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

Martin Hoenigl, Prof, [1,2,3#], Jon Salmanton-García, PhD,[4,5], Matthias Egger, MD,[1,3], Jean-Pierre Gangneux, Prof, [6], Tihana Bicanic, MD,[7], Sevtap Arikan-Akdagli, Prof, [8], Ana Alastruey-Izquierdo, PhD, [9], Nikolai Klimko, Prof, [10], Aleksandra Barac, MD,[11], Volkan Özenci, Prof, [12,13], Eelco F. J. Meijer, MD,[14,15,1], Nina Khanna, MD,[17], Matteo Bassetti, Prof, [18,19], Riina Rautemaa-Richardson, MD,[20,21], Katrien Lagrou, Prof, [22,23], Kai-Manuel Adam, MD,[16], Emin Halis Akalin, Prof, [24], Murat Akova, Prof, [25], Valentina Arsic Arsenijevic, MD, [26], Avinash Aujayeb, MD, [27], Ola Blennow, MD, [28], Stéphane Bretagne, Prof, [29], François Danion, MD,[30], Blandine Denis, MD, [31], Nick Alexander de Jonge, MD,[32], Guillaume Desoubeaux, Prof, [33], Lubos Drgona, MD,[34], Nurettin Erben, MD,[35], Andrea Gori, MD, [36,37], Julio García Rodríguez, PhD [38], Carolina Garcia-Vidal, MD, [39], Daniele Roberto Giacobbe, MD, [18,19], Anna L. Goodman, MD, [40], Petr Hamal, MD,[41], Helena Hammarström, MD,[42], Christina Toscano, MD, [43], Fanny Lanternier, Prof,[44], Cornelia Lass-Flörl, Prof, [45], Deborah E. A. Lockhart, PhD, [46,47], Thomas Longval, MD, [48], Laura Loughlin, MD, [49], Tadeja Matos, MD, [50], Malgorzata Mikulska, Prof, [18,19], Manjusha Narayanan, FRCPath [51], Sonia Martín-Pérez, MD, [52], Juergen Prattes, MD,[1,2,3,4], Benedict Rogers, MBChB [53], Laman Rahimli, MD, [4,5], Maite Ruiz, PhD,[54,55], Emmanuel Roilides, Prof,[56], Michael Samarkos, Prof, [57], Ulrike Scharmann, MD, [58], Uluhan Sili, Prof, [59], Ogun Resat Sipahi, Prof, [60], Alena Sivakova, MD,[61], Joerg Steinmann, Prof, [58,62], Janina Trauth, MD, [63], Ozge Turhan, Prof, [64], Jens Van Praet, MD, [65], Antonio Vena, PhD, [18,19], P. Lewis White, Prof, [66], Birgit Willinger, Prof, [67], Anna Maria Tortorano, PhD, [68], Maiken C. Arendrup, Prof,[69,70,71], Philipp Koehler, MD,[4,5,72*], Oliver A. Cornely, Prof, [4,5,72,73*#] - on behalf of the ECMM *Candida* III Study Group$

[*] Shared Senior authorship

## Affiliations

[1]Division of Infectious Diseases, Medical University of Graz, Graz, Austria

[2]Biotech Med, Graz

[3]Translational Medical Mycology Research Unit, ECMM Excellence Center for Medical Mycology, Medical University of Graz, Graz, Austria

[4]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany

[5]University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD),Cologne, Germany

[6]Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), UMR_S 1085, F-35000 Rennes, France

[7]Institute of Infection and Immunity, St George's University of London, London, UK

[8]Hacettepe University Medical School, Department of Medical Microbiology, Ankara, Turkey

[9]Mycology Reference Laboratory, National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain.

[10]Department of Clinical Mycology, Allergy and Immunology, North Western State Medical University, St Petersburg, Russia

[11] Clinic for Infectious and tropical diseases, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

[12] Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden

[13] Department of Clinical Microbiology, Karolinska University Hospital, Sweden

[14] Canisius Wilhelmina Hospital (CWZ), Medical Microbiology and Infectious Diseases, Nijmegen, the Netherlands

[15] Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, the Netherlands.

[16] Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, the Netherlands

[17] Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, Basel, Switzerland

[18] Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

[19] IRCCS Ospedale Policlinico San Martino, Infectious Diseases Unit, Genoa, Italy

[20]Mycology Reference Centre Manchester and Department of Infectious Diseases, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK

[21] Division of Evolution, Infection and Genomics, Faculty of Biology, Medicine and Health, University of Manchester, UK

[22] Laboratory of Clinical Microbiology, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium

[23] Department of Laboratory Medicine and National Reference Center for Mycosis, UZ Leuven, Leuven, Belgium

[24] Bursa Uludag University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bursa, Turkey

[25] Hacettepe University Medical School Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey

[26]Faculty of Medicine University of Belgrade, Institute of Microbiology and Immunology, Medical Mycology Reference Laboratory (MMRL), Belgrade, Institute of Public Health of Vojvodina, Centre for Microbiology - Novi Sad, Serbia

[27] Northumbria Healthcare NHS Foundation Trust, Northshields, UK

[28] Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

[29] Laboratory of Parasitology and Mycology, Saint Louis University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

[30] Department of Infectious Diseases, CHU de Strasbourg; Université de Strasbourg, Strasbourg, France

[31] Department of Infectious Diseases, Hôpital Saint-Louis, Fernand Widal, Lariboisière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

[32] Department of Hematology, Amsterdam University Medical Centers, Amsterdam, the Netherlands

[33] Department of Parasitology-Mycology-Tropical medicine, CHRU de Tours, Tours, France

[34]Department of Oncohematology, Comenius University and National Cancer Institute, Bratislava, Slovakia

[35] Eskisehir Osmangazi University, Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, Eskisehir, Turkey

[36]Department of Internal Medicine, Infectious Diseases Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy.

[37]Department of Pathophysiology and Transplantation and Centre for Multidisciplinary Research in Health Science (MACH), University of Milan, 20122 Milan, Italy.

[38] Microbiology Department, La Paz University Hospital, Madrid, Spain

[39] Department of Infectious Diseases, Hospital Clinic de Barcelona, Barcelona, Spain.

[40] Department of Infection, Guy's and St Thomas' NHS Foundation Trust) but if space/capacity please add a secondary one- which is MRC Clinical Trials Unit at University College London

[41] Department of Microbiology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic

[42] Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[43] Laboratory of Clinical Microbiology and Molecular Biology, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

[44] Paris Cité Université, Necker Hospital, APHP, Paris, France

[45]Institute of Hygiene and Medical Microbiology Innsbruck Medical University, Innsbruck Medical University, Excellence Center for Medical Mycology (ECMM), Innsbruck, Austria

[46] Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN,, United Kingdom

[47] Institute of Medical Sciences, School of Medicine Medical Sciences & Nutrition, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom

[48] Centre Hospitalier de Versailles, Hématologie, Le Chesnay, France

[49] Belfast Health and Social Care Trust, Belfast, United Kingdom

[50] Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[51] Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

[52] Hospital Nuestra Señora de Sonsoles, Ávila, Spain

[53] University Hospitals of Leicester NHS Trust, Department of Clinical Microbiology, Leicester, United Kingdom

[54] Unit of Infectious Diseases and Microbiology, Institute of Biomedicine of Seville, University Hospital Virgen del Rocio, Seville, Spain

[55] Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Madrid, Spain.

[56] Hippokration General Hospital, Infectious Diseases Department, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

[57] 1st Department of Medicine, Laikon General Hospital, Medical School, National & Kapodistrian University of Athens, Greece

[58] Institute of Medical Microbiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[59] Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey

[60] Ege University Medical School Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey

[61] Department of Microbiology of St. Anne's Faculty Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic

[62] Institute for Clinical Hygiene, Medical Microbiology and Infectiology, Paracelsus Medical University, Klinikum Nürnberg, Nuremberg, Germany

[63] Department of Medicine II, Section of Infectious Diseases, Justus-Liebig-University Giessen, Giessen, Germany

[64] Akdeniz University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Antalya, Turkey

[65] AZ Sint-Jan Brugge Oostende AV, Nephrology and Infectious Diseases, Brugge, Belgium

[66] Public Health Wales, Microbiology Cardiff and Cardiff University, School of Medicine, Cardiff , United Kingdom

[67] Division of Clinical Microbiology, Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

[68] Universita degli Studi di Milano, Milano, Italy

[69]Unit of Mycology, Statens Serum Institut, Copenhagen, Denmark

[70]Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark

[71]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[72] German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany

[73] University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany

**§ ECMM *Candida* III Study Group contributors:**

Mario Tumbarello[1], Alida Fe Talento[2], Alba C Ruiz[3], Zdenek Racil[4], Igor Stoma[5], María Calbacho[6], Eric Van Wijngaerden[7], Júlia Henriques[8], Harriett Jordan[9], Valentina Ferroni[10], Ozlem Koyuncu Ozyurt[11], Christopher Milacek[12], Robert Krause[13], Christoph Zurl[13], Matthijs Backx[14], Ang Li[15], Raphael Seufert[16], Rok Tomazin[17], Yael Blankenheim [18,19], Julio Dávila-Valls[20], Paloma García-Clemente[21], Tomas Freiberger[22], Jochem Buil [23], Jacques F. Meis [24], Deniz Akyol [25], Hélène Guegan[26], Clare Logan [27]

Affiliations

[1]Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy

[2]Beaumont Hospital Dublin – Dublin, Ireland

[3]University and Polytechnic La Fe Hospital, Valencia, Spain

4 Institut of Hematology and Blood Transfuzion, Prague, Czech Republic

[5]Minsk Scintifical and Practical Center of Surgery, Transplantology and Hematology; Gome State University, Misnk, Belarus

[6] Hospital 12 Octubre, Hematology, Madrid, Spain

[7]Department of General Internal Medicine, UZ Leuven, Leuven, Belgium

[8]Laboratory of Clinical Microbiology and Molecular Biology, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

[9]Department of Infection, Guy's and St Thomas' NHS Foundation Trust, St Thomas Hospital, Westminister Bridge, London, United Kingdom

[10]Department of Internal Medicine Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

[11]Akdeniz University, Faculty of Medicine, Department of Medical Microbiology, Antalya, Turkey

[12]Department of Internal Medicine II, Division of Pulmonology, Medical University of Vienna, Vienna, Austria

[13]Division of Infectious Diseases, Medical University of Graz, Graz, Austria

[14]Public Health Wales, Microbiology, Cardiff , United Kingdom

[15]Newcastle Hospitals, Newcastle Upon Tyne, United Kingdom

[16] Institute for Clinical Hygiene, Medical Microbiology and Infectiology, Paracelsus Medical University, Klinikum Nürnberg, Nuremberg, Germany

[17] Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[18]University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD); Cologne, Germany

[19]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany

[20]Hospital Nuestra Señora de Sonsoles, Ávila Spain

[21]La Paz University Hospital, Madrid, Spain

[22]Centre of Cardiovascular Surgery and Transplantation, Brno, and Faculty of Medicine, Masaryk University, Brno, Czech Republic

[23]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, the Netherlands

[24]Canisius Wilhelmina Hospital (CWZ), Medical Microbiology and Infectious Diseases, Nijmegen, the Netherlands; Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, the Netherlands.

[25]Ege University Medical School Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey

[26] Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), UMR_S 1085, F-35000 Rennes, France

[27]Institute of Infection and Immunity, St George's University of London, London, UK

# Corresponding author:

Prof. Dr. Martin Hoenigl, MD,

Division of Infectious Diseases, Department of Internal Medicine,

Medical University of Graz,

Auenbruggerplatz 15, 8036-Graz, Austria

Email: hoeniglmartin@gmail.com

Phone: +4331638531425

Alternate Corresponding author:

Prof. Dr. Oliver A. Cornely

University of Cologne, Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), and University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), Cologne, Germany

Herderstraße 52-54

50931 Cologne, Germany

Phone: +49 221 478 88795| Fax: +49 221 478 1421445

E-mail: oliver.cornely@uk-koeln.de

**Author's ORCID**

| | |
|---|---|
| Martin HOENIGL | 0000-0002-1653-2824 |
| Jon SALMANTON-GARCÍA | 0000-0002-6766-8297 |
| Matthias EGGER | 0000-0002-7795-4406 |
| Jean-Pierre GANGNEUX | 0000-0002-4974-5607 |
| Tihana BICANIC | 0000-0002-2676-838X |
| Sevtap ARIKAN-AKDAGLI | 0000-0001-9807-6764 |
| Ana ALASTRUEY-IZQUIERDO | 0000-0001-8651-4405 |
| Nikolai KLIMKO | 0000-0001-6095-7531 |
| Volkan ÖZENCI | 0000-0002-8069-4027 |

| | |
|---|---|
| Eelco F J MEIJER | 0000-0002-0226-024X |
| Nina KHANNA | 0000-0002-2642-419X |
| Matteo BASSETTI | 0000-0002-0145-9740 |
| Riina RAUTEMAA-RICHARDSON | 0000-0002-1071-6040 |
| Katrien LAGROU | 0000-0001-8668-1350 |
| Kai Manuel ADAM | 0000-0003-3639-872X |
| Emin Halis AKALIN | 0000-0001-7530-1279 |
| Murat AKOVA | 0000-0002-6904-9473 |
| Valentina ARSIC ARSENIJEVIC | 0000-0001-8132-3300 |
| Avinash AUJAYEB | 0000-0002-0859-5550 |
| Ola BLENNOW | 0000-0002-7167-7882 |
| Stephane BRETAGNE | 0000-0001-6870-3800 |
| Francois DANION | 0000-0003-3907-0658 |
| Nick DE JONGE | 0000-0002-9901-0887 |
| Guillaume DESOUBEAUX | 0000-0001-7945-9890 |
| Lubos DRGONA | 0000-0002-5089-3201 |
| Nurettin ERBEN | 0000-0003-0373-0132 |
| Daniele Roberto GIACOBBE | 0000-0003-2385-1759 |
| Anna GOODMAN | 0000-0003-0643-9017 |
| Andrea GORI | 0000-0001-6587-4794 |
| Petr HAMAL | 0000-0002-5361-8125 |
| Helena HAMMARSTRÖM | 0000-0002-5859-1056 |
| Cristina TOSCANO | 0000-0002-4674-6065 |
| Cornelia LASS-FLÖRL | 0000-0002-2946-7785 |
| Deborah E. A. LOCKHART | 0000-0002-4262-3842 |
| Tadeja MATOS | 0000-0002-5696-1412 |
| Małgorzata MIKULSKA | 0000-0002-5535-4602 |
| Thomas LONGVAL | 0000-0002-0254-1519 |
| Jens VAN PRAET | 0000-0002-7125-7001 |
| Sonia Martín-Pérez | 0000-0001-5809-7165 |
| Juergen PRATTES | 0000-0001-5751-9311 |
| Laman RAHIMLI | 0000-0003-2266-445X |
| Zdeněk RÁČIL | 0000-0003-3511-4596 |

| | |
|---|---|
| Benedict ROGERS | 0000-0002-7041-6744 |
| Emmanuel ROILIDES | 0000-0002-0202-364X |
| Michael SAMARKOS | 0000-0001-9630-9712 |
| Ulrike SCHARMANN | 0000-0001-7689-7799 |
| Uluhan SILI | 0000-0002-9939-9298 |
| Alena SIVAKOVA | 0000-0002-9224-4613 |
| Jörg STEINMANN | 0000-0002-3181-3667 |
| Ozge TURHAN | 0000-0003-1494-9973 |
| Antonio VENA | 0000-0002-0697-3992 |
| P Lewis WHITE | 0000-0003-3056-4205 |
| Birgit WILLINGER | 0000-0001-7921-5749 |
| Anna Maria TORTORANO | 0000-0003-2093-8250 |
| Maiken Cavling ARENDRUP | 0000-0002-4747-0144 |
| Philipp KOEHLER | 0000 -0002 -7386 -7495 |
| Oliver A. CORNELY | 0000-0001-9599-3137 |

Contributors:

| | |
|---|---|
| Julio Dávila -Valls | 0000-0002-5185-2073 |
| Tomas Freiberger | 0000-0001-6532-7053 |
| Alida Fe Talento | 0000-0003-1271-2550 |
| Christopher MILACEK | 0000-0002-6924-0075 |

## Abstract

### Background

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

### Methods

Participating hospital located in 20 European countries (number of eligible hospitals per country determined by population size) included the first ~10 culture proven candidemia cases after 01-July-2018 and entered data into the ECMM *Candida* III database on the FungiScope® platform. EQUAL *Candida* Scores reflecting adherence to recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Infectious Disease Society of America (IDSA) Guidelines were assessed.

### Findings

A total of 632 candidemia cases were included from 64 institutions. Overall 90-day mortality was 42.9% (265/617),, and older age, intensive care unit (ICU) admission, higher Charlson Comorbidity Index 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 restricted to cases who survived >7 days after diagnosis (adjusted hazard ratios between 1.075 and 1.089 per 1 point decrease; $p<0.0001$). Median duration of hospitalization was 16 days following diagnosis of candidemia and was prolonged specifically for

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

**Interpretation**

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

**Funding**

The study was funded by an Investigator Initiated Research Grant from SCYNEXIS, Inc..

**Word Count Abstract:** 300

**Key Words:** *Candida tropicalis, Candida auris, Candida albicans, Candida parapsilosis, Candida glabrata*, mortality, guidelines

## Research in context

**Evidence before this study:** Despite advances in management including improved central venous catheter management, candidemia remains associated with high mortality. International guidelines for the diagnosis and management of candidemia were created with the ultimate goal of improving patient outcomes and survival, but whether this is actually the result (e.g. also for first-line treatment with echinocandins) has not been comprehensively evaluated. In 2018, the European Confederation of Medical Mycology (ECMM) introduced the EQUAL *Candida* score (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 score was derived from recommendations of the two most prominent guidelines for candidemia, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline, and the Infectious Diseases Society of America (IDSA) guideline. While this score has been shown to be predictive of mortality in subgroups of candidemia cases in a few small single centre studies, larger multicentre evaluations on whether the score and whether following each guideline recommendation (=score variable) separately correlates with clinical outcomes was lacking and not found in the Pub Med database [Search strategy – Data source: Pub Med, articles written in English; Date range: published between January 1, 2012 and September 1, 2022; Search terms: "(Candida* OR candidemia*) AND (EQUAL OR guideline OR recommendations OR guidance)"; we also searched the reference lists of all relevant publications for additional case reports]..

**Added value of this study:** This study collected data on epidemiology, risk factors, treatment, and outcomes of culture proven candidemia from 64 institutions in 20 European countries in order to assess how adherence to guideline recommendations correlate with outcomes. Patient enrollment per country and number of participating centers were stratified by population size. Overall 90-mortality was 42.9%, and older age, intensive care unit (ICU) admission, higher Charlson

Comorbidity Index and *Candida tropicalis* as causative pathogen, as well as emerging and rare *Candida* spp. (including *C. auris*) as causative pathogens were independent predictors of mortality in Cox regression analyses. Lower EQUAL *Candida* Scores, reflecting less adherence to guideline recommendations, remained an independent predictor of mortality in the multivariable Cox regression analyses after adjusting for age, ICU admission and rare *Candida spp.* (adjusted hazard ratios between 1.075 and 1.089 per 1 point decrease; $p<0.0001$). Absence of each diagnostic/therapeutic measure (including absence of initial echinocandin treatment) was accompanied by increased mortality compared to the overall cohort, emphasizing the importance of every single variable in successful management. Initial echinocandin treatment was associated with longer duration of hospitalization among survivors.

**Implications of all the available evidence:** While across Europe overall mortality of candidemia in adults remains high at 43%, adherence to clinical guideline recommendations may increase survival. Of note this was also shown for more controversial guideline recommendations, such as performance of ophthalmoscopy or echocardiography. Echinocandins may not only be associated with increased overall survival, but also longer duration of hospitalization, including directly causing prolonged hospitalization in 1 out of 7 patients with candidemia, 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-life's, which may allow for earlier discharge and outpatient therapy, reducing costs and hospital stay associated risks (e.g., nosocomial infection).

92

## Introduction

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

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

International guidelines for the diagnosis and management of candidemia were created with the ultimate goal of improving patient outcomes and survival, but whether this is actually the result has been rarely evaluated. In 2018, the European Confederation of Medical Mycology (ECMM) introduced the EQUAL scores (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 candidemia, the

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

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

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

## Methods

### Study design and participating centers

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

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

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

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

**Statistical analysis and ethics**

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

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

To investigate the association of baseline risk factors with survival, univariable and multivariable Cox 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 (n=597). Causative *Candida* spp. was the only variable that differed between the multivariable models; for one of these models, emerging *Candida* spp. that were defined before(23) (i.e., *C. kefyr*, *C. guilliermondii*, *C. lusitaniae*, *C. dubliniensis* , *C. famata*, *C. inconspicua*, *C. rugosa*, *C. norvegiensis*) were grouped together with *C. auris* into the variable "*C. auris* and other emerging *Candida* spp.), while the other model included *C. tropicalis*, respectively. The proportionality of hazard assumption was evaluated by fitting an interaction between a variable of interest and linear follow-up time. We used the Akaike Information Criterion (AIC) 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 > 7 days and who had data on duration of follow up available (n=443). Lastly, we estimated multivariable Cox models for each variable of the EQUAL *Candida* score adjusted for significant baseline risk factors.

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

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

## Role of the funding source

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

## Results

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

Patient demographic and clinical characteristics, risk factors, treatment, and outcomes as well as distribution of *Candida* spp. in the overall study cohort, survivors and non-survivors are separately displayed in detail in **Supplemental Table 1 (Appendix Page 8-12)**. The majority (368/632; 58%) were male and median age was 65 years (IQR 53-73). Underlying hematological/oncological malignancy (247/632; 39%), ICU admission (234/632; 37%), and recent major surgery (164/632; 26%), were the most common underlying conditions. Candidemia was classified as catheter related bloodstream infection (CRBSI) in 21% (130/632) of cases. In about one third of cases (224/632; 35%) echocardiography was reported, showing cardiac involvement in 11% (25/224) of those examined. Eye exam was reported in 27% (169/632) of cases showing ocular involvement in 11% (19/169) of those examined. Overall mortality was 46.4% (286/617); in 37% of those (77/209), investigators attributed death to candidemia; 30-day mortality was 37.6% (232/617), 90-day mortality 42.9% (265/617), 180-day mortality 45.1% (278/617). Median duration of hospitalization was 15 days (IQR 4-30 days) after the diagnosis of candidemia. The vast majority (502/620; 81%) received treatment consultation by an infectious diseases or microbiology expert and echinocandins were the first line antifungal treatment in 56% (353/632) of cases. Initial echinocandin treatment was associated with longer duration of hospitalization among survivors receiving echinocandins versus other antifungals (median 24 days, IQR 15-40 days vs. median 16 days, IQR 7-33 days; $p<0.0001$). In those in whom candidemia was treated for at least 14 days, 78% (239/306) survived, compared to 66% (67/102) in those treated for less than 14 days ($p=0.01$), but who survived beyond day 14 after diagnosis. Hospital stay was prolonged specifically for the purpose of completing

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

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

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

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

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

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

**Supplemental Figure 1 (Appendix Page 13)** shows EQUAL *Candida* Scores, Score variables and demographic data in survivors and non-survivors who survived >7 days after candidemia diagnosis. ROC curve analysis revealed an AUC of 0.718 for the proportion of the maximum EQUAL *Candida* score for predicting overall mortality, with an optimal cut-off of 78.1% of the max score (which translates to >14 in those without CVC and >16 in those with CVC). Adjusted HR per point increase in EQUAL *Candida* scores for patients with CVCs 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 longer than 7 days are displayed in **Table 2**. After adjustment for baseline variables (model #1), a decrease in one score point translated to an aHR of 1.075 (95% CI 1.043 - 1.109) in CVC carriers and an aHR of 1.089 (95% CI 1.051 – 1.129) in those without a CVC. ECMM *Candida* scores below the calculated Youden cut-off were associated with an aHR of 3.53 (95% CI 2.01 – 5.98; all p<0.0001).

**Table 3** outlines overall mortality rates for each variable of the EQUAL Candida score if absent, followed by results of multivariable Cox regression model evaluating each score variable if absent adjusted for significant baseline risk factors. Absence of each diagnostic/therapeutic measure was associated with higher mortality (50.5% - 70.5%) compared to the mortality in the overall cohort (46.4%; 286/617). In the multivariable Cox model for patients who survived > 7 days and adjusted for the baseline predictors, absence of ophthalmoscopy, echocardiography, treatment of ≥14 days

after first negative blood culture, and also absence of stepdown to fluconazole therapy were all significant predictors of mortality with aHRs between 1.71 and 3.64.

## Discussion

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

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

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

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

Many known risk factors for *Candida* infections in the ICU such as previous surgery, TPN, CVC, broad spectrum antibiotics, diabetes (5), neutropenia, or solid organ transplantation (7) were present in relevant proportions of our study population. Age, severe hepatic failure, organ failure at the onset of IC, and septic shock (OR 2.12, 95% CI 1.24-3.63, p=0.006) were previously associated with 30-day mortality in candidemia cases (3). In this study, not only did older age, higher Charlson comorbidity index and ICU admission stand out as independent baseline predictors of candidemia mortality, but so did candidemia caused by rare *Candida tropicalis*, and – to a lesser extend – also candidemia causes by emerging or rare *Candida* spp., particularly *C. kefyr* and *C. guilliermondii* but also *C. auris*. With an increase of species other than *Candida albicans* (26) and the emergence of new resistant species, including but not limited to *C. auris* and fluconazole resistant *C. parapsilosis* (27, 28) this may manifest as major risk factors applicable to larger proportions of candidemia patients in the future (9). While ID consultation was previously shown protective against mortality with a hazard ratio of 0·81 (95% CI 0·73-0·91; p<0·0001) after propensity score weighting (10), consultation by an ID or microbiology expert was protective in our study only for avoiding early mortality even after adjusting for baseline risk factors (aHR 0·58, 95% CI 0·44-0·70; p<0·001), a result that may outline the value of early consultation, but also be confounded by the fact that some patients may die before they can receive a consultation. Once patients survived 3 days or longer after diagnosis, ID/microbiology expert consultation did not translate to a significant survival benefit.

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

Despite its large size (64 institutions in 20 European countries) this multicentre multinational study comes along 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 outcomes. In addition, EQUAL *Candida* scores may be higher in long-term survivors versus those with an early fatal outcome, given the fact that some of the diagnostic and treatment recommendations take time and may not be available in 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 cannot rule out that even after this adjustment survival duration may remain a confounder, particularly for length of therapy. However, the fact that when the analysis was limited to include only patients surviving more than 14 days, survival remained longer for patients receiving treatment for >14 days [78% (239/306) versus 66% (67/102)], indicates that treatment duration may have an impact on longer term survival. Importantly, availability of fungal diagnostics, ID/microbiology consultations and also access to antifungal drugs varies across the world with more limited access in low and middle income countries, limiting generalizability of our results to other settings (32).

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

In conclusion, we found that across Europe overall 90-day mortality of candidemia remains high at 43%. Importantly, our study indicates that adherence to clinical guideline recommendations may increase survival. Lastly, current first line candidemia treatments with echinocandins are not only associated with increased overall survival, but also longer duration of hospitalization, including directly causing prolonged hospitalization in 1 out of 7 patients with candidemia, 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-life, which may allow for earlier discharge and outpatient therapy, reducing costs and hospital stay associated risks (e.g., nosocomial infection).

Author contributions:

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

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

Accessed and verified all data: MH, OH and JSG

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

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

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

Conflicts of Interest

MH reports grants and research funding from Astellas, Gilead, MSD, Pfizer, Euroimmun, F2G, Pulmocide, IMMY, Mundipharma and Scynexis.

JSG has received lecture honoraria from Gilead and Pfizer, outside of the submitted work.

JPG has received lecture honoraria from Gilead, 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.

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

AA-I has received honoraria for educational talks of behalf of Gilead and Pfizer, outside of the submitted work.

NK was a speaker for Astellas, Gilead Sciences, Merck/MSD, and Pfizer and an adviser for Gilead Sciences, Merck/MSD, and Pfizer, all outside the submitted work.

KL received consultancy fees from MRM Health, MSD and Gilead, speaker fees from FUJIFILM WAKO, Pfizer and Gilead and a service fee from Thermo fisher Scientific and TECOmedical

NKh is a member of the Gilead, Merck Sharp & Dohme AG (MSD) and Pfizer advisory boards for invasive fungal infections, chair of the DSMB of Pulmocide, and reports grants from The Swiss National Science Foundation (grant number 32003B_204944 and the National Centre of Competence in Research AntiResist Grant 51NF40_180541), outside the submitted work.

MB reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from Bayer, BioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, and Shionogi.

MA had research grants from Pfizer, honoraria from Pfizer, Gilead and, Sanofi for contributing educational activities which were paid to the university funds; none related with the submitted work.

VAA reports research funding from Pfizer

BD reports receipt of speaker fees, advisory Board fees from Gilead sciences, advisory Board fees from Pfizer, outside the submitted work.

FD declares personal fees from Gilead, Pfizer, outside the submitted work.

GD has received lecture honoraria from Gilead and Pfizer, outside of the submitted work. He was also invited to symposia and congresses by the two aforementioned companies.

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

Outside the submitted work, DRG reports investigator-initiated grants from Pfizer, Shionogi, and Gilead Italia and speaker fees and/or advisory board fees from Pfizer and Tillotts Pharma.

FD declares personal fees from Gilead and Pfizer, outside the submitted work.AG reports COI with the following companies: JANNSEN, VIIV, MSD, BMS, ABBVIE, GILEAD, NOVARTIS, PFIZER, ASTELLAS, ASTRAZENECA, ANGELINI

CGV reports Grant support from Gilead and MSA, and personal fees from Gilead Science, MSD, Novartis, Pfizer, Janssen, Lilly.

FL reports receipt of speaker fees from Gilead, Pfizer and F2G and advisory board fees from F2G

MM has received speaker fees from Janssen, Gilead, Mundipharma, MSD and Pfizer

ORS has received speaker's honorarium from Astellas, Pfizer and Kocak Farma.

ER reports grants to his institutions from Astellas, MSD, Scynexis, Shionogi, GSK, Pfizer, Gilead and Allergan. He has served as consultant to Amplyx, Astellas, Gilead, MSD, Pfizer, Scynexis, GSK and Shionogi.

JP has received research funding from MSD and Pfizer and lecture honoraria from Gilead Sciences, Pfizer, Associates of Cape Cod and Swedish Orphan Biovitrium GmbH, outside of the submitted work.

JS has received lecture honoraria from Gilead and Pfizer, outside of the submitted work

PLW: Performed diagnostic evaluations and received meeting sponsorship from Associates of Cape Cod, Bruker, Dynamiker, and Launch Diagnostics; Speaker's fees, expert advice fees and meeting sponsorship from Gilead; and speaker and expert advice fees from Pfizer and expert advice fees from F2G

BW reports personal fees from MSD, Pfizer, Gilead, Shionogi, Euroimmun, Immy, CapeCod and grants to her institution from Pfizer, Shionogi and

AMT has received lecture honoraria from Gilead

MCA has, over the past 5 years, received research grants/contract work (paid to the SSI) from Amplyx, Basilea, Cidara, F2G, Gilead, Novabiotics and Scynexis, and speaker honoraria (personal fee) from Astellas, Chiesi, Gilead, MSD, and SEGES. She is the current chairman of the EUCAST-AFST.

PK reports grants or contracts from German Federal Ministry of Research and Education (BMBF) B-FAST (Bundesweites Forschungsnetz Angewandte Surveillance und Testung) and NAPKON (Nationales Pandemie Kohorten Netz, German National Pandemic Cohort Network) of the Network University Medicine (NUM) and the State of North Rhine-Westphalia; Consulting fees Ambu GmbH, Gilead Sciences, Mundipharma Resarch Limited, Noxxon N.V. and Pfizer Pharma; Honoraria for lectures from Akademie für Infektionsmedizin e.V., Ambu GmbH, Astellas Pharma, BioRad Laboratories Inc., European Confederation of Medical Mycology, Gilead Sciences, GPR Academy Ruesselsheim, HELIOS Kliniken GmbH, medupdate GmbH, MedMedia, MSD Sharp & Dohme GmbH, Pfizer Pharma GmbH, Scilink Comunicación Científica SC and University Hospital and LMU Munich; Participation on an Advisory Board from Ambu GmbH, Gilead Sciences, Mundipharma Resarch Limited and Pfizer Pharma; A pending patent currently reviewed at the German Patent and Trade Mark Office; Other non-financial interests from Elsevier, Wiley and Taylor & Francis online outside the submitted work.MH received research funding

from Gilead Sciences, Astellas, Mudipharma, Euroimmune, MSD, Pulmocide, Scynexis, F2G and Pfizer, all outside the submitted work.

OAC reports grants and personal fees from Actelion, personal fees from Allecra Therapeutics, personal fees from Al-Jazeera Pharmaceuticals, grants and personal fees from Amplyx, grants and personal fees from Astellas, grants and personal fees from Basilea, personal fees from Biosys, grants and personal fees from Cidara, grants and personal fees from DaVolterra, personal fees from Entasis, grants and personal fees from F2G, grants and personal fees from Gilead, personal fees from Grupo Biotoscana, personal fees from IQVIA, grants from Janssen, personal fees from Matinas, grants from Medicines Company, grants and personal fees from MedPace, grants from Melinta Therapeutics, personal fees from Menarini, grants and personal fees from Merck/MSD, personal fees from Mylan, personal fees from Nabriva, personal fees from Noxxon, personal fees from Octapharma, personal fees from Paratek, grants and personal fees from Pfizer, personal fees from PSI, personal fees from Roche Diagnostics, grants and personal fees from Scynexis, personal fees from Shionogi, grants from DFG, German Research Foundation, grants from German Federal Ministry of Research and Education, grants from Immunic, personal fees from Biocon, personal fees from CoRe Consulting, personal fees from Molecular Partners, from MSG-ERC, from Seres, other from Wiley (Blackwell), outside the submitted work.

All other authors declare no conflict of interest for this study.

**Funding**

The study was partly funded by an Investigator Initiated Research Grant from Scynexis (PIs Hoenigl and Cornely). The funder had no influence on the study design or on the analysis of the results.

**Data sharing statement:**

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

455 **Table 1.** Univariable and multivariable Cox regression model for predictors of mortality in candidemia
456 (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 ≥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)** | | | |
| *C. albicans (274)* | 0.92 | 0.72 – 1.16 | 0.475 |

| | | | |
|---|---|---|---|
| | | | |
| *C. glabrata (127)* | 0.88 | 0.65 – 1.18 | 0.385 |
| *C. parapsilosis (80)* | 0.98 | 0.70 – 1.38 | 0.916 |
| *C. tropicalis (44)* | 1.78 | 1.16 - 2.57 | **0.0071** |
| *C. krusei (12)* | 0.84 | 0.31 – 2.25 | 0.726 |
| *C. auris (15)* | 1.39 | 0.69 – 2.81 | 0.357 |
| *C. dubliniensis (9)* | 0.69 | 0.22 – 2.15 | 0.519 |
| *C. guilliermondii (6)* | 3.64 | 1.62 – 8.18 | **0.0018** |
| *C. lusitaniae (5)* | 1.23 | 0.39 – 3.84 | 0.719 |
| *C. kefyr (5)* | 3.27 | 1.22 – 8.80 | **0.019** |
| Other *Candida* Species (9)* | 0.75 | 0.24 – 2.33 | 0.617 |
| *C. auris and other emerging Candida species (46)$* | 1.54 | 1.03 - 2.30 | **0.034** |
| *C. auris and rare Candida 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)**<br>**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** |

| | | | |
|---|---|---|---|
| *C. tropicalis* | 1.71 | 1.15 – 2.55 | **0.0085** |
| | | | |
| **Model #2 (AIC = 3175)**<br><br>**Variables** | **Multivariable hazard ratio** | **95% CI** | **p-value** |
| Age | 1.39 | 1.18 – 1.63 | **<0.0001** |
| ICU | 1.77 | 1.39 – 2.25 | **<0.0001** |
| *C.auris* and other emerging *Candida* species § | 1.50 | 0.99 – 2.26 | 0.056 |
| Charlson Comorbidity Index (excluding age) | 1.06 | 1.02 – 1.11 | **0.0056** |

Abbreviations: *AIC = Akaike Information Criterion; BMI = body mass index; CRBSI = catheter related bloodstream infection:, ECMO= extracorporeal membrane oxygenation; ICU = intensive care unit; ID = infectious diseases; SOT = solid organ transplant; TPN = total parenteral nutrition*

* *Others include: Candida norvegensis (n=1), Candida digboensis (n=1), Candida rugosa (n=3), Candida pelliculosa (n=2), Candida inconspicua (n=2; one coinfected with C. norvegensis), and Candida famata (n=1)*

*$ C. auris and C. kefyr*, *C. guilliermondii*, *C. lusitaniae*, *C. dubliniensis* , *C. famata*, *C. inconspicua*, *C. rugosa*, *C. norvegensis*.

*§ C. auris and all other Candida spp. with 10 or fewer isolates.*

457

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

| Variable | Multivariable hazard ratio | 95% CI | p-value |
|---|---|---|---|
| EQUAL *Candida* score risk per % of actual/max score proportion decrease | 1.016 | 1.009 – 1.023 | **<0.0001** |
| EQUAL *Candida* score risk per 10% of actual/max score proportion decrease | 1.175 | 1.099 – 1.257 | **<0.0001** |
| | | | |
| * Risk per decrease in point *Candida* score for CVC carriers | 1.075 | 1.043 - 1.109 | **<0.0001** |
| Risk per decrease in point *Candida* score for patients **without** CVC | 1.089 | 1.051 – 1.129 | **<0.0001** |
| | | | |
| °EQUAL *Candida* score ≤78.1% of max Score | 3.53 | 2.01 - 5.98 – | **<0.0001** |
| | | | |
| Risk reduction comparingmaximum and minimum *Candida* score | 0.20 | 0.10 – 0.39 | **<0.0001** |

**Table explanation:**

***** With CVC max *Candida* score = 22 points which refers to 4.5% per point

Without CVC max *Candida* 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*

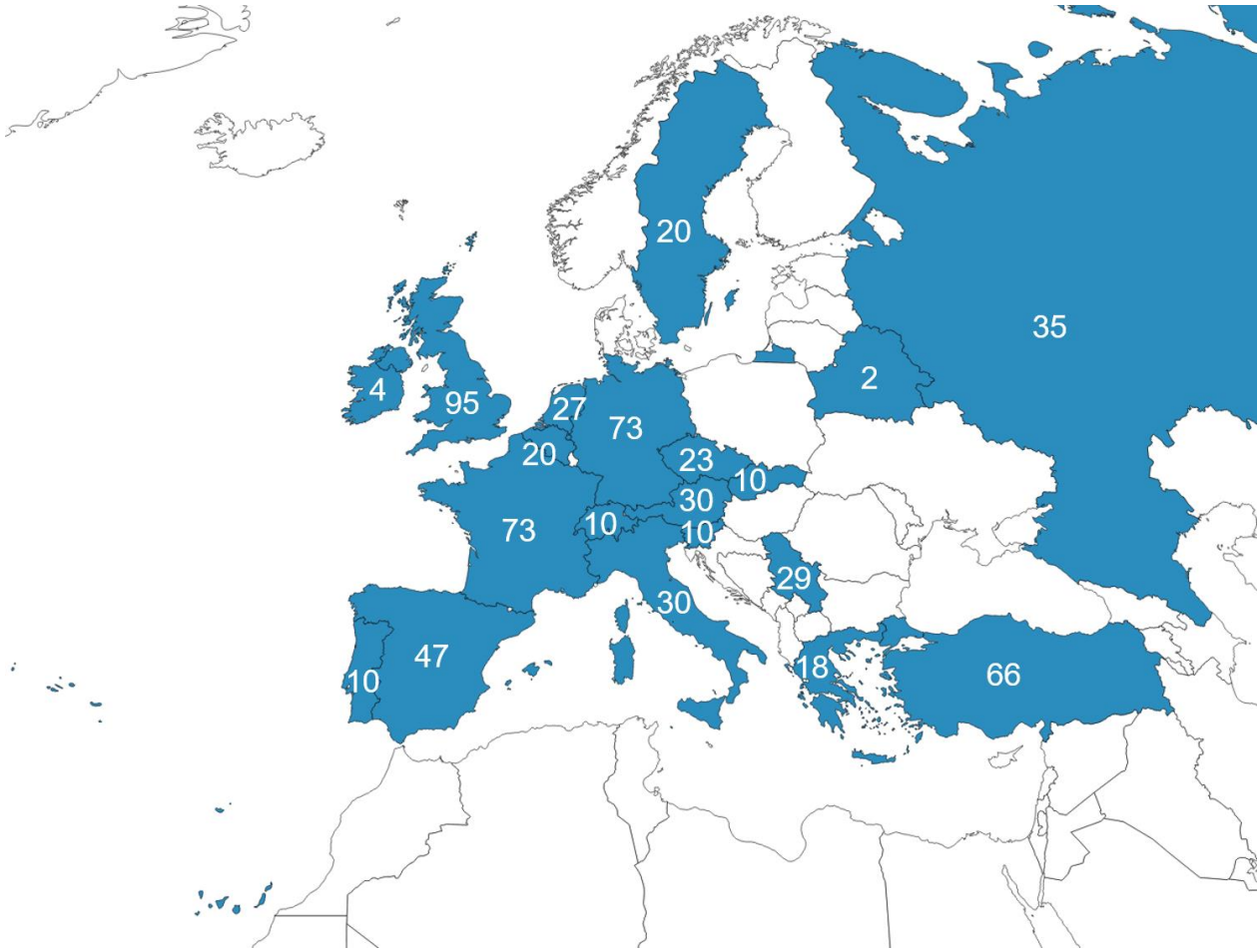
462 **Table 3.** Absolute mortality rates for EQUAL score variables if absent, as well as multivariable Cox
463 regression models [each variable adjusted for age, ICU, Charlson comorbidity index (excluding age),
464 *Candida tropicalis*] for score variables for prediction of mortality in patients with invasive candidiasis
465 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 ≤ 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 ≤ 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.<br>*CVC carriers only | | | |

466

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




468

**Figure 2.** Study flowchart.

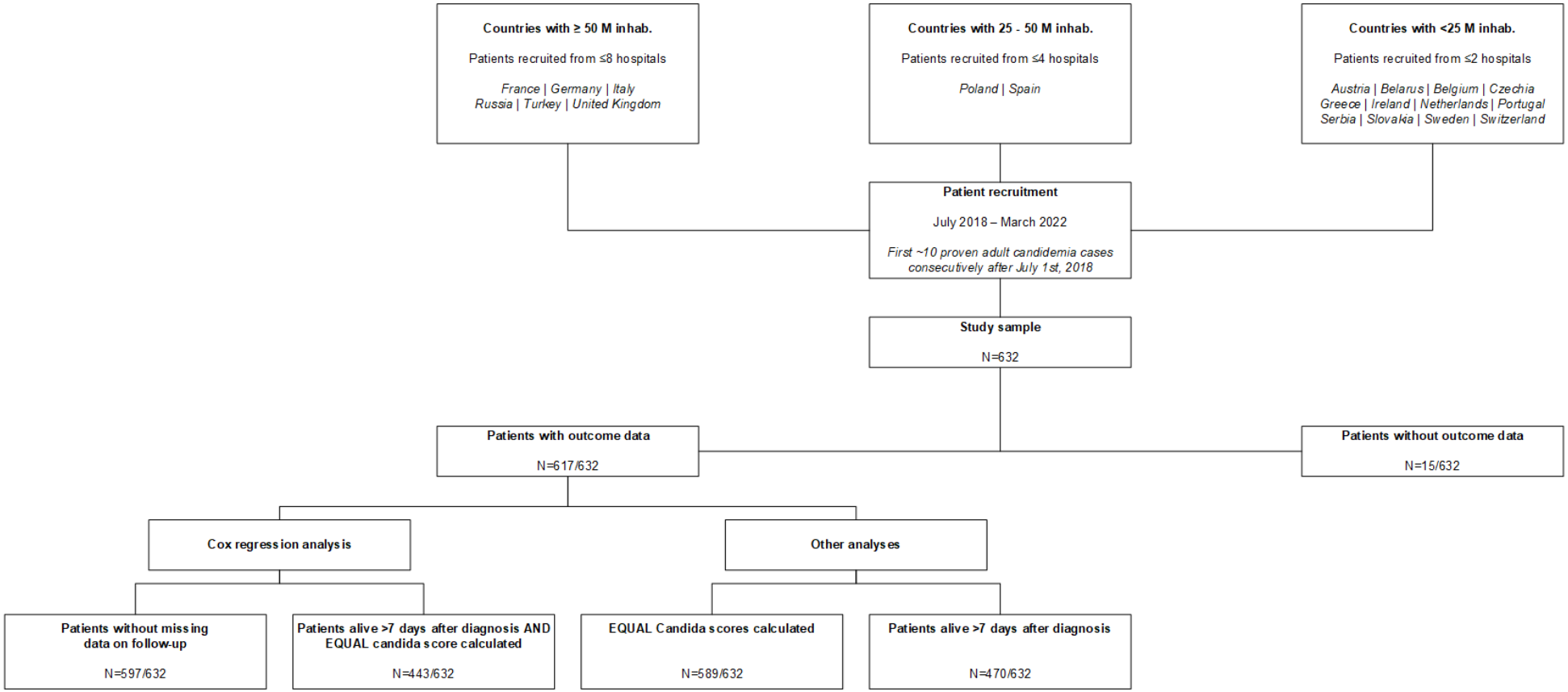
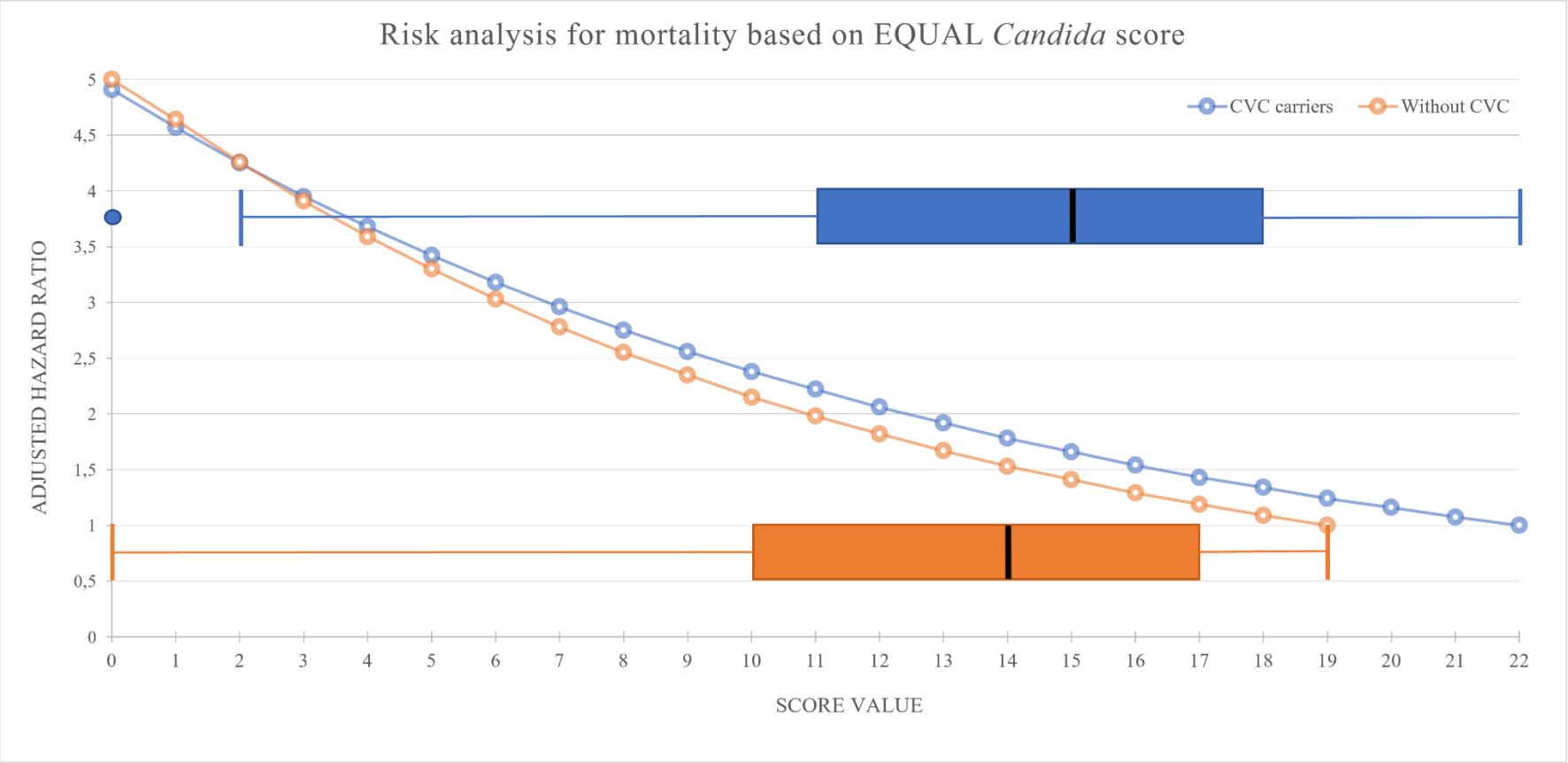


**Figure 3.** Adjusted* hazard ratios per point increase in EQUAL Candida scores for patients with central venous catheters (CVCs, blue) and those without (orange), as well as Boxplots




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

481

## References


1. Egger M, Hoenigl M, Thompson GR, 3rd, Carvalho A, Jenks JD. Let's talk about Sex Characteristics - as a Risk Factor for Invasive Fungal Diseases. Mycoses. 2022;65(6):599-612.
2. Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. Journal of fungi (Basel, Switzerland). 2017;3(4):10.3390/jof3040057.
3. Bassetti M, Giacobbe DR, Vena A, Trucchi C, Ansaldi F, Antonelli M, et al. Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project. Crit Care. 2019;23(1):219.
4. Koehler P, Stecher M, Cornely OA, Koehler D, Vehreschild M, Bohlius J, et al. Morbidity and mortality of candidaemia in Europe: an epidemiologic meta-analysis. Clin Microbiol Infect. 2019;25(10):1200-12.
5. Muskett H, Shahin J, Eyres G, Harvey S, Rowan K, Harrison D. Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. Crit Care. 2011;15(6):R287.
6. Hoenigl M, Seidel D, Sprute R, Cunha C, Oliverio M, Goldman GH, et al. COVID-19-associated fungal infections. Nat Microbiol. 2022;7(8):1127-40.
7. Keighley CL, Pope A, Marriott DJE, Chapman B, Bak N, Daveson K, et al. Risk factors for candidaemia: A prospective multi-centre case-control study. Mycoses. 2021;64(3):257-63.
8. Strollo S, Lionakis MS, Adjemian J, Steiner CA, Prevots DR. Epidemiology of Hospitalizations Associated with Invasive Candidiasis, United States, 2002-2012(1). Emerg Infect Dis. 2016;23(1):7-13.
9. Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, et al. Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect. 2014;20(4):O245-54.
10. Mejia-Chew C, O'Halloran JA, Olsen MA, Stwalley D, Kronen R, Lin C, et al. Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study. Lancet Infect Dis. 2019;19(12):1336-44.
11. Mellinghoff SC, Hoenigl M, Koehler P, Kumar A, Lagrou K, Lass-Florl C, et al. EQUAL Candida Score: An ECMM score derived from current guidelines to measure QUAlity of Clinical Candidaemia Management. Mycoses. 2018;61(5):326-30.
12. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18 Suppl 7:19-37.
13. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.
14. El Zakhem A, El Eid R, Istambouli R, Tamim H, Kanj SS. The Utility of EQUAL Candida Score in Predicting Mortality in Patients with Candidemia. J Fungi (Basel). 2022;8(3).
15. Leepattarakit T, Tulyaprawat O, Vongseenin C, Rujirachun P, Wattanachayakul P, Phichinitikorn P, et al. EQUAL Candida score, an effective tool for predicting the outcomes of Candida tropicalis candidaemia: A retrospective cohort study. Mycoses. 2022;65(4):473-80.
16. Hoenigl M, Gangneux JP, Segal E, Alanio A, Chakrabarti A, Chen SC, et al. Global Guidelines and Initiatives from the European Confederation of Medical Mycology to improve Patient Care and Research Worldwide: New Leadership is about Working Together. Mycoses. 2018;61(11):885-94.
17. Tortorano AM, Peman J, Bernhardt H, Klingspor L, Kibbler CC, Faure O, et al. Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2004;23(4):317-22.
18. Klingspor L, Tortorano AM, Peman J, Willinger B, Hamal P, Sendid B, et al. Invasive Candida infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006-2008). Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2015;21(1):87.e1-.e10.

19. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clin Microbiol Infect. 2012;18 Suppl 7:9-18.
20. Salmanton-García J, Busca A, Cornely OA, Corradini P, Hoenigl M, Klimko N, et al. EPICOVIDEHA: A Ready to Use Platform for Epidemiological Studies in Hematological Patients With COVID-19. Hemasphere. 2021;5(7):e612.
21. Seidel D, Durán Graeff LA, Vehreschild M, Wisplinghoff H, Ziegler M, Vehreschild JJ, et al. FungiScope(™) -Global Emerging Fungal Infection Registry. Mycoses. 2017;60(8):508-16.
22. Koehler P, Arendrup MC, Arikan-Akdagli S, Bassetti M, Bretagne S, Klingspor L, et al. ECMM CandiReg-A ready to use platform for outbreaks and epidemiological studies. Mycoses. 2019;62(10):920-7.
23. Papon N, Courdavault V, Clastre M, Bennett RJ. Emerging and emerged pathogenic Candida species: beyond the Candida albicans paradigm. PLoS Pathog. 2013;9(9):e1003550.
24. Cornely FB, Cornely OA, Salmanton-García J, Koehler FC, Koehler P, Seifert H, et al. Attributable mortality of candidemia after introduction of echinocandins. Mycoses. 2020;63(12):1373-81.
25. Mazi PB, Olsen MA, Stwalley D, Rauseo AM, Ayres C, Powderly WG, et al. Attributable Mortality of Candida Bloodstream Infections in the Modern Era: A Propensity Score Analysis. Clin Infect Dis. 2022.
26. Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nat Rev Dis Primers. 2018;4:18026.
27. Alcoceba E, Gómez A, Lara-Esbrí P, Oliver A, Beltrán AF, Ayestarán I, et al. Fluconazole-resistant Candida parapsilosis clonally related genotypes: first report proving the presence of endemic isolates harbouring the Y132F ERG11 gene substitution in Spain. Clin Microbiol Infect. 2022;28(8):1113-9.
28. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-Resistant Candida auris Infections in Critically Ill Coronavirus Disease Patients, India, April-July 2020. Emerg Infect Dis. 2020;26(11):2694-6.
29. Moreno-García E, Puerta-Alcalde P, Gariup G, Fernández-Ruiz M, López Cortés LE, Cuervo G, et al. Early Stepdown From Echinocandin to Fluconazole Treatment in Candidemia: A Post Hoc Analysis of Three Cohort Studies. Open Forum Infectious Diseases. 2021;8(6):ofab250.
30. Hoenigl M, Sprute R, Arastehfar A, Perfect JR, Lass-Flörl C, Bellmann R, et al. Invasive candidiasis: investigational drugs in the clinical development pipeline and mechanisms of action. Expert Opin Investig Drugs. 2022;31(8):795-812.
31. Hoenigl M, Sprute R, Egger M, Arastehfar A, Cornely OA, Krause R, et al. The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin. Drugs. 2021; 81(15):1703-1729.
32. Driemeyer C, Falci DR, Oladele RO, Bongomin F, Ocansey BK, Govender NP, et al. The current state of clinical mycology in Africa: a European Confederation of Medical Mycology and International Society for Human and Animal Mycology survey. The Lancet Microbe. 2022;3(6):e464-e470.
33. Salmanton-Garcia JH, M; Gagneux, JP, Segal, E; Alstruey-Izquierdo, A; Arikan-Akdagli, S; Özenci, V; Vena, A; Cornely, OA. The current state of laboratory mycology in Europe: A European Confederation of Medical Mycology survey. Lancet Microbe. 2022.