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

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Corresponding Author:	Martin Hoenigl, MD Medical University of Graz San Diego, California AUSTRIA
First Author:	Martin Hoenigl, MD
Order of Authors:	Martin Hoenigl, MD
	Jon Salmanton-García
	Matthias Egger
	Jean-Pierre Gangneux, Prof
	Tihana Bicanic
	Sevtap Arikan-Akdagli, Prof
	Ana Alastruey-Izquierdo
	Nikolai Klimko, Prof
	Aleksandra Barac
	Volkan Özenci, Prof
	Eelco F. J Meijer
	Nina Khanna
	Matteo Bassetti, Prof
	Riina Rautemaa-Richardson
	Katrien Lagrou, Prof
	Kai-Manuel Adam
	Emin Halis Akalin
	Murat Akova, Prof
	Valentina Arsic-Arsenijevic
	Avinash Aujayeb
	Ola Blennow
	Stéphane Bretagne, Prof
	François Danion
	Blandine Denis
	Nick A. de Jonge
	Guillaume Desoubeaux
	Lubos Drgona
	Nurettin Erben
	Andrea Gori

	Julio García Rodríguez
	Carolina Garcia-Vidal
	Daniele Roberto Giacobbe
	Anna L. Goodman
	Petr Hamal
	Helena Hammarström
	Christina Toscano
	Fanny Lanternier
	Cornelia Lass-Flörl, Prof
	Deborah E. A. Lockhart
	Thomas Longval
	Laura Loughlin
	Tadeja Matos
	Malgorzata Mikulska
	Manjusha Narayanan
	Sonia Martín-Pérez
	Juergen Prattes
	Benedict Rogers
	Laman Rahimli
	Maite Ruiz
	Emmanuel Roilides
	Michael Samarkos
	Ulrike Scharmann
	Uluhan Sili
	Oguz Resat Sipahi
	Alena Sivakova
	Joerg Steinmann
	Janina Trauth
	Ozge Turhan
	Jens Van Praet
	Antonio Vena
	P. Lewis White, Prof
	Birgit Willinger, Prof
	Anna Maria Tortorano
	Maiken C. Arendrup
	Philipp Koehler
	Oliver A. Cornely, Prof
Manuscript Region of Origin:	AUSTRIA
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 Each participating hospital (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 in 20 European countries. 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%).

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, Spain4 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

207	Nikolai KLIMKO	0000-0001-6095-7531
208	Volkan ÖZENCI	0000-0002-8069-4027
209	Eelco F J MEIJER	0000-0002-0226-024X
210	Nina KHANNA	0000-0002-2642-419X
211	Matteo BASSETTI	0000-0002-0145-9740
212	Riina RAUTEMAA-RICHARDSON	0000-0002-1071-6040
213	Katrien LAGROU	0000-0001-8668-1350
214	Kai Manuel ADAM	0000-0003-3639-872X
215	Emin Halis AKALIN	0000-0001-7530-1279
216	Murat AKOVA	0000-0002-6904-9473
217	Valentina ARSIC ARSENIJEVIC	0000-0001-8132-3300
218	Avinash AUJAYEB	0000-0002-0859-5550
219	Ola BLENNOW	0000-0002-7167-7882
220	Stephane BRETAGNE	0000-0001-6870-3800
221	Francois DANION	0000-0003-3907-0658
222	Nick DE JONGE	0000-0002-9901-0887
223	Guillaume DESOUBEAUX	0000-0001-7945-9890
224	Lubos DRGONA	0000-0002-5089-3201
225	Nurettin ERBEN	0000-0003-0373-0132
226	Daniele Roberto GIACOBBE	0000-0003-2385-1759
227	Anna GOODMAN	0000-0003-0643-9017
228	Andrea GORI	0000-0001-6587-4794
229	Petr HAMAL	0000-0002-5361-8125
230	Helena HAMMARSTRÖM	0000-0002-5859-1056
231	Cristina TOSCANO	0000-0002-4674-6065
232	Cornelia LASS-FLÖRL	0000-0002-2946-7785
233	Deborah E. A. LOCKHART	0000-0002-4262-3842
234	Tadeja MATOS	0000-0002-5696-1412
235	Małgorzata MIKULSKA	0000-0002-5535-4602
236	Thomas LONGVAL	0000-0002-0254-1519
237	Jens VAN PRAET	0000-0002-7125-7001
238	Sonia Martín-Pérez	0000-0001-5809-7165
239	Juergen PRATTES	0000-0001-5751-9311

240	Laman RAHIMLI	0000-0003-2266-445X
241	Zdeněk RÁČIL	0000-0003-3511-4596
242	Benedict ROGERS	0000-0002-7041-6744
243	Emmanuel ROILIDES	0000-0002-0202-364X
244	Michael SAMARKOS	0000-0001-9630-9712
245	Ulrike SCHARMANN	0000-0001-7689-7799
246	Uluhan SILI	0000-0002-9939-9298
247	Alena SIVAKOVA	0000-0002-9224-4613
248	Jörg STEINMANN	0000-0002-3181-3667
249	Ozge TURHAN	0000-0003-1494-9973
250	Antonio VENA	0000-0002-0697-3992
251	P Lewis WHITE	0000-0003-3056-4205
252	Birgit WILLINGER	0000-0001-7921-5749
253	Anna Maria TORTORANO	0000-0003-2093-8250
254	Maiken Cavling ARENDRUP	0000-0002-4747-0144
255	Philipp KOEHLER	0000 -0002 -7386 -7495
256	Oliver A. CORNELY	0000-0001-9599-3137
257		
258	Contributors:	
259	Julio Dávila -Valls	0000-0002-5185-2073
260	Tomas Freiberger	0000-0001-6532-7053
261	Alida Fe Talento	0000-0003-1271-2550
262	Christopher MILACEK	0000-0002-6924-0075
263		
264		

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

Each participating hospital (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 in 20 European countries. 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%).

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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.

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).

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 χ^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**. 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 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.

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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.

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

593 Despite its large size (64 institutions in 20 European countries) this multicentre multinational study
594 comes along with some limitations. Not all requested data were available for all patients, and the
595 presented data reflect a real-life scenario with no predefined fungal diagnostic strategies or
596 treatment protocols, potentially affecting the ability to make an early diagnosis and outcomes. In
597 addition, EQUAL *Candida* scores may be higher in long-term survivors versus those with an early
598 fatal outcome, given the fact that some of the diagnostic and treatment recommendations take time
599 and may not be available in patients with an early fatal outcome. We therefore adjusted our analyses
600 to exclude all patients with a fatal outcome within the first 7 days after diagnosis but cannot rule
601 out that even after this adjustment survival duration may remain a confounder, particularly for
602 length of therapy. However, the fact that when the analysis was limited to include only patients
603 surviving more than 14 days, survival remained longer for patients receiving treatment for >14
604 days [78% (239/306) versus 66% (67/102)], indicates that treatment duration may have an impact
605 on longer term survival. Importantly, availability of fungal diagnostics, ID/microbiology
606 consultations and also access to antifungal drugs varies across the world with more limited access
607 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.

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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.

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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.

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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.

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Data sharing statement:

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

Table 1. Univariable and multivariable Cox regression model for predictors of mortality in candidemia (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) **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) **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.

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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*

722 **Table 3.** Absolute mortality rates for EQUAL score variables if absent, as well as multivariable Cox
723 regression models [each variable adjusted for age, ICU, Charlson comorbidity index (excluding age),
724 *Candida tropicalis*] for score variables for prediction of mortality in patients with invasive candidiasis
725 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. *CVC carriers only			

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

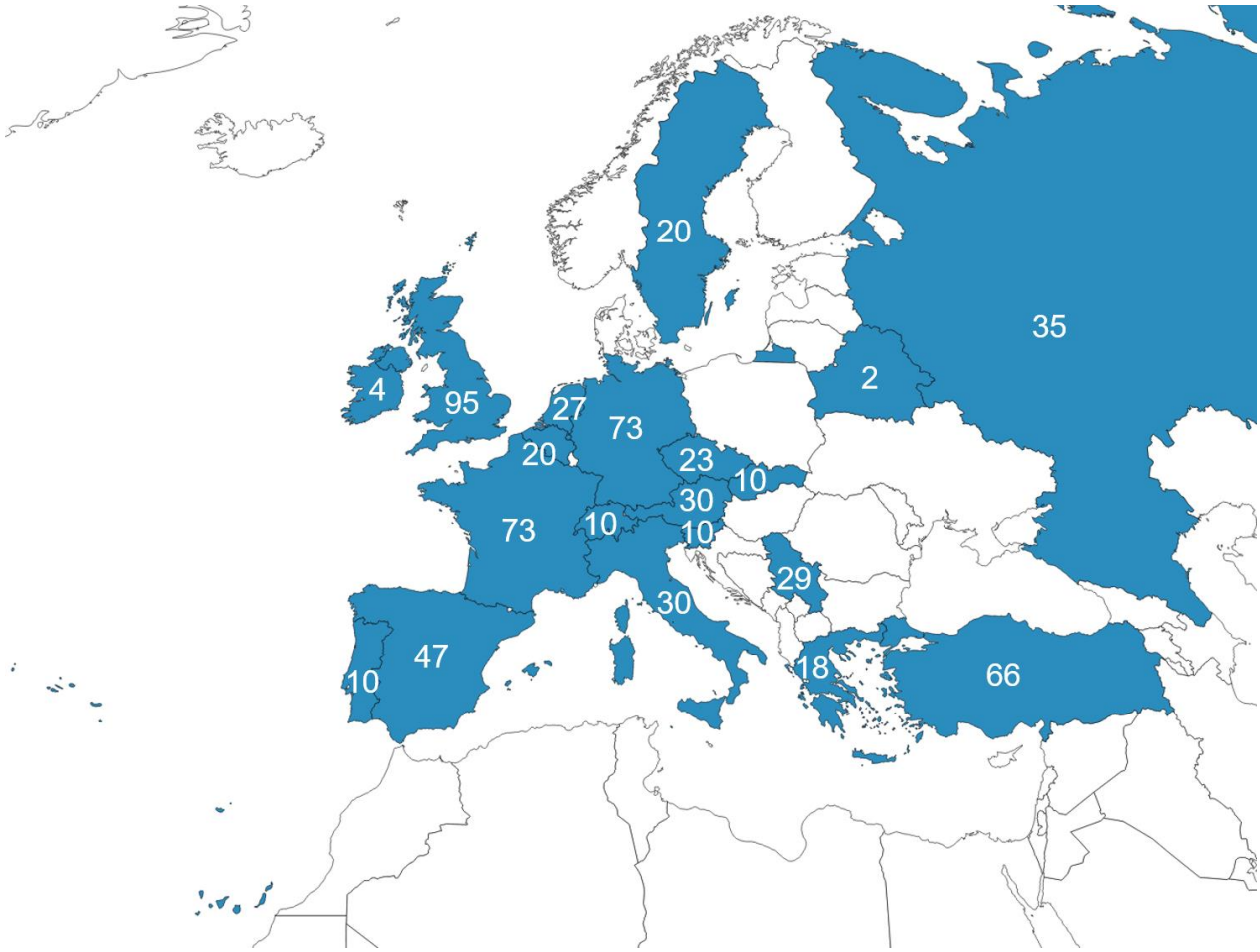


Figure 2. Study flowchart.

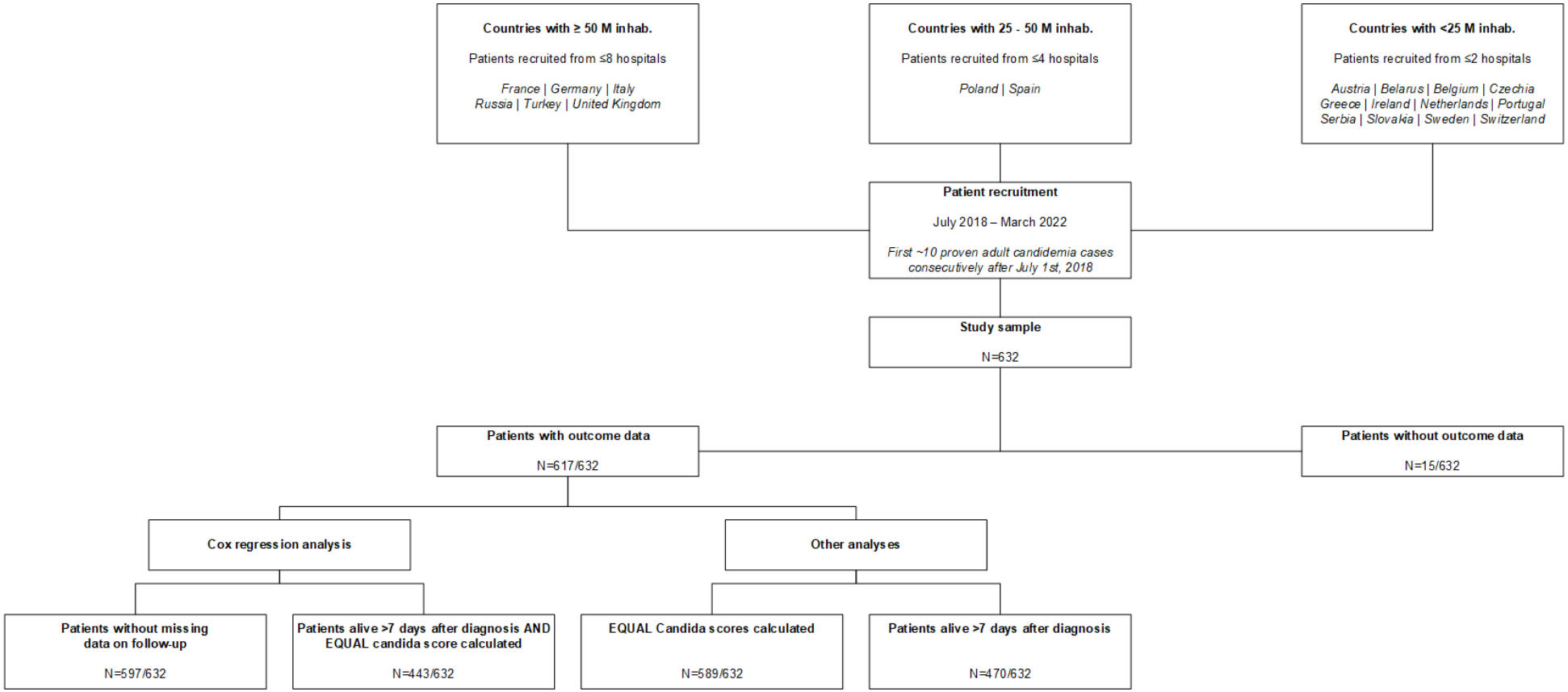
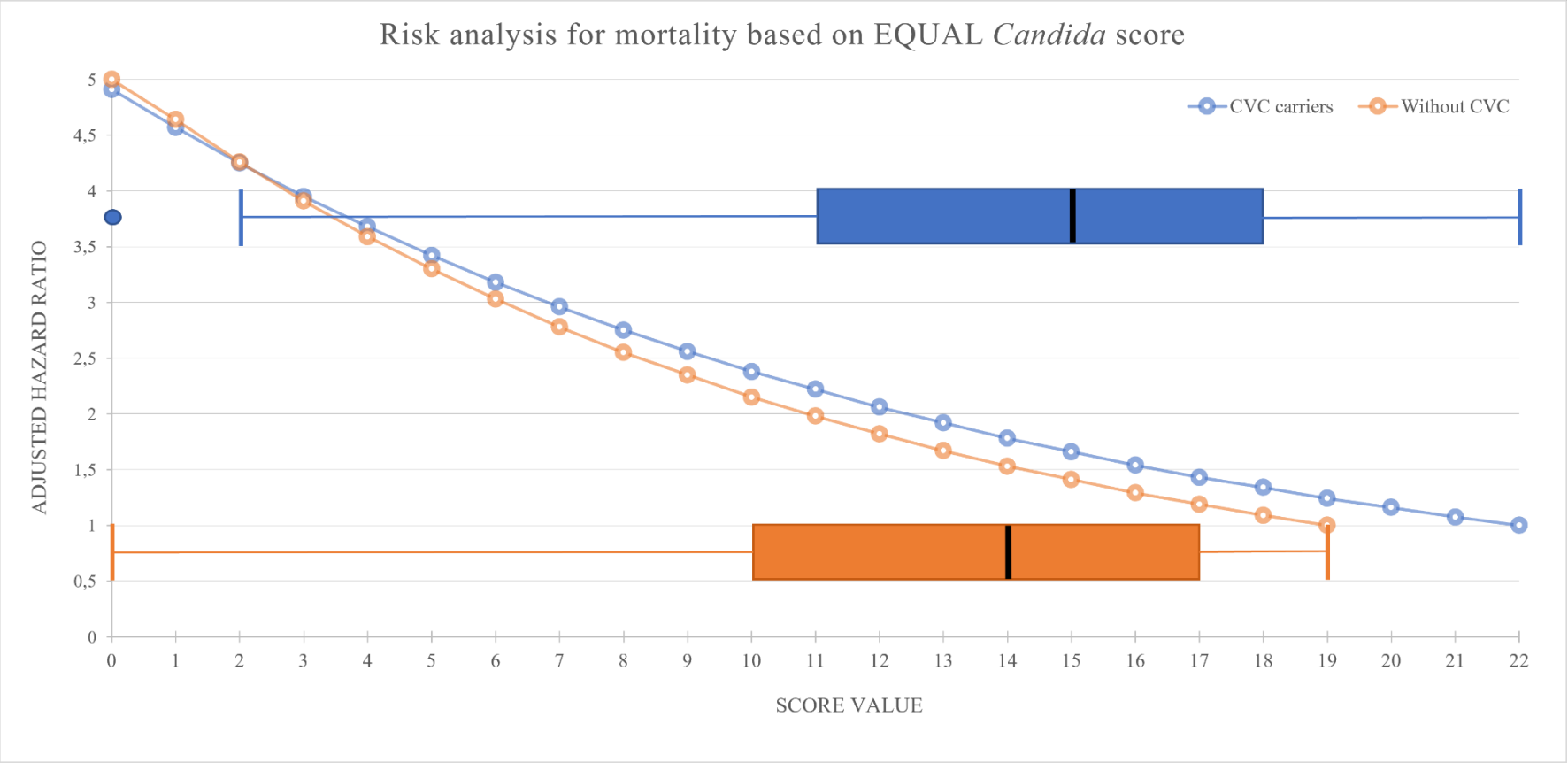


Figure 3. Adjusted* hazard ratios per point increase in EQUAL Candida scores for patients with central venous catheters (CVCs, blue) and those without (orange), as well as Boxplots



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

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