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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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1 **Guideline adherence predicts Survival of Candidemia in Europe: Results from**
2 **the ECMM *Candida* III multinational European Observational Cohort Study**

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264 **Abstract**

265

266 **Background**

267 The European Confederation of Medical Mycology (ECMM) collected data on epidemiology, risk
268 factors, treatment, and outcomes of culture proven candidemia across Europe in order to assess
269 how adherence to guideline recommendations correlate with outcomes.

270 **Methods**

271 Each participating hospital (number of eligible hospitals per country determined by population
272 size) included the first ~10 culture proven candidemia cases after 01-July-2018 and entered data
273 into the ECMM *Candida* III database on the FungiScope[®] platform. EQUAL *Candida* Scores
274 reflecting adherence to recommendations of the European Society of Clinical Microbiology and
275 Infectious Diseases (ESCMID) and Infectious Disease Society of America (IDSA) Guidelines were
276 assessed.

277 **Findings**

278 A total of 632 candidemia cases were included from 64 institutions in 20 European countries.
279 Overall 90-day mortality was 42.9% (265/617),, and older age, intensive care unit (ICU) admission,
280 higher Charlson Comorbidity Index and *Candida tropicalis* as causative pathogen were
281 independent baseline predictors of mortality in Cox regression analysis. EQUAL *Candida* Score
282 remained an independent predictor of mortality in the multivariable Cox regression analyses after
283 adjusting for the baseline predictors, even after restricted to cases who survived >7 days after
284 diagnosis (adjusted hazard ratios between 1.075 and 1.089 per 1 point decrease; p<0.0001). Median
285 duration of hospitalization was 16 days following diagnosis of candidemia and was prolonged

286 specifically for completion of parenteral therapy in 16% (100/621) of patients. Initial echinocandin
287 treatment was associated with lower overall mortality and also with longer duration of
288 hospitalization among survivors.

289 **Interpretation**

290 While overall mortality of candidemia was high, our study indicates that adherence to clinical
291 guideline recommendations, reflected by higher EQUAL *Candida* Scores, may increase survival.
292 Echinocandin treatment was associated with increased overall survival, but also longer duration of
293 hospitalization (hospitalization was prolonged only for completing treatment in 16%).

294

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308 **Research in context**

309 **Evidence before this study:** Despite advances in management including improved central venous
310 catheter management, candidemia remains associated with high mortality. International guidelines
311 for the diagnosis and management of candidemia were created with the ultimate goal of improving
312 patient outcomes and survival, but whether this is actually the result (e.g. also for first-line
313 treatment with echinocandins) has not been comprehensively evaluated. In 2018, the European
314 Confederation of Medical Mycology (ECMM) introduced the EQUAL *Candida* score (ECMM
315 scores to measure quality of disease management) allowing for quantification of guideline
316 adherence as a surrogate marker for the quality of diagnostic and therapeutic management. The
317 score was derived from recommendations of the two most prominent guidelines for candidemia,
318 the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline, and
319 the Infectious Diseases Society of America (IDSA) guideline. While this score has been shown to
320 be predictive of mortality in subgroups of candidemia cases in a few small single centre studies,
321 larger multicentre evaluations on whether the score and whether following each guideline
322 recommendation (=score variable) separately correlates with clinical outcomes was lacking and
323 not found in the Pub Med database.

324 **Added value of this study:** This study collected data on epidemiology, risk factors, treatment, and
325 outcomes of culture proven candidemia from 64 institutions in 20 European countries in order to
326 assess how adherence to guideline recommendations correlate with outcomes. Patient enrollment
327 per country and number of participating centers were stratified by population size. Overall 90-
328 mortality was 42.9%, and older age, intensive care unit (ICU) admission, higher Charlson
329 Comorbidity Index and *Candida tropicalis* as causative pathogen, as well as emerging and rare
330 *Candida* spp. (including *C. auris*) as causative pathogens were independent predictors of mortality
331 in Cox regression analyses. Lower EQUAL *Candida* Scores, reflecting less adherence to guideline

332 recommendations, remained an independent predictor of mortality in the multivariable Cox
333 regression analyses after adjusting for age, ICU admission and rare *Candida spp.* (adjusted hazard
334 ratios between 1.075 and 1.089 per 1 point decrease; $p < 0.0001$). Absence of each
335 diagnostic/therapeutic measure (including absence of initial echinocandin treatment) was
336 accompanied by increased mortality compared to the overall cohort, emphasizing the importance
337 of every single variable in successful management. Initial echinocandin treatment was associated
338 with longer duration of hospitalization among survivors.

339 **Implications of all the available evidence:** While across Europe overall mortality of candidemia
340 in adults remains high at 43%, adherence to clinical guideline recommendations may increase
341 survival. Of note this was also shown for more controversial guideline recommendations, such as
342 performance of ophthalmoscopy or echocardiography. Echinocandins may not only be associated
343 with increased overall survival, but also longer duration of hospitalization, including directly
344 causing prolonged hospitalization in 1 out of 7 patients with candidemia, due to the fact that no
345 oral alternatives to azoles are available. This limitation could be overcome by new antifungals with
346 oral bioavailability or longer half-life's, which may allow for earlier discharge and outpatient
347 therapy, reducing costs and hospital stay associated risks (e.g., nosocomial infection).

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353 **Introduction**

354 Invasive candidiasis (IC) including candidemia remains the most frequent invasive fungal infection
355 in the hospital setting affecting males and females alike (1), with around 700,000 cases of IC
356 occurring globally per year (2), 7.07 episodes per 1,000 ICU admissions in Europe (3), and an
357 estimated overall pooled annual incidence rate of 3.88/100,000 population in Europe (4). Known
358 risk factors for developing candidemia/IC in the intensive care unit (ICU) include (abdominal)
359 surgery, total parenteral nutrition (TPN), renal replacement therapy, central venous catheter (CVC),
360 broad spectrum antibiotics, diabetes (5, 6), as well as neutropenia, solid organ transplantation,
361 significant liver, respiratory or cardiovascular disease, and intravenous drug use (7).

362 Despite advances in management including first-line treatment with echinocandins and improved
363 CVC management, IC remains associated with high mortality (8). Of approximately 79 cases
364 occurring in Europe per day, an estimated 29 (37%) patients are expected to have fatal outcome at
365 day 30 (4). Predictors of mortality in candidemia include older age, primary source (i.e., not CVC
366 related) and sepsis/septic shock (9) In contrast, early adequate antifungal treatment is efficacious
367 (9), as is consultation by an infectious diseases specialist with a hazard ratio of 0.81 (95% CI 0.73-
368 0.91; $p < 0.0001$) after propensity score weighting (10).

369 International guidelines for the diagnosis and management of candidemia were created with the
370 ultimate goal of improving patient outcomes and survival, but whether this is actually the result
371 has been rarely evaluated. In 2018, the European Confederation of Medical Mycology (ECMM)
372 introduced the EQUAL scores (ECMM scores to measure quality of disease management) allowing
373 for quantification of guideline adherence as a surrogate marker for the quality of diagnostic and
374 therapeutic management; the EQUAL *Candida* score was the first score published (11). The score
375 was derived from recommendations of the two most prominent guidelines for candidemia, the

376 European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline (12),
377 and the Infectious Diseases Society of America (IDSA) guideline (13).

378 In recent single centre studies, the EQUAL candida score (11) was shown to predict mortality in
379 CVC-associated candidemia in general (14), and *C. tropicalis* candidemia (15), however, larger
380 multicentre evaluations are lacking.

381 Therefore the ECMM (16) designed and conducted the *CANDIDA* III study - its third pan European
382 multicenter study over the past 25 years (17, 18) - to collect data on epidemiology, risk factors,
383 treatment, and outcomes of culture proven candidemia across Europe, as well as to assess how
384 adherence to guideline recommendations for managing candidemia correlates with outcomes.

385

386 **Methods**

387 **Study design and participating centers**

388 For this European multicenter observational cohort study, each participating hospital included the
389 first ~10 blood culture proven adult candidemia cases occurring consecutively after July 1st, 2018.
390 Candidemia was, defined according to ESCMID criteria (19). The primary objective was to assess
391 how adherence to guideline recommendations correlate with outcomes. Secondary objectives
392 included to assess epidemiology, risk factors, treatment, and outcome of candidemia across Europe.

393 To give a realistic picture of candidemia in Europe, the target number of eligible hospitals per
394 country was determined by population size. As general guidance, up to a maximum of eight
395 hospitals were allowed for each of the six ECMM countries with populations >50 million (i.e.,
396 France, Germany, Italy, Russia, Turkey, and United Kingdom; mean population of these countries
397 is 82.5 million), up to a maximum of four hospitals for each ECMM countries with population >25
398 million and <50 million (i.e., Spain and Poland; mean population of these countries 42 million),
399 and up to two hospitals for each of the remaining 16 ECMM countries with population <25 million
400 (mean population 9.4 million) were invited to contribute. Hospitals were recruited by ECMM
401 council representatives of each participating country, or via the EPICOVIDEHA (20) and
402 FungiScope[®] networks (21) and among the ECMM Global Guidelines contributor and fellow
403 groups (16).

404 Between July 2018 and March 2022, participating centres entered data on patient demographics,
405 risk factors and characteristics, duration of hospitalization (maximum duration of follow-up 90
406 days), diagnostic procedures, causative *Candida* species, treatment characteristics including
407 antifungal treatment, whether hospital stay was prolonged only for completion of parenteral
408 antifungal treatment, and outcomes, into the ECMM *Candida* Registry - *CandiReg* – FungiScope[®]

409 (NCT 01731353), which was described previously (21, 22), on www.clinicalsurveys.net (EFS Fall
410 2018 Questback, Cologne, Germany).

411 **Statistical analysis and ethics**

412 All statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL,
413 USA) and R (version 4.3.1; www.r-project.org). Descriptive statistical analysis was performed for
414 most variables including distribution of *Candida* species and prolonged hospital stay for parenteral
415 antifungal treatment. EQUAL *Candida* Scores (11) reflecting adherence to recommendations of
416 ESCMID and IDSA Guidelines were assessed for every case that provided the prerequisite data in
417 for all of the EQUAL *Candida* Score variables. Data were summarized employing frequencies,
418 percentages, median or interquartile range as appropriate. Categorical data were tested using χ^2 or
419 Fisher's exact test if a cell value was under 5, and continuous variables were summarized using
420 median (interquartile range, IQR) and compared with Student's t-test / Mann-Whitney's U or
421 ANOVA / Kruskal-Wallis' H, depending on their non-/normal distribution. Two-sided $p < .05$ was
422 taken as cut-off for statistical significance.

423 Further analyses on EQUAL *Candida* Scores were restricted to cases who survived at least 7 days
424 after diagnosis (n=470), to exclude patients where earlier mortality may have precluded treating
425 physicians from implementing measures recommended in the guidelines, and thereby potentially
426 biasing our results towards lower scores in non-survivors. Scores were divided by the maximum
427 achievable score (19 for those without CVC and 22 for those with CVC) to calculate a proportion
428 of the achievable maximum for each case and compared between survivors and non-survivors. For
429 these EQUAL *Candida* score proportions, receiver operating characteristic (ROC) curve analyses
430 were performed and area under the curve (AUC) values were calculated. Optimal cutoff was
431 determined using Youdens index.

432

433 To investigate the association of baseline risk factors with survival, univariable and multivariable
434 Cox proportional hazard models (non-overlapping and non-mutually exclusive variables with
435 $p < 0.1$ included) were estimated for patients without missing data on duration of follow up, with
436 duration of follow up capped at day 180 ($n=597$). Causative *Candida* spp. was the only variable
437 that differed between the multivariable models; for one of these models, emerging *Candida* spp.
438 that were defined before(23) (i.e., *C. kefyr*, *C. guilliermondii*, *C. lusitaniae*, *C. dubliniensis*, *C.*
439 *famata*, *C. inconspicua*, *C. rugosa*, *C. norvegiensis*) were grouped together with *C. auris* into the
440 variable “*C. auris* and other emerging *Candida* spp.”), while the other model included *C. tropicalis*,
441 respectively. The proportionality of hazard assumption was evaluated by fitting an interaction
442 between a variable of interest and linear follow-up time. We used the Akaike Information Criterion
443 (AIC) to compare the relative quality of multivariable Cox models for baseline risk factors.

444 We then used a multivariable Cox proportional hazards model to measure the relative hazard for
445 death between different EQUAL *Candida* scores when adjusting for significant baseline prognostic
446 factors in patients who survived > 7 days and who had data on duration of follow up available
447 ($n=443$). Lastly, we estimated multivariable Cox models for each variable of the EQUAL *Candida*
448 score adjusted for significant baseline risk factors.

449 The proportional hazards assumption was tested using the Schoenfeld residuals test for the overall
450 model and individual covariates. The resultant model and all other Cox models did not significantly
451 violate the proportional hazards assumption for individual covariates or the global model. As
452 candidemia diagnosis was the starting point for follow-up and the primary effect of interest
453 (EQUAL *Candida* score) as well as all other covariates were established at baseline, immortal time
454 bias was not considered.

455 The study was performed in accordance with the ethical standards laid down in the 1964
456 Declaration of Helsinki and its later amendments. For the database, retrospective data entry, and
457 data analysis a central ethical approval was obtained at the University of Cologne, Germany (EK
458 17-485) that indicates that, generally, neither informed consent nor IRB approval individual to each
459 participating hospital would be required. Each participating hospital was required to obtain local
460 IRB confirmation or approval as deemed necessary by local regulations/authorities.

461

462 **Role of the funding source**

463 The sponsor of the study had no role in study design, data collection, data analysis, data
464 interpretation, or writing of the report. The corresponding authors had both full access to all the
465 data in the study and had final responsibility for the decision to submit for publication.

466 **Results**

467 A total of 632 patients with candidemia were included from 64 institutions in 20 European
468 countries (**Figure 1**). The study flow is depicted in **Figure 2**.

469 Patient demographic and clinical characteristics, risk factors, treatment, and outcomes as well as
470 distribution of *Candida* spp. in the overall study cohort, survivors and non-survivors are separately
471 displayed in detail in **Supplemental Table 1**. The majority (368/632; 58%) were male and median
472 age was 65 years (IQR 53-73). Underlying hematological/oncological malignancy (247/632; 39%),
473 ICU admission (234/632; 37%), and recent major surgery (164/632; 26%), were the most common
474 underlying conditions. Candidemia was classified as catheter related bloodstream infection
475 (CRBSI) in 21% (130/632) of cases. In about one third of cases (224/632; 35%) echocardiography
476 was reported, showing cardiac involvement in 11% (25/224) of those examined. Eye exam was
477 reported in 27% (169/632) of cases showing ocular involvement in 11% (19/169) of those
478 examined. Overall mortality was 46.4% (286/617); in 37% of those (77/209), investigators
479 attributed death to candidemia; 30-day mortality was 37.6% (232/617), 90-day mortality 42.9%
480 (265/617), 180-day mortality 45.1% (278/617). Median duration of hospitalization was 15 days
481 (IQR 4-30 days) after the diagnosis of candidemia. The vast majority (502/620; 81%) received
482 treatment consultation by an infectious diseases or microbiology expert and echinocandins were
483 the first line antifungal treatment in 56% (353/632) of cases. Initial echinocandin treatment was
484 associated with longer duration of hospitalization among survivors receiving echinocandins versus
485 other antifungals (median 24 days, IQR 15-40 days vs. median 16 days, IQR 7-33 days; $p < 0.0001$).
486 In those in whom candidemia was treated for at least 14 days, 78% (239/306) survived, compared
487 to 66% (67/102) in those treated for less than 14 days ($p = 0.01$), but who survived beyond day 14
488 after diagnosis. Hospital stay was prolonged specifically for the purpose of completing parenteral

489 antifungal treatment in 16% (100/621) by a median of 2 days. *Candida albicans* was the most
490 common causative pathogen (46%; 287/621) followed by *C. glabrata* 21% (133/621), *C.*
491 *parapsilosis* 13% (83/621), *C. tropicalis* 7% (46/621), *C. krusei* and *C. auris* (each 3%; 16/621).

492 Informed by univariable Cox regression modelling (**Table 1**), we evaluated two multivariable Cox
493 regression models consisting of three non-overlapping non-mutually exclusive baseline predictors
494 of mortality older age, Charlson Comorbidity Index (CCI) excluding age, ICU admission, and –
495 for model #1 – also *C. tropicalis* as causative pathogen, with the latter being replaced by *C. auris*
496 plus emerging *Candida* spp. for model #2. Informed by AIC values (**Table 1**) we decided to use
497 the baseline parameters of model #1 for further adjustments of the remaining risk models.

498 Initial echinocandin treatment was associated with lower overall mortality (42%, 148/353) versus
499 those without initial echinocandin therapy (53%, 126/236; $p=0.007$), also when adjusted for
500 baseline risk factors [adjusted hazard ratio (aHR) 0.56, 95% confidence interval (CI) 0.44 – 0.72;
501 $p<0.0001$].

502 While consultation by an infectious disease (ID) physician or microbiologist was associated with
503 better survival in the overall cohort (aHR for consultation 0.58, 95%CI 0.44 – 0.7; $p=0.0001$), this
504 effect started vanishing once patients who had a fatal outcome within two days of diagnosis of
505 candidemia were excluded (aHR 0.71, 95%CI 0.51 – 0.99; $p=0.042$), with no significant
506 differences in patients who survived for three days or longer, driven in part by the fact that the
507 majority of those patients (421/509, 83%) received consultation.

508 The EQUAL *Candida* Score was available for 589 cases with candidemia. Scores correlated
509 significantly with duration of hospitalization ($r= 0.442$; $p<0.0001$) and – even after exclusion of
510 patients hospitalized ≤ 7 days ($n=119$; EQUAL *Candida* actual/max score proportion median 0.42,
511 IQR 0.27-0.59 in those hospitalized 7 days or shorter *versus* 0.77, IQR 0.63-0.86 in those

512 hospitalized > 7 days; $p < 0.0001$) - were significantly higher in patients who survived versus those
513 who died ($p < 0.0001$). In those hospitalized >7 days there was no correlation between duration of
514 hospitalization and EQUAL *Candida* actual/max score proportion (Pearson's $r = 0.054$; $p = 0.26$).

515 **Supplemental Figure 1** shows EQUAL *Candida* Scores, Score variables and demographic data
516 in survivors and non-survivors who survived >7 days after candidemia diagnosis. ROC curve
517 analysis revealed an AUC of 0.718 for the proportion of the maximum EQUAL *Candida* score for
518 predicting overall mortality, with an optimal cut-off of 78.1% of the max score (which translates
519 to >14 in those without CVC and >16 in those with CVC). Adjusted HR per point increase in
520 EQUAL *Candida* scores for patients with CVCs and those without are displayed in **Figure 3**.

521 Results of the multivariable Cox regression model for risk of mortality with percent decrease in
522 EQUAL *Candida* score in patients who survived longer than 7 days are displayed in **Table 2**. After
523 adjustment for baseline variables (model #1), a decrease in one score point translated to an aHR of
524 1.075 (95% CI 1.043 - 1.109) in CVC carriers and an aHR of 1.089 (95% CI 1.051 - 1.129) in
525 those without a CVC. ECMM *Candida* scores below the calculated Youden cut-off were associated
526 with an aHR of 3.53 (95% CI 2.01 - 5.98; all $p < 0.0001$).

527 **Table 3** outlines overall mortality rates for each variable of the EQUAL *Candida* score if absent,
528 followed by results of multivariable Cox regression model evaluating each score variable if absent
529 adjusted for significant baseline risk factors. Absence of each diagnostic/therapeutic measure was
530 associated with higher mortality (50.5% - 70.5%) compared to the mortality in the overall cohort
531 (46.4%; 286/617). In the multivariable Cox model for patients who survived > 7 days and adjusted
532 for the baseline predictors, absence of ophthalmoscopy, echocardiography, treatment of ≥ 14 days
533 after first negative blood culture, and also absence of stepdown to fluconazole therapy were all
534 significant predictors of mortality with aHRs between 1.71 and 3.64.

536 **Discussion**

537 We performed a multicenter observational study of candidemia, involving 64 hospitals from 20
538 countries across Europe. Our main finding is that overall 90-day mortality of candidemia remains
539 high at 42.9% (265/617). However, adherence to clinical guideline recommendations, as reflected
540 by higher EQUAL *Candida* scores, was a strong independent predictor of survival. Other findings
541 included that candidemia caused by rare *Candida* spp. may be a relevant independent baseline
542 predictor of survival, in addition to known predictors such as older age and ICU admission. In
543 terms of treatment, initial echinocandin treatment was associated with increased overall survival,
544 but also with longer duration of hospitalization.

545 The overall mortality of 46% found in this study (90-day mortality 43%), of which 37% was
546 directly attributable to candidemia according to investigators, confirms that candidemia is still a
547 major threat to patients and a medical emergency. The rate is as high or even slightly higher than
548 rates reported earlier, such as the overall mortality of 43% in Germany, with attributable mortality
549 of 26% (24), and previous ECMM European cohort studies where 37.9% mortality was observed
550 between 1997-1999 (that study included neonates and children)(17), and 38.8% observed in
551 surgical ICU patients between 2006-2008 (18). Also, from the United States a 90-day crude
552 mortality of 42.4% for *Candida* BSI cases were reported, which was more than twice as high than
553 the 17.1% observed among matched controls. Following propensity score-matching, the
554 attributable risk difference for 90-day mortality was 28.4% with hazard ratio (HR) of 2.12 (95%
555 CI, 1.98-2.25, $p < 0.001$) in that study (25).

556 Our study identified adherence to international guideline recommendations as a major protective
557 factor. With every point decrease of the EQUAL *Candida* score, reflecting a decrease in adherence
558 to guideline recommendations, hazards increased by 8.9% for patients with CVC and 7.5% for
559 patients without CVC, making survival less likely. Adjustment for the baseline risk factors age, ICU

560 admission, Charlson comorbidity index and *Candida tropicalis* did not change that outcome. In
561 addition, absence of each diagnostic/therapeutic measure was accompanied by increased mortality
562 compared to the overall cohort, emphasizing the importance of every single variable in successful
563 management.

564 Many known risk factors for *Candida* infections in the ICU such as previous surgery, TPN, CVC,
565 broad spectrum antibiotics, diabetes (5), neutropenia, or solid organ transplantation (7) were
566 present in relevant proportions of our study population. Age, severe hepatic failure, organ failure
567 at the onset of IC, and septic shock (OR 2.12, 95% CI 1.24-3.63, p=0.006) were previously
568 associated with 30-day mortality in candidemia cases (3). In this study, not only did older age,
569 higher Charlson comorbidity index and ICU admission stand out as independent baseline predictors
570 of candidemia mortality, but so did candidemia caused by rare *Candida tropicalis*, and – to a lesser
571 extend – also candidemia causes by emerging or rare *Candida* spp., particularly *C. kefyr* and
572 *C. guilliermondii* but also *C. auris*. With an increase of species other than *Candida albicans* (26)
573 and the emergence of new resistant species, including but not limited to *C. auris* and fluconazole
574 resistant *C. parapsilosis* (27, 28) this may manifest as major risk factors applicable to larger
575 proportions of candidemia patients in the future (9). While ID consultation was previously shown
576 protective against mortality with a hazard ratio of 0.81 (95% CI 0.73-0.91; p<0.0001) after
577 propensity score weighting (10), consultation by an ID or microbiology expert was protective in
578 our study only for avoiding early mortality even after adjusting for baseline risk factors (aHR 0.58,
579 95% CI 0.44-0.70; p<0.001), a result that may outline the value of early consultation, but also be
580 confounded by the fact that some patients may die before they can receive a consultation. Once
581 patients survived 3 days or longer after diagnosis, ID/microbiology expert consultation did not
582 translate to a significant survival benefit.

583 Finally, our study showed that initial echinocandin treatment was associated with increased overall
584 survival, but also longer duration of hospitalization, as hospitalization was prolonged only for
585 completing parenteral antifungal treatment in 16% (i.e. patients where step-down to fluconazole
586 (29) was not an option). Importantly, this may change in the near future, with a loaded antifungal
587 pipeline (30), that includes rezafungin, an echinocandin with improved penetration into the
588 peritoneal fluid and prolonged half-life allowing once weekly injection, and ibrexafungerp, a novel
589 antifungal class with an echinocandin like mechanism of action and excellent oral bioavailability
590 (31), both of may facilitate earlier hospital discharge of those patients in whom stepping down to
591 fluconazole is not an option.

592 Despite its large size (64 institutions in 20 European countries) this multicentre multinational study
593 comes along with some limitations. Not all requested data were available for all patients, and the
594 presented data reflect a real-life scenario with no predefined fungal diagnostic strategies or
595 treatment protocols, potentially affecting the ability to make an early diagnosis and outcomes. In
596 addition, EQUAL *Candida* scores may be higher in long-term survivors versus those with an early
597 fatal outcome, given the fact that some of the diagnostic and treatment recommendations take time
598 and may not be available in patients with an early fatal outcome. We therefore adjusted our analyses
599 to exclude all patients with a fatal outcome within the first 7 days after diagnosis but cannot rule
600 out that even after this adjustment survival duration may remain a confounder, particularly for
601 length of therapy. However, the fact that when the analysis was limited to include only patients
602 surviving more than 14 days, survival remained longer for patients receiving treatment for >14
603 days [78% (239/306) versus 66% (67/102)], indicates that treatment duration may have an impact
604 on longer term survival. Importantly, availability of fungal diagnostics, ID/microbiology
605 consultations and also access to antifungal drugs varies across the world with more limited access
606 in low and middle income countries, limiting generalizability of our results to other settings (32).

607 While the geographical distribution of our sample is reflective of Europe including its laboratory
608 capacities (33), it is still likely that those settings with better access to diagnostics and antifungals
609 are overrepresented.

610 In conclusion, we found that across Europe overall 90-day mortality of candidemia remains high
611 at 43%. Importantly, our study indicates that adherence to clinical guideline recommendations may
612 increase survival. Lastly, current first line candidemia treatments with echinocandins are not only
613 associated with increased overall survival, but also longer duration of hospitalization, including
614 directly causing prolonged hospitalization in 1 out of 7 patients with candidemia, due to the fact
615 that no oral alternatives to azoles are available. This limitation could be overcome by new
616 antifungals with oral bioavailability or longer half-life, which may allow for earlier discharge and
617 outpatient therapy, reducing costs and hospital stay associated risks (e.g., nosocomial infection).

618 Author contributions:

619 Substantial contribution to study concept and design: MH, PK, OC, JSG, JK, MAr, JPG, SAA, TB.

620 Substantial contribution to the acquisition of data for the work: All authors.

621 Accessed and verified all data: MH, OH and JSG

622 Substantial contribution to the statistical analysis or interpretation of data: MH, ME.

623 Drafting the manuscript: MH, ME, JSG, PK, OC.

624 Critical review of the manuscript and final approval for publication: all authors

625

626 Conflicts of Interest

627 MH reports grants and research funding from Astellas, Gilead, MSD, Pfizer, Euroimmun, F2G, Pulmocide,
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629 JSG has received lecture honoraria from Gilead and Pfizer, outside of the submitted work.

630 JPG has received lecture honoraria from Gilead, MundiPharma and Pfizer, outside of the submitted work.

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632 sciences, research grants from Pfizer and MSD and advisory Board fees from Mundipharma.

633 SAA reports research grant from Cidara, lecture honoraria from Gilead, and travel grant from Astellas.

634 AA-I has received honoraria for educational talks of behalf of Gilead and Pfizer, outside of the submitted
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648 **VAA reports research funding from Pfizer**

649 BD reports receipt of speaker fees, advisory Board fees from Gilead sciences, advisory Board fees from
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651 FD declares personal fees from Gilead, Pfizer, outside the submitted work.

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654 LD reports lecture honoraria from Pfizer, MSD and Teva, outside the submitted work

655 Outside the submitted work, DRG reports investigator-initiated grants from Pfizer, Shionogi, and Gilead
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674 BW reports personal fees from MSD, Pfizer, Gilead, Shionogi, Euroimmun, Immy, CapeCod and grants to
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712 **Data sharing statement:**

713 Case level data will be available from the authors by request.

714 **Table 1.** Univariable and multivariable Cox regression model for predictors of mortality in candidemia
 715 (n=597)

Variable	Univariable hazard ratio	95% CI	p-value
Demographics			
Male, Sex	1.19	0.93 – 1.52	0.160
Age	1.37	1.18 – 1.60	<0.0001
Coexisting conditions			
BMI \geq 30	1.01	0.74 - 1.39	0.946
SOT	0.61	0.25 – 1.49	0.278
Haematological/Oncological malignancy	1.13	0.89 – 1.44	0.323
Neutropenia (<500/microL)	1.06	0.75 – 1.50	0.754
Major surgery including abdominal surgery	0.95	0.72 – 1.25	0.704
Diabetes mellitus (Type I or II)	0.99	0.75 – 1.31	0.930
Clinical factors			
ICU admission	1.71	1.34 – 2.17	<0.0001
CRBSI	0.89	0.66 – 1.19	0.426
Prosthetic heart valve	1.00	0.71 – 1.42	0.981
Mechanical ventilation	1.32	1.02 – 1.71	0.033
ECMO	1.32	0.65 – 2.670	0.441
TPN	0.83	0.62 – 1.11	0.212
Charlson Comorbidity Index	1.09	1.05 – 1.13	<0.0001
Charlson Comorbidity Index (excluding age)	1.07	1.03 – 1.11	0.0019
Candida spp. (n)			
<i>C. albicans</i> (274)	0.92	0.72 – 1.16	0.475

<i>C. glabrata</i> (127)	0.88	0.65 – 1.18	0.385
<i>C. parapsilosis</i> (80)	0.98	0.70 – 1.38	0.916
<i>C. tropicalis</i> (44)	1.78	1.16 - 2.57	0.0071
<i>C. krusei</i> (12)	0.84	0.31 – 2.25	0.726
<i>C. auris</i> (15)	1.39	0.69 – 2.81	0.357
<i>C. dubliniensis</i> (9)	0.69	0.22 – 2.15	0.519
<i>C. guilliermondii</i> (6)	3.64	1.62 – 8.18	0.0018
<i>C. lusitaniae</i> (5)	1.23	0.39 – 3.84	0.719
<i>C. kefyr</i> (5)	3.27	1.22 – 8.80	0.019
Other <i>Candida</i> Species (9)*	0.75	0.24 – 2.33	0.617
<i>C. auris</i> and other emerging <i>Candida</i> species (46)§	1.54	1.03 - 2.30	0.034
<i>C. auris</i> and rare <i>Candida</i> species (49)§	1.39	0.93 - 2.09	0.108
Clinical course (i.e., not baseline variables)			
Mixed fungal infections	2.45	0.57-10.5	0.226
Initial Echinocandin treatment	0.55	0.44 - 0.70	<0.0001
Infection consultation (ID or microbiology)	0.56	0.43 - 0.74	<0.0001
Model #1 (AIC=3172)			
Variables	Multivariable hazard ratio	95% CI	p-value
Age	1.34	1.15 – 1.57	0.0002
ICU	1.83	1.44 – 2.33	<0.0001
Charlson Comorbidity Index (excluding Age)	1.07	1.02 – 1.12	0.0035

<i>C. tropicalis</i>	1.71	1.15 – 2.55	0.0085
Model #2 (AIC = 3175)	Multivariable hazard ratio	95% CI	p-value
Variables			
Age	1.39	1.18 – 1.63	<0.0001
ICU	1.77	1.39 – 2.25	<0.0001
<i>C. auris</i> and other emerging <i>Candida</i> species §	1.50	0.99 – 2.26	0.056
Charlson Comorbidity Index (excluding age)	1.06	1.02 – 1.11	0.0056
<p>Abbreviations: <i>AIC</i> = Akaike Information Criterion; <i>BMI</i> = body mass index; <i>CRBSI</i> = catheter related bloodstream infection.; <i>ECMO</i>= extracorporeal membrane oxygenation; <i>ICU</i> = intensive care unit; <i>ID</i> = infectious diseases; <i>SOT</i> = solid organ transplant; <i>TPN</i> = total parenteral nutrition</p> <p>* Others include: <i>Candida norvegensis</i> (n=1), <i>Candida digboensis</i> (n=1), <i>Candida rugosa</i> (n=3), <i>Candida pelliculosa</i> (n=2), <i>Candida inconspicua</i> (n=2; one coinfecting with <i>C. norvegensis</i>), and <i>Candida famata</i> (n=1)</p> <p>§ <i>C. auris</i> and <i>C. kefyr</i>, <i>C. guilliermondii</i>, <i>C. lusitaniae</i>, <i>C. dubliniensis</i>, <i>C. famata</i>, <i>C. inconspicua</i>, <i>C. rugosa</i>, <i>C. norvegensis</i>.</p> <p>§ <i>C. auris</i> and all other <i>Candida</i> spp. with 10 or fewer isolates.</p>			

717 **Table 2.** Multivariable cox regression (adjusted for age, ICU, Charlson Comorbidity Index (excluding age),
 718 *Candida tropicalis*) model for risk of mortality with percent decrease in EQUAL *Candida* score in patients
 719 who survived longer than 7 days (n= 443)

Variable	Multivariable hazard ratio	95% CI	p-value
EQUAL <i>Candida</i> score risk per % of actual/max score proportion decrease	1.016	1.009 – 1.023	<0.0001
EQUAL <i>Candida</i> score risk per 10% of actual/max score proportion decrease	1.175	1.099 – 1.257	<0.0001
* Risk per decrease in point <i>Candida</i> score for CVC carriers	1.075	1.043 - 1.109	<0.0001
Risk per decrease in point <i>Candida</i> score for patients without CVC	1.089	1.051 – 1.129	<0.0001
°EQUAL <i>Candida</i> score ≤78.1% of max Score	3.53	2.01 - 5.98 –	<0.0001
Risk reduction comparing maximum and minimum <i>Candida</i> score	0.20	0.10 – 0.39	<0.0001
Table explanation:			
* With CVC max <i>Candida</i> score = 22 points which refers to 4.5% per point Without CVC max <i>Candida</i> score = 19 points which refers to 5.3% per point			
° Multivariable hazard ratio for calculated threshold with max. sensitivity/specificity for prediction of death			
Abbreviation: CVC = central venous catheter			

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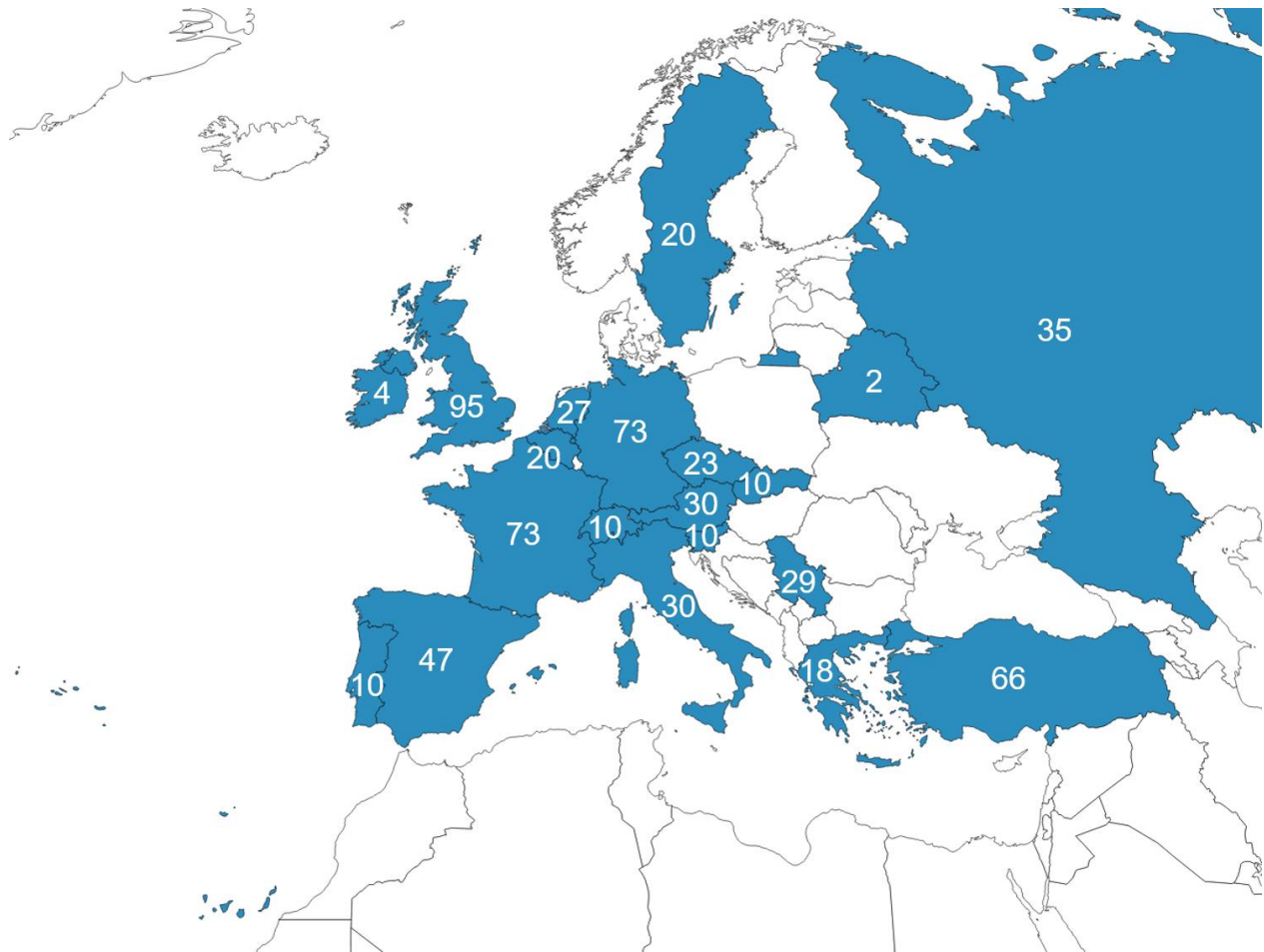
721 **Table 3.** Absolute mortality rates for EQUAL score variables if absent, as well as multivariable Cox
 722 regression models [each variable adjusted for age, ICU, Charlson comorbidity index (excluding age),
 723 *Candida tropicalis*] for score variables for prediction of mortality in patients with invasive candidiasis
 724 who survived longer than seven days (n= 443)

	Absolute mortality rates		
Absence of Diagnostic measures			
Initial blood cultures of 40mL	58.2% (32/55)		
Species identification	58.1% (25/43)		
Susceptibility testing	60.0% (53/89)		
Ophthalmoscopy	58.6% (224/382)		
Echocardiography	56.6% (189/334)		
Absence of Treatment measures			
Start echinocandin treatment	53.0% (132/249)		
Stepdown to fluconazole	55.2% (229/415)		
Treatment for 14d after first BC neg.	70.5% (196/278)		
CVC removal \leq 24h*	50.5% (194/384)		
	Multivariable hazard ratio	95% CI	p-value
Absence of Diagnostic measures			
Initial blood cultures of 40 mL	1.26	0.69 - 2.30	0.455
Species identification	1.46	0.76 – 2.82	0.302
Susceptibility testing	1.40	0.86 - 2.29	0.260
Ophthalmoscopy	2.19	1.55 – 3.11	<0.0001
Echocardiography	1.77	1.27 - 2.46	0.0006
Follow up BC until negative	1.28	0.91 - 1.80	0.159
Absence of Treatment measures			
Start echinocandin treatment	1.23	0.874 – 1.72	0.260

Stepdown to fluconazole	1.71	1.17 – 2.50	0.0058
Treatment for 14d after first BC neg.	3.64	2.62 – 5.06	<0.0001
CVC removal \leq 24h*	1.41	0.96 – 2.05	0.078
CVC removal > 24h <72h	1.21	0.77 – 1.90	0.417
Abbreviations: BC, blood culture; CVC, central venous catheter.			
*CVC carriers only			

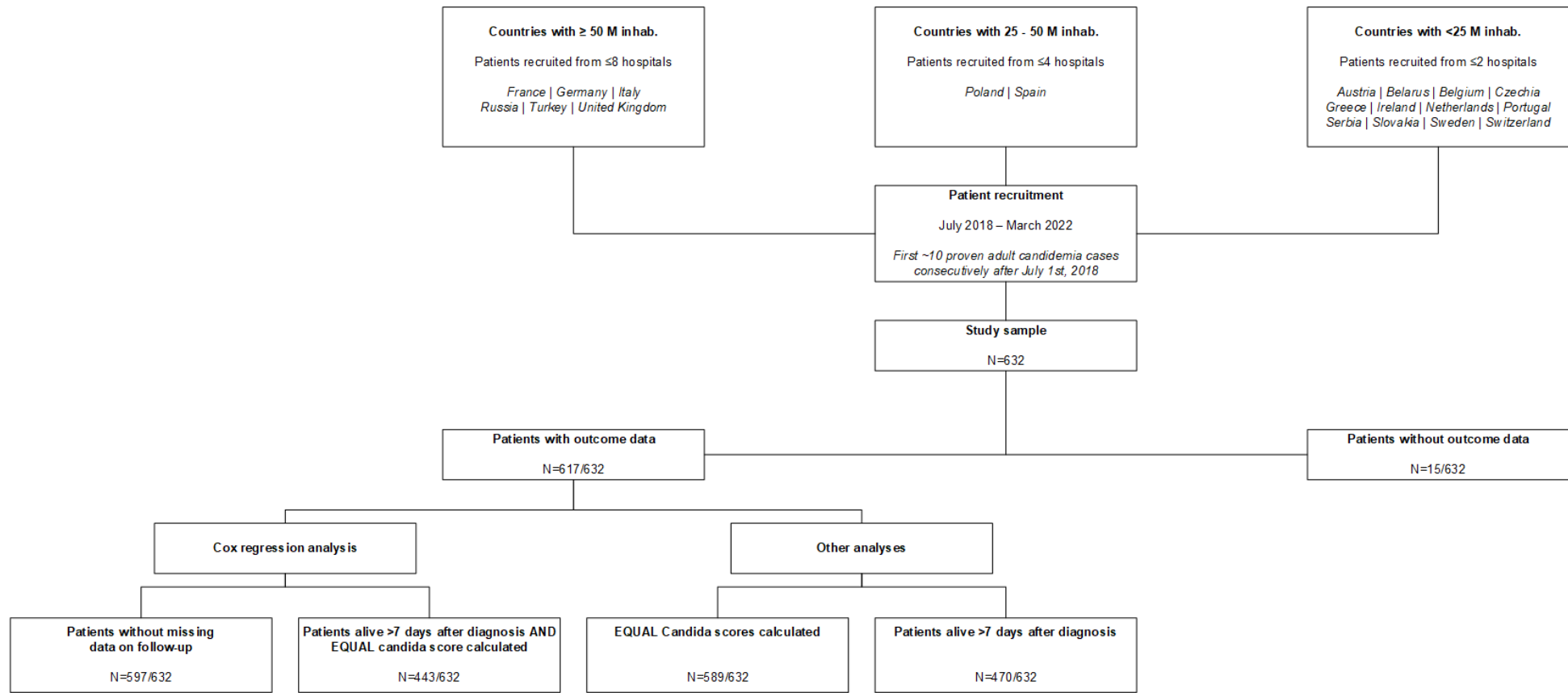
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726 **Figure 1.** Participating European countries and number of cases per country included.



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728 **Figure 2.** Study flowchart.



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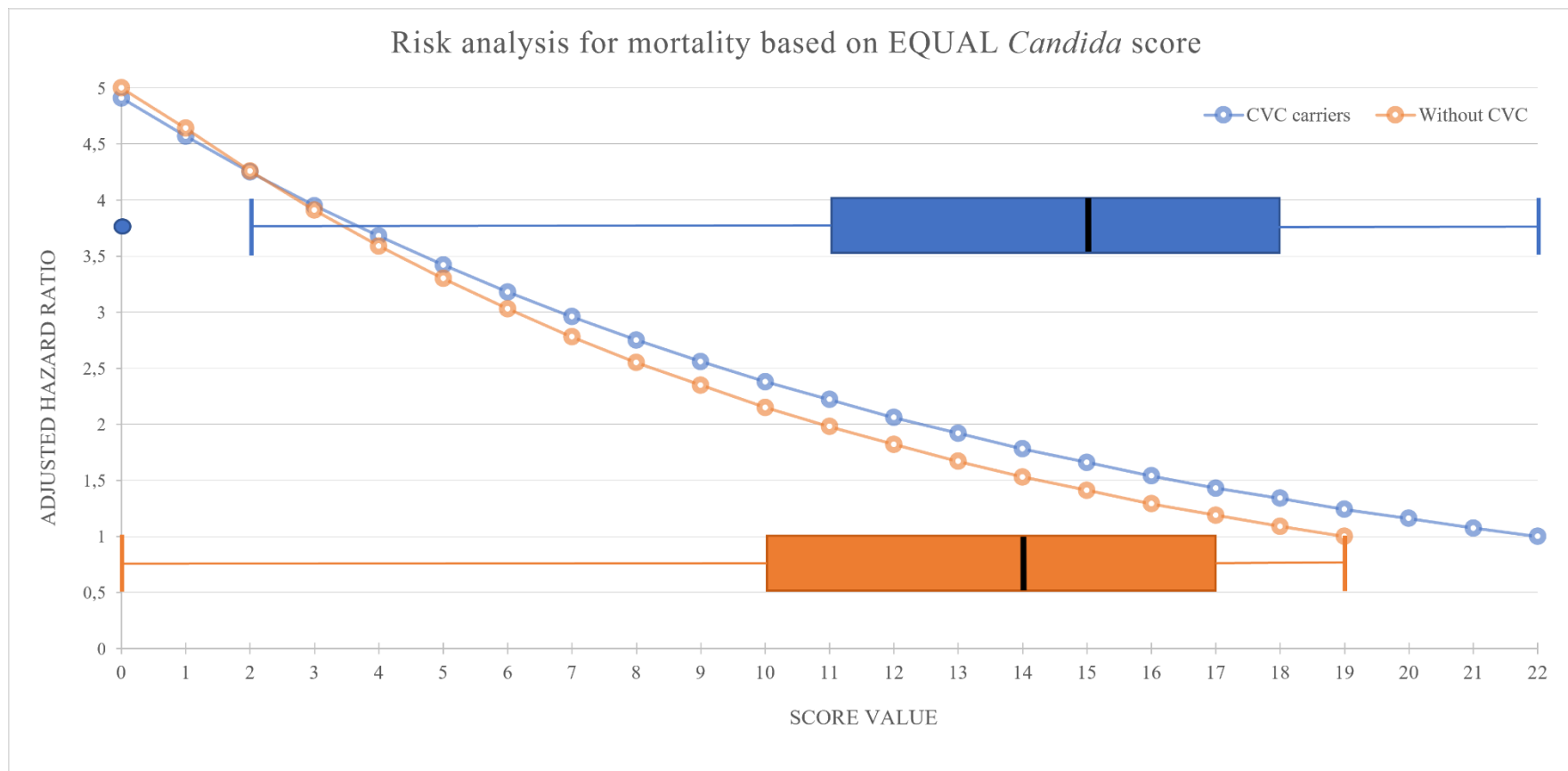
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735 **Figure 3.** Adjusted* hazard ratios per point increase in EQUAL Candida scores for patients with central venous catheters (CVCs, blue) and those
736 without (orange), as well as Boxplots



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739 Legend: *adjusted for age, ICU, Charlson comorbidity index (excluding age), and *Candida tropicalis*

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