the purpose of completing parenteral antifungal treatment in 100 (16%) of 621 patients by a median of 14 days (IQR 3–23). *C albicans* was the most common causative pathogen (287/621 [46%]), followed by *C glabrata* (133/621 [21%]), *C parapsilosis* (83/621 [13%]), *C tropicalis* (46/621 [7%]), *C krusei* (16/621 [3%]), and *C auris* (16/621 [3%]).

Informed by univariable Cox regression modelling (table 1), we fitted two multivariable Cox regression models consisting of three non-overlapping, non-mutually exclusive baseline predictors of mortality: increasing age, Charlson comorbidity index score (excluding age), and ICU admission. Furthermore, an additional predictor was included in each of the two models: *C tropicalis* as causative pathogen in the first

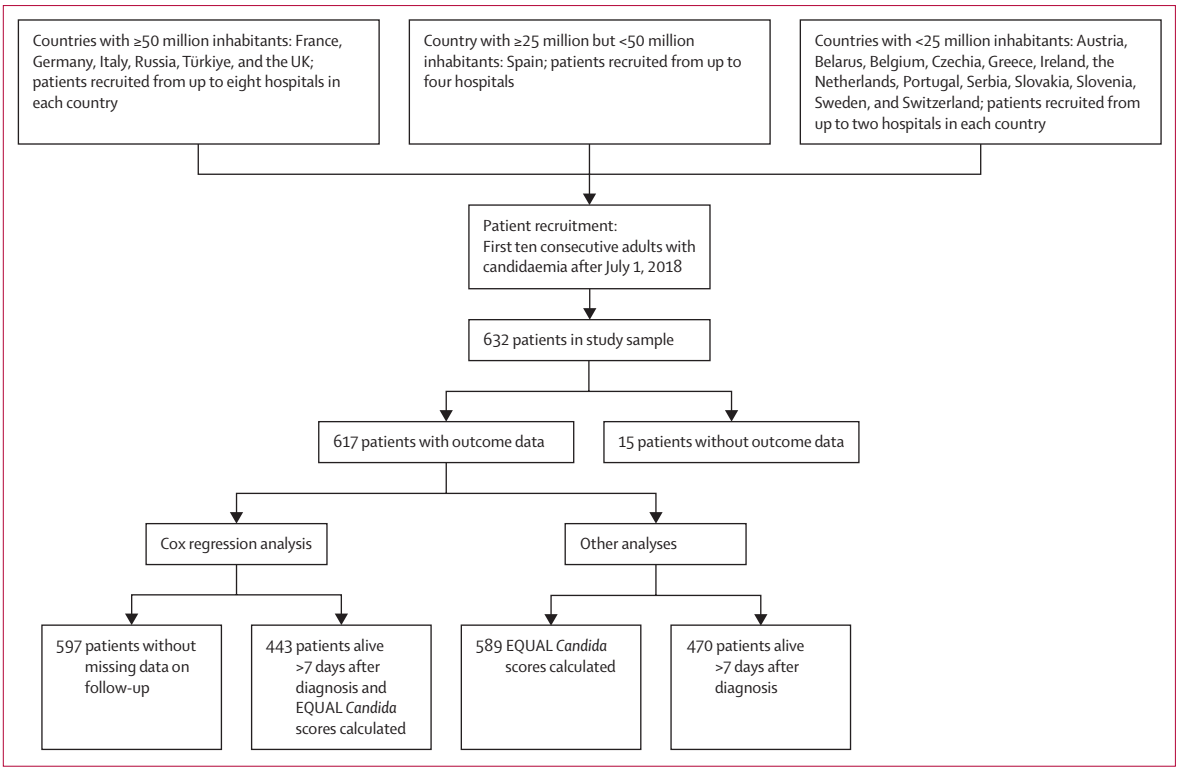

***Figure 2*: Study flowchart**
EQUAL *Candida*=European Confederation of Medical Mycology Quality of Clinical Candidaemia Management.

model, and *C auris* and other emerging *Candida* spp in the second model. Informed by the Akaike information criterion values (table 1), we decided to use the baseline parameters of the first model for further adjustments of the remaining risk models.

Overall mortality was lower in patients receiving initial echinocandin treatment (148/353 [42%]) than in those not receiving such therapy (138/264 [52%]; p=0·011), also when adjusted for baseline risk factors (adjusted HR 0·56 [95% CI 0·44–0·72]; p<0·0001).

Although consultation with an infectious diseases physician or microbiologist was associated with better survival in the overall cohort (adjusted HR 0·58 [95% CI 0·44–0·70; p=0·0001), this effect lessened once patients who had a fatal outcome within 2 days of diagnosis of candidaemia (n=59) were excluded (0·71 [0·51–0·99]; p=0·042). No differences were found when patients who had a fatal outcome within 3 days were excluded (0·72 [0·51–1·03]; p=0·071), driven in part by the fact that the majority of these patients (421/509 [83%]) received consultation.

The EQUAL *Candida* score was available for 589 patients with candidaemia. Ratio scores correlated with duration of hospital stay (Pearson's *r*=0·44; p<0·0001). After excluding patients hospitalised for 7 days or less (n=119), no correlation was found between duration of hospital stay and the ratio scores (Pearson's *r*=0·05; p=0·26), indicating that 7 days was enough time for completing most guideline recommendations. Even after the exclusion of patients hospitalised for 7 days or less (n=119; median ratio score 0·42 [IQR 0·27–0·59] in patients hospitalised for 7 days or less *vs* 0·77 [0·63–0·86] in those hospitalised for more than 7 days; p<0·0001), ratio scores were higher in patients who survived (median ratio score 0·76 [IQR 0·64–0·91]) than in those who died (0·68 [0·55–0·82]; p<0·0001; appendix p 16).

EQUAL *Candida* scores, score variables, and demographic data of survivors and non-survivors who survived for more than 7 days after candidaemia diagnosis are shown in the appendix (p 16). ROC curve analysis showed an AUC of 0·718 for the proportion of the maximum EQUAL *Candida* score for predicting overall mortality, with an optimal cutoff of 78·1% of the maximum score (which translates to >14 in patients without a CVC and >16 in those with a CVC). Adjusted HR per point increase in EQUAL *Candida* scores for patients with a CVC and those without are displayed in figure 3.

Results of the multivariable Cox regression model for risk of mortality with percent decrease in EQUAL *Candida* score in patients who survived for more than 7 days after diagnosis are displayed in table 2. After adjustment for baseline variables of the first model, a decrease in one score point translated to an adjusted HR of 1·08 (95% CI 1·04–1·11; p<0·0001) in patients with a CVC and 1·09 (1·05–1·13; p<0·0001) in those without a

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	Hazard ratio (95% CI)	p value
Univariable models		
Sex		
Female (n=248)	1 (ref)	..
Male (n=349)	1·19 (0·93–1·52)	0·16
Age (per 20 years; n=597)	1·37 (1·18–1·60)	<0·0001
BMI		
<30 kg/m² (n=496)	1 (ref)	..
≥30 kg/m² (n=101)	1·01 (0·74–1·39)	0·95
Solid organ transplant		
No (n=583)	1 (ref)	..
Yes (n=14)	0·61 (0·25–1·49)	0·28
Haematological or oncological malignancy		
No (n=358)	1 (ref)	..
Yes (n=239)	1·13 (0·89–1·44)	0·32
Neutropenia (<500 cells per µL)		
No (n=516)	1 (ref)	..
Yes (n=61)	1·06 (0·75–1·50)	0·75
Major surgery including abdominal surgery		
No (n=437)	1 (ref)	..
Yes (n=160)	0·95 (0·72–1·25)	0·70
Type 1 or 2 diabetes		
No (n=461)	1 (ref)	..
Yes (n=136)	0·99 (0·75–1·31)	0·93
ICU admission		
No (n=371)	1 (ref)	..
Yes (n=226)	1·71 (1·34–2·17)	<0·0001
Catheter-related bloodstream infection		
No (n=470)	1 (ref)	..
Yes (n=127)	0·89 (0·66–1·19)	0·43
Prosthetic heart valve		
No (n=519)	1 (ref)	..
Yes (n=78)	1·00 (0·71–1·42)	0·98
Mechanical ventilation		
No (n=366)	1 (ref)	..
Yes (n=150)	1·32 (1·02–1·71)	0·033
Extracorporeal membrane oxygenation		
No (n=582)	1 (ref)	..
Yes (n=15)	1·32 (0·65–2·67)	0·44
Total parenteral nutrition		
No (n=465)	1 (ref)	..
Yes (n=132)	0·83 (0·62–1·11)	0·21
Charlson comorbidity index (per score increase; n=597)	1·09 (1·05–1·13)	<0·0001
Charlson comorbidity index (excluding age; per score increase; n=597)	1·07 (1·03–1·11)	0·0019
Candida albicans		
No (n=314)	1 (ref)	..
Yes (n=274)	0·92 (0·72–1·16)	0·48
Candida glabrata		
No (n=461)	1 (ref)	..
Yes (n=127)	0·88 (0·65–1·18)	0·39

(Table 1 continues in next column)

	Hazard ratio (95% CI)	p value
(Continued from previous column)		
Candida parapsilosis		
No (n=508)	1 (ref)	..
Yes (n=80)	0·98 (0·70–1·38)	0·92
Candida tropicalis		
No (n=544)	1 (ref)	..
Yes (n=44)	1·78 (1·16–2·57)	0·0071
Candida krusei		
No (n=576)	1 (ref)	..
Yes (n=12)	0·84 (0·31–2·25)	0·73
Candida auris		
No (n=573)	1 (ref)	..
Yes (n=15)	1·39 (0·69–2·81)	0·36
Candida dubliniensis		
No (n=579)	1 (ref)	..
Yes (n=9)	0·69 (0·22–2·15)	0·52
Candida guilliermondii		
No (n=582)	1 (ref)	..
Yes (n=6)	3·64 (1·62–8·18)	0·0018
Candida lusitaniae		
No (n=583)	1 (ref)	..
Yes (n=5)	1·23 (0·39–3·84)	0·72
Candida kefyr		
No (n=583)	1 (ref)	..
Yes (n=5)	3·27 (1·22–8·80)	0·019
Other *Candida* spp*		
No (n=579)	1 (ref)	..
Yes (n=9)	0·75 (0·24–2·33)	0·62
Candida auris and other emerging *Candida* spp†		
No (n=542)	1 (ref)	..
Yes (n=46)	1·54 (1·03–2·30)	0·034
Candida auris and rare *Candida* spp‡		
No (n=539)	1 (ref)	..
Yes (n=49)	1·39 (0·93–2·09)	0·11
Mixed fungal infections		
No (n=551)	1 (ref)	..
Yes (n=37)	2·45 (0·57–10·5)	0·23
Initial echinocandin treatment		
No (n=249)	1 (ref)	..
Yes (n=348)	0·55 (0·44–0·70)	<0·0001
Infection consultation with an infectious diseases or microbiology expert		
No (n=113)	1 (ref)	..
Yes (n=475)	0·56 (0·43–0·74)	<0·0001

(Table 1 continues in next column)

CVC. Ratio scores below the calculated Youden cutoff of 78·1% of the maximum score were associated with an adjusted HR of 3·53 (2·01–5·98; p<0·0001).

Overall mortality rates for variables of the EQUAL *Candida* score that were not performed or completed, followed by results of the multivariable Cox regression model evaluating each of the not performed score

	Hazard ratio (95% CI)	p value
(Continued from previous column)		
First multivariable model (AIC=3172)		
Age (per 20 years)	1·34 (1·15–1·57)	0·0002
ICU admission		
No	1 (ref)	..
Yes	1·83 (1·44–2·33)	<0·0001
Charlson comorbidity index (excluding age; per score increase)	1·07 (1·02–1·12)	0·0035
Candida tropicalis		
No	1 (ref)	..
Yes	1·71 (1·15–2·55)	0·0085
Second multivariable model (AIC=3175)		
Age (per 20 years)	1·39 (1·18–1·63)	<0·0001
ICU admission		
No	1 (ref)	..
Yes	1·77 (1·39–2·25)	<0·0001
Candida auris and other emerging *Candida* spp†		
No	1 (ref)	..
Yes	1·50 (0·99–2·26)	0·056
Charlson comorbidity index (excluding age; per score increase)	1·06 (1·02–1·11)	0·0056

AIC=Akaike information criterion. ICU=intensive care unit. *Other *Candida* spp include: *C norvegensis* (n=1), *C digboensis* (n=1), *C rugosa* (n=3), *C pelliculosa* (n=2), *C inconspicua* (n=2; one patient coinfected with *C norvegensis*), and *C famata* (n=1). †Other emerging *Candida* spp include: *C kefyr* (n=5), *C guilliermondii* (n=6), *C lusitaniae* (n=5), *C dubliniensis* (n=5), *C famata* (n=1), *C inconspicua* (n=2; one patient coinfected with *C norvegensis*), *C rugosa* (n=3), and *C norvegensis* (n=1). ‡Rare *Candida* spp include species with ten or fewer isolates: *C kefyr* (n=5), *C guilliermondii* (n=6), *C lusitaniae* (n=5), *C dubliniensis* (n=5), *C norvegensis* (n=1), *C digboensis* (n=1), *C rugosa* (n=3), *C pelliculosa* (n=2), *C inconspicua* (n=2; one patient coinfected with *C norvegensis*), and *C famata* (n=1).

Table 1: **Univariable and multivariable Cox regression models for predictors of mortality in patients with candidaemia (n up to 597)**

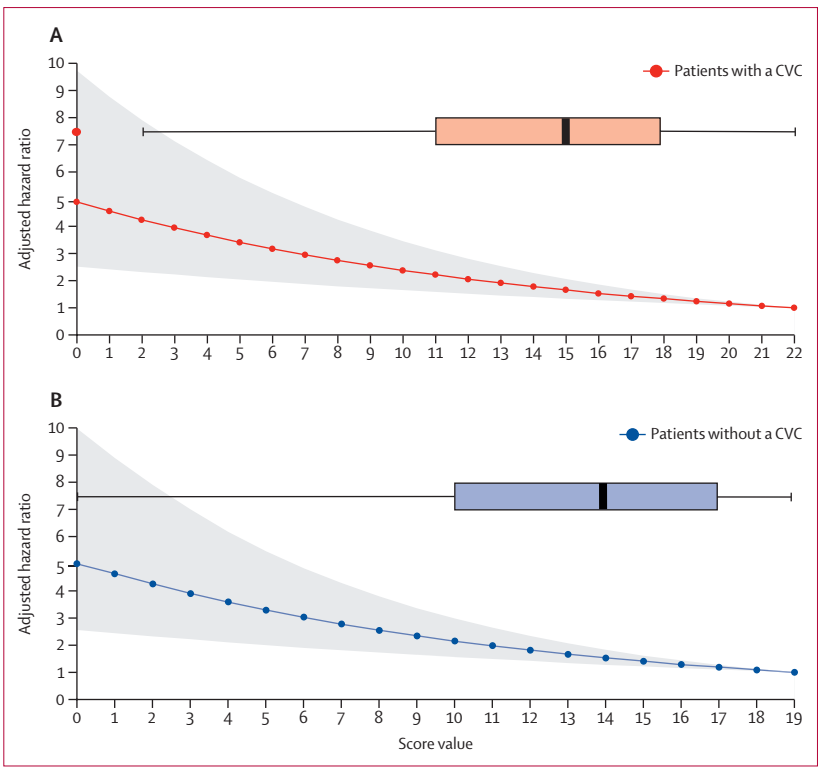

Figure 3: **Mortality risk per point increase in EQUAL *Candida* scores for patients with a CVC and those without one, and boxplots of the distribution of score values in the two groups**
Hazard ratios and associated 95% CI were adjusted for age, intensive care unit admission, Charlson comorbidity index (excluding age), and *Candida tropicalis*. Boxplots show the median (midline) and IQR (range of the box); whiskers extend 1·5 times the IQR and any counts beyond these ranges (ie, outliers) are indicated by a circle. (A) Patients with a CVC. (B) Patients without a CVC. CVC=central venous catheter. EQUAL *Candida*=European Confederation of Medical Mycology Quality of Clinical Candidaemia Management.

variables (adjusted for significant baseline risk factors), are outlined in table 3. Mortality in patients for whom guideline-recommended diagnostic or therapeutic measures were not performed was higher (51–71%; table 3) than in the overall cohort (286/617 [46%]). In the multivariable Cox model comparing the effect of guideline-recommended diagnostic or therapeutic measures for patients who survived for more than 7 days and adjusted for the baseline predictors, the following not-performed or not-completed measures were predictors of mortality: ophthalmoscopy (adjusted HR 2·19 [95% CI 1·55–3·11]; p<0·0001), echocardiography (1·77 [1·27–2·46]; p=0·0006), treatment for 14 days or more after the first negative blood culture (3·64 [2·62–5·06]; p<0·0001), and step-down therapy to fluconazole (1·71 [1·17–2·50]; p=0·0058).

Discussion

We did a multicentre observational study of candidaemia, involving 64 hospitals from 20 countries across Europe. Our main finding is that overall 90-day mortality due to candidaemia remains high (265/617 [43%]). However, adherence to clinical guideline recommendations, as reflected by higher EQUAL *Candida* scores, was a strong independent predictor of survival. Other findings included that candidaemia caused by rare *Candida* spp might be a relevant independent baseline predictor of mortality, in addition to known predictors such as increasing age and ICU admission. In terms of treatment, initial echinocandin treatment was associated with increased overall survival, but also with longer duration of hospital stay, compared with treatment with other antifungals.

The overall mortality of 46% found in this study (90-day mortality of 43%), of which 37% was directly attributable to candidaemia according to investigators, suggests that candidaemia is still a major threat to patients and a medical emergency. The rate is as high or even slightly higher than rates reported earlier, such as 43% overall mortality from a study in Germany, with 26% mortality attributable to candidaemia;[24] 37·9% mortality between 1997 and 1999, from a previous ECMM European cohort study including neonates and children;[17] and 38·8% mortality from another ECMM European cohort study of patients admitted to surgical ICU between 2006 and 2008.[18] Additionally, a

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	Adjusted hazard ratio (95% CI)	p value
EQUAL *Candida* score risk per 1% decrease of the ratio score	1·02 (1·01–1·02)	<0·0001
EQUAL *Candida* score risk per 10% decrease of the ratio score	1·18 (1·10–1·26)	<0·0001
Risk per point decrease in EQUAL *Candida* score for patients with a central venous catheter*	1·08 (1·04–1·11)	<0·0001
Risk per point decrease in EQUAL *Candida* score for patients without a central venous catheter*	1·09 (1·05–1·13)	<0·0001
Risk reduction comparing maximum and minimum EQUAL *Candida* score	0·20 (0·10–0·39)	<0·0001
Optimal EQUAL *Candida* score cutoff for predicting risk		
EQUAL *Candida* score >78·1% of the maximum score†	1 (ref)	..
EQUAL *Candida* score ≤78·1% of the maximum score†	3·53 (2·01–5·98)	<0·0001

The ratio score is the actual EQUAL *Candida* score divided by the maximum achievable EQUAL *Candida* score. EQUAL *Candida*=European Confederation of Medical Mycology Quality of Clinical Candidaemia Management. *The maximum EQUAL *Candida* score is 22 points (ie, 4·5% per point) for patients with a central venous catheter, and 19 points (ie, 5·3% per point) for patients without a central venous catheter. †Multivariable hazard ratio for calculated threshold with maximum sensitivity and specificity for prediction of death.

Table 2: **Multivariable Cox regression models (adjusted for age, intensive care unit admission, Charlson comorbidity index [excluding age], and *Candida tropicalis*) for risk of mortality with percent decrease in EQUAL *Candida* score in patients with candidaemia who survived for more than 7 days (n=443)**

	Absolute mortality rates	Adjusted hazard ratio (95% CI)	p value
Diagnostic measures			
Initial blood cultures of 40 mL			
Performed	253/557 (45%)	1 (ref)	..
Not performed	32/55 (58%)	1·26 (0·69–2·30)	0·46
Species identification			
Performed	260/570 (46%)	1 (ref)	..
Not performed	25/43 (58%)	1·46 (0·76–2·82)	0·30
Susceptibility testing			
Performed	230/520 (44%)	1 (ref)	..
Not performed	53/89 (60%)	1·40 (0·86–2·29)	0·26
Ophthalmoscopy			
Performed	56/219 (26%)	1 (ref)	..
Not performed	224/382 (59%)	2·19 (1·55–3·11)	<0·0001
Echocardiography			
Performed	90/267 (34%)	1 (ref)	..
Not performed	189/334 (57%)	1·77 (1·27–2·46)	0·0006
Follow-up blood cultures until negative			
Performed	126/360 (35%)	1 (ref)	..
Not performed	148/230 (64%)	1·28 (0·91–1·80)	0·16
Treatment measures			
Start of echinocandin treatment			
Performed	148/353 (42%)	1 (ref)	..
Not performed	138/264 (52%)	1·23 (0·87–1·72)	0·26
Step-down therapy to fluconazole			
Performed	50/186 (27%)	1 (ref)	..
Not performed	236/431 (55%)	1·71 (1·17–2·50)	0·0058
Treatment for ≥14 days after the first negative blood culture			
Performed	85/325 (26%)	1 (ref)	..
Not performed	196/278 (71%)	3·64 (2·62–5·06)	<0·0001
Central venous catheter removal ≤24 h*			
Performed	86/216 (40%)	1 (ref)	..
Not performed	194/384 (51%)	1·41 (0·96–2·05)	0·78
Central venous catheter removal >24 h but <72 h*			
Performed	39/82 (48%)	1 (ref)	..
Not performed†	155/302 (51%)	1·21 (0·77–1·90)	0·42

EQUAL *Candida*=European Confederation of Medical Mycology Quality of Clinical Candidaemia Management. *Patients with a central venous catheter only. †Not performed indicates that catheter was not removed within 72 h.

Table 3: **Absolute mortality rates for patients for whom EQUAL *Candida* score variables were either performed or not performed (n up to 617), and corresponding multivariable Cox regression models (adjusted for age, intensive care unit admission, Charlson comorbidity index [excluding age], and *Candida tropicalis*) for prediction of mortality in patients with candideamia who survived for more than 7 days (n=443)**

90-day crude mortality of 42·4% in patients with *Candida* bloodstream infections was reported in the USA, which was more than two times as high as the 17·1% mortality observed among matched controls.[25] After propensity score-matching, the attributable risk difference for 90-day mortality was 28·4% (HR 2·12 [95% CI 1·98–2·25], p<0·001).[25]

Our study identified adherence to international guideline recommendations as a major protective factor, even after adjustment for the baseline risk factors (age, ICU admission, Charlson comorbidity index, and *C tropicalis*). With every point decrease of the EQUAL *Candida* score, reflecting a decrease in adherence to guideline recommendations, risk of death increased by 9% for patients with a CVC and 8% for patients without a CVC. Additionally, patients for whom guideline-recommended diagnostic or therapeutic measures were not performed had higher mortality rates than the overall cohort, emphasising the importance of every single guideline recommendation in the successful management of candidaemia.

Many known risk factors for *Candida* infections in the ICU (eg, previous surgery, total parenteral nutrition, CVC, broad spectrum antibiotics, diabetes, neutropenia, or solid organ transplantation[5–7]) were present in relevant proportions in our study population. Increasing age, severe hepatic failure, organ failure at the onset of invasive candidiasis, and septic shock were previously associated with increased 30-day mortality in patients with candidaemia.[3] In this study, increasing age, point increases in the Charlson comorbidity index score, ICU admission, and *C tropicalis* as causative pathogen were independent baseline predictors of candidaemia mortality. Additionally, candidaemia caused by rare *C tropicalis*, and candidaemia caused by emerging or rare *Candida* spp, particularly *C kefyr, C guilliermondii*, and *C auris*, were also significant baseline predictors in the univariable models. An increase of species other than *C albicans*[26] and the emergence of new resistant species, including but not limited to *C auris* and fluconazole-resistant *C parapsilosis*,[27,28] could manifest as major risk factors applicable to larger proportions of patients with candidaemia in the future.[9] Although obtaining an

infectious disease consultation has previously been shown to be protective against mortality with an HR of 0·81 (95% CI 0·73–0·91; p<0·0001) after propensity score weighting,[10] our study found that consultation by an infectious diseases or microbiology expert was protective particularly against mortality within 1 day or 2 days after diagnosis, even after adjusting for baseline risk factors (adjusted HR 0·58 [95% CI 0·44–0·70]; p<0·0001). Although this result suggests the value of early consultation, it might have been confounded by the fact that some patients had died before they could receive consultation. When patients survived longer than 3 days after diagnosis, doing a consultation with an infectious diseases or microbiology expert did not translate to survival benefit (adjusted HR 0·72 [95% CI 0·51–1·03]; p=0·071).

Finally, our study showed that initial echinocandin treatment was associated with increased overall survival, but also increased duration of hospital stay: hospital stay was extended only to complete parenteral antifungal treatment in patients for whom step-down therapy to fluconazole[29] was not an option (100/621 [16%]). Importantly, in the near future, earlier hospital discharge for these patients might be favoured by an enriched antifungal pipeline,[30] which includes rezafungin, an echinocandin with improved penetration into the peritoneal fluid and extended half-life allowing a once-per-week administration, and ibrexafungerp, a novel antifungal class with an echinocandin-like mechanism of action and excellent oral bioavailability.[31]

Despite its large size (64 institutions in 20 European countries), this multicentre multinational study comes with some limitations. Not all requested data were available for all patients, and the presented data reflect a real-life scenario with no predefined fungal diagnostic strategies or treatment protocols, potentially affecting the ability to make an early diagnosis and thereby clinical outcomes. Additionally, EQUAL *Candida* scores might be higher in long-term survivors than in patients with an early fatal outcome because the provision of some of the diagnostic and treatment recommendations takes time and might not be available for patients with an early fatal outcome. We therefore adjusted our analyses to exclude all patients with a fatal outcome within the first 7 days after diagnosis, but we cannot rule out that, even after this adjustment, survival duration might remain a confounder, particularly for length of therapy. However, when the analysis was limited to include only patients who survived at least 14 days after diagnosis, survival was longer for patients receiving treatment for 14 days or more (239/306 [78%]) than for patients who were treated for less than 14 days (67/102 [66%]), indicating that increased treatment duration might be associated with longer-term survival. Importantly, availability of fungal diagnostics, provision of consultations by infectious diseases and microbiology experts, and access to antifungal drugs vary globally, with more limited access in low-income and middle-income countries than in high-income countries, limiting generalisability of our results to other settings.[32] Although the geographical distribution of our sample is reflective of Europe, including its laboratory capacities,[33] the settings with better access to diagnostics and antifungals were probably over-represented.

In conclusion, we found that across Europe overall 90-day mortality of candidaemia remains high at 43%. Importantly, our study indicates that adherence to clinical guideline recommendations could increase survival. We also observed that current first-line candidaemia treatments with echinocandins are associated not only with increased overall survival, but also with longer duration of hospital stay, including being a direct cause of extended hospital stay, due to the fact that no oral alternatives to azoles are available. This limitation could be overcome by new antifungals with oral bioavailability or longer half-lives, which could allow for earlier discharge and outpatient therapy, reducing costs and risks associated with hospital stay (eg, nosocomial infection).

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Contributors
MH, PK, OAC, JS-G, MCA, J-PG, SA-A, and TB made substantial contributions to the study concept and design. MH, OAC, and JS-G accessed and verified all data. MH and ME made substantial contributions to the statistical analysis and interpretation of data. MH, ME, JS-G, PK, 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. MH, PK, OAC, and JS-G had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
MH reports grants and research funding from Astellas Pharma, Gilead Sciences, MSD, Pfizer, Euroimmun, F2G, Pulmocide, IMMY, and Mundipharma, outside of the submitted work, as well as Scynexis. JS-G has received lecture honoraria from Gilead Sciences and Pfizer, outside of the submitted work. J-PG has received lecture honoraria from Gilead Sciences, Mundipharma, and Pfizer, outside of the submitted work. TB reports receipt of speaker fees, advisory board fees, and research fellowship funding from Gilead Sciences; research grants from Pfizer and MSD; and advisory board fees from Mundipharma, all outside of the submitted work. SA-A reports research grants from Cidara Therapeutics, lecture honoraria from Gilead Sciences, and travel grants from Astellas Pharma, all outside of the submitted work. AA-I has received honoraria for educational talks on behalf of Gilead Sciences and Pfizer, outside of the submitted work. NKl was a Speaker for Astellas Pharma, Gilead Sciences, Merck/MSD, and Pfizer; and an Adviser for Gilead Sciences, Merck/MSD, and Pfizer, all outside of the submitted work. KL received consultancy fees from MRM Health, MSD, and Gilead Sciences; speaker fees from FUJIFILM Wako, Pfizer, and Gilead Sciences; and a service fee from Thermo Fisher Scientific and TECOmedical, all outside of the submitted work. NKh is a member of the Gilead Sciences, MSD, and Pfizer advisory boards for invasive fungal infections, and Chair of Pulmocide's Data and Safety

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Data sharing

Case-level deidentified participant data and data dictionary will be available from the corresponding author (hoeniglmartin@gmail.com) 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 subanalyses of the dataset.

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