American Journal of Transplantation xxx (xxxx) xxx

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

# Invasive *Candida* infections in solid organ transplant recipients between 2008 and 2020

Lilly Meyer [1,**], Jaromil Frossard [2], Peter W. Schreiber [1], Oriol Manuel [3], Frederic Lamoth [3,4], Nina Khanna [5], Katia Boggian [6], Laura Walti [7], Christian Garzoni [8], Christian van Delden [9], Nicolas J. Mueller [1], Dionysios Neofytos [9,*], for the Swiss Transplant Cohort Study[†]

[1] *Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland*
[2] *Data Center of the Swiss Transplant Cohort Study, Basel University Hospital, Basel, Switzerland*
[3] *Division of Infectious Diseases and Transplantation Center, University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland*
[4] *Institute of Microbiology, Department of Pathology and Laboratory Medicine, University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland*
[5] *Division of Infectious Diseases, University and University Hospital Basel, Basel, Switzerland*
[6] *Division of Infectious Diseases, Infection Prevention and Travel Medicine, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*
[7] *Department of Infectious Diseases, Inselspital, Berne University Hospital, University of Berne, Berne, Switzerland*
[8] *Clinic of Internal Medicine and Infectious Diseases, Clinica Luganese Moncucco, Lugano, Switzerland*
[9] *Transplant Infectious Diseases Unit, Service of Infectious Diseases, University Hospitals Geneva, University of Geneva, Geneva, Switzerland*

ARTICLE INFO

*Keywords:*
invasive candidiasis
candidemia
solid organ transplant recipients
epidemiology
outcomes

ABSTRACT

Contemporary data on the epidemiology and outcomes of invasive candidiasis (IC) in solid organ transplant recipients (SOTr) are limited. This retrospective multicenter cohort study, nested within the Swiss Transplant Cohort Study, describes the epidemiology and outcomes of IC in SOTr from 2008 to 2020. Among 4755 patients identified, 205 (4.3%) had 262 episodes of IC. One-year cumulative incidence of IC was 2.8% (95% confidence interval [CI], 2.4, 3.3) and decreased during the study period ($P = .046$). Candidemia was less frequently encountered (0.67%, 95% CI, 0.47, 0.94) than intra-abdominal (1.4%, 95% CI, 1.1, 1.7) and other infection sites (0.93%, 95% CI, 0.68, 1.2). Most infections occurred in the first year posttransplant (65.3%, 171/262), with *Candida albicans* being the most common species (69.6%, 181/262), followed by *C. glabrata* (27.4%, 32/117). All-cause 12-week mortality was 23.5%, highest in liver (34.5%) and heart (30%) transplant recipients.

*Abbreviations:* CI, confidence interval; GIT, gastrointestinal tract; HR, hazard ratio; IC, invasive candidiasis; IQR, interquartile range; SOT, solid organ transplantation; SOTr, solid organ transplant recipients; SSI, surgical site infection; STCS, Swiss Transplant Cohort Study.

* Corresponding author. Dionysios Neofytos, Transplant Infectious Diseases Unit, Service of Infectious Diseases, University Hospitals Geneva, Rue Gabrielle-Perret-Gentil 4, CH-1211 Genève 14, Switzerland.
** Corresponding author. Lilly Meyer, Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland.
*E-mail addresses:* lillmeye@gmail.com (L. Meyer), dionysios.neofytos@hug.ch (D. Neofytos).
[†] Swiss Transplant Cohort Study members are listed in the Acknowledgments

https://doi.org/10.1016/j.ajt.2025.07.2480
Received 5 March 2025; Received in revised form 23 July 2025; Accepted 23 July 2025
Available online xxxx

Candidemia was associated with a high 12-week mortality (51.1%), significantly impacting 1-year posttransplant mortality, especially if it occurred in the first 3 months (hazard ratio, 26; 95% CI, 14.2, 47.4). In conclusion, we report high rates of IC, predominantly intra-abdominal, with decreasing incidence during the study period. Mortality remains high, especially for liver and heart transplant recipients and in patients with candidemia. Those observations can inform future prophylactic and other strategies in the care of SOTr.

## 1. Introduction

With a 1-year cumulative incidence of 1.9%, invasive candidiasis (IC) is the most common invasive fungal infection following solid organ transplantation (SOT) and is associated with a high (up to 27.3%) 30-day mortality.[1-3] Prior reports have shown that IC occurs commonly in the first 90 days after transplantation, with candidemia being the predominant infection, followed by intra-abdominal candidiasis.[4] *Candida albicans* remains the most prevalent *Candida* species for invasive infection. Yet, there has been a steady shift toward non-*albicans Candida* spp. over the past 2 decades, associated with worse outcomes in solid organ transplant recipients (SOTr).[4-7] Contemporary data on epidemiologic and clinical features of IC in SOTr are limited, with most published multicenter data covering surveillance periods before 2010 or being restricted to specific transplant types or infection sites.[1-4,8,9] We performed a multicenter cohort study over a 13-year period on the epidemiology and outcomes of invasive *Candida* infection in SOTr using the Swiss Transplant Cohort Study (STCS).

## 2. Material and methods

### 2.1. Study design

This study was a nested project within the STCS, a prospective national cohort of SOTr in Switzerland, which includes >93% of all transplant recipients since May 2008, as previously described.[10,11] Prior to transplant, written informed consent is obtained for each patient. Data, including data on infectious complications, are prospectively collected at prespecified scheduled patient visits by dedicated study coordinators. To assure the accuracy and reproducibility of the data collected, the STCS Central Data Center performs regular data monitoring and in-depth data quality audits.[10,12] In this study, we included all adult (≥18 years old) SOTr of heart, kidney, liver, lung, pancreas, and pancreas-kidney that have been enrolled in the STCS between May 1, 2008, and December 31, 2020. The follow-up ended on December 31, 2021. For patients who received more than 1 transplant, only the first transplant was considered, and patient follow-up was stopped at the time of the second transplant. Patients were excluded if they were <18 years old, had not signed or retracted an informed consent form, or if they presented a document attesting refusal. The study was approved by the STCS Scientific Committee and the relevant ethics committees (CCER 2022-02111).

### 2.2. Objectives

The primary objective was to describe the cumulative incidence of IC, overall, and according to the type of transplant for all IC events and by IC site (candidemia versus intra-abdominal IC versus other). As secondary objectives, we described the (a) characteristics of *Candida* infection, (b) distribution of *Candida* spp. by transplant type and infection site, and (c) all-cause 12-week mortality.

### 2.3. Data collection

All patients were identified using the STCS database. The following data were directly retrieved from the database: (i) demographics (age at transplantation, gender, ethnicity); (ii) SOT variables: comorbidities at baseline; donor type (living versus deceased); transplant history; transplant center; cold ischemia time; blood group compatibility; induction and initial maintenance immunosuppression administered; and cytomegalovirus and Epstein-Barr-virus donor and recipient (R) serology status; (iii) IC specific variables: type of infection (proven and probable; monomicrobial and polymicrobial); *Candida* species (*C. albicans* versus *C.* non-*albicans*); timing of IC posttransplant and site(s) of infection, antifungal prophylaxis, and treatment administered; and (iv) outcome data: death, graft loss, and the need for retransplantation.

Microbiological identification of non-*albicans Candida* spp. and data on antifungal susceptibility are not available in the STCS database. However, individual chart review was performed with the collection of detailed microbiological data on all IC cases due to non-*albicans Candida* spp. included in this study. Antifungal prophylaxis and treatment were recorded in the STCS database until 2019; since then, recording of antimicrobial prophylaxis and treatment data has been limited to a dichotomous variable (yes/no); thus, no information on specific antifungal substances was available for the whole study period. However, detailed information on institutional antifungal prophylaxis strategies by SOT type was collected via the transplant centers and is presented in detail in Supplementary Table 1. There is no standard universal strategy for donor *Candida* spp. colonization/infection screening across the different transplant

centers; hence, relevant data are not available and were not included in this study.

### 2.4. Definitions

All infectious disease events were confirmed by transplant infectious disease specialists at each center, using consensus definition guidelines by the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group and the STCS Infectious Diseases Working Group definitions, when applicable.[10,12-14] Briefly, proven IC required histo/cytopathology, or direct microscopy of *Candida* spp. obtained from a normally sterile site with hyphae, or a positive culture for *Candida* spp. from a normally sterile site and clinical or radiological abnormalities consistent with an infectious disease process, or a positive blood culture for *Candida* spp. Probable IC required the presence of at least one host factor in addition to clinical and mycological criteria. Clinical findings depended on the site of infection: for instance, the presence of small, target-like abscesses in the liver or spleen in cases of hepatosplenic candidiasis, biliary tract structural or other abnormalities or collections in biliary infections, peritonitis, abdominal collections, or other abnormalities in gastrointestinal tract (GIT) infections, retinal exudates in endophthalmitis, tracheal ulcers, plaques, and pseudomembranes on bronchoscopy for tracheobronchitis, and urinary tract symptoms with fever, and pathologic sediment in cases of urinary tract infections. Mycological criteria included direct microscopy, culture, or polymerase chain reaction (PCR) and serum b-D-glucan results (different b-D-glucan tests might have been used at different centers, with cutoff positivity used as per the test manufacturer for each center).[12] Infection sites as reported in the STCS included candidemia; GIT, liver, and biliary tract; mucocutaneous; respiratory tract; and surgical site infections (SSIs). All GIT, liver, and biliary tract infections were analyzed together as intra-abdominal IC. Of all respiratory tract infections recorded in the STCS database, only proven infections, confirmed by local principal investigators after dedicated chart review, were included in this study. The confirmed respiratory tract infections included diagnosis of empyema, parenchymal/endo-/peribronchial invasive infection, tracheobronchitis, and lung abscess, based on the abovementioned criteria. Mucocutaneous *Candida* infections were excluded from all further IC analyses. Patients could have more than 1 episode of IC during the study period and 1 episode could affect more than 1 site. Episodes were defined as polymicrobial if more than 1 *Candida* spp. was identified at the same site. Induction immunosuppressive treatment was reported within $\pm$7 days from the day of transplant. Maintenance immunosuppressive treatment was reported from the day of transplant until the end of follow-up. Pancreas and pancreas-kidney transplant recipients were included in the same group due to the small number of pancreas transplantations. There is not a formal definition of renal failure in the STCS, which is defined according to clinical assessment based on creatinine and estimated glomerular filtration rate (eGFR) values and renal replacement therapies or not.

### 2.5. Statistical analysis

Patient and donor characteristics were described as counts and percentages for categorical data and as median and interquartile range (IQR) for quantitative data. Cumulative incidence was calculated for all SOT categories and by SOT category considering IC as the primary event of interest and the following as competing events: death, complete graft failure, or a second transplant, whichever comes first. In addition, cumulative incidence was calculated by transplant period for all SOT categories and by SOT category. Cumulative incidence curves were reported at the patient level. When split by infection site or species, the cumulative incidence curves were reported on the subset of the event associated with the mentioned pathogen/species. To quantify 12-week mortality among patients with IC, we used the Kaplan-Meier method. We looked at the cumulative 12-week mortality after IC and the 12-week mortality after IC based on infection sites, *Candida* spp. (*C. albicans* versus non-*albicans Candida* spp.), and across different transplant types. A time-varying Cox proportional hazard model stratified by transplant organ was applied to assess the impact of IC on 1-year mortality. The model was constructed using the start/stop format including coding for the periods "pre-infection," "0-3 months," "3-6 months," and "6-12 months," and the infection sites "candidemia," "intra-abdominal," and "other." The infection sites follow a hierarchical order (candidemia $>$ intra-abdominal $>$ other) according to their assumed respective risk for mortality. Results were presented both unadjusted and adjusted using the Holm correction to control for multiple testing.[15] The Gray's and log-rank tests were used to compare cumulative incidence and mortality curves, respectively, separated by transplant type, infection site, and *Candida* species.[16] The Rosner-Glynn-Lee method was used to compare the time from transplantation until IC.[17,18] All statistical analyses were conducted using R version 4.4, utilizing packages from the «tidyverse» suite for data manipulation and visualization, «survival» and "tidycmprsk" for survival analysis, and «gtsummary» for summary statistics.[19-23] Statistical significance was assessed at a two-sided 0.05 level for all analyses.

## 3. Results

### 3.1. Cohort characteristics

From 7396 SOTr enrolled in the STCS during the 13-year study period, 4755 patients were included in this study (Supplementary Fig. S1). Among those, 205/4755 (4.3%) patients had 262 episodes of IC. Table 1 shows the baseline characteristics of 205 SOTr with IC: 84 (41%) liver, 58 (28.3%) kidney, 39 (19%) lung, 14 (6.8%) pancreas and pancreas-kidney, and 10 (4.9%) heart recipients. The median age of patients with IC was 56 years (IQR, 48, 63), and 94/205 (45.9%) patients were female. The baseline characteristics of the 4550 SOTr without IC are presented in Supplementary Table 2.

**Table 1**
Baseline characteristics of solid organ transplant recipients with invasive *Candida* infections.

| | SOTr without IC N = 4550 (%) | SOTr with IC N = 205 (%) | Heart N = 10 (%) | Kidney N = 58 (%) | Liver N = 84 (%) | Lung N = 39 (%) | Pancreas ± kidney N = 14 (%) |
|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | |
| Age at TPX, years (median, IQR) | 55 (45, 62) | 56 (48, 63) | 62 (51, 63) | 61 (51, 70) | 56 (48, 62) | 56 (51, 60) | 42 (35, 49) |
| Sex, female | 1586 (34.9) | 94 (45.9) | 0 (0) | 34 (58.6) | 33 (39.3) | 16 (41) | 11 (78.6) |
| Ethnicity, white patients[a] | 4142 (91.5) | 188 (92.2) | 10 (100) | 54 (93.1) | 78 (92.9) | 36 (94.7) | 10 (71.4) |
| Comorbidities | | | | | | | |
| Cardiovascular/pulmonary | 2703 (59.4) | 141 (68.8) | 10 (100) | 44 (75.9) | 41 (48.8) | 38 (97.4) | 8 (57.1) |
| Diabetes mellitus | 959 (21.1) | 68 (33.2) | 2 (20) | 24 (41.4) | 21 (25) | 7 (17.9) | 14 (100) |
| Hypertension | 2797 (61.5) | 92 (44.9) | 4 (40) | 51 (87.9) | 20 (23.8) | 10 (25.6) | 7 (50) |
| Malignancy | 1072 (23.6) | 53 (25.9) | 0 (0) | 11 (19) | 37 (44) | 5 (12.8) | 0 (0) |
| Metabolic/endocrine | 2336 (51.3) | 110 (53.7) | 10 (100) | 31 (53.4) | 36 (42.9) | 26 (66.7) | 7 (50) |
| Renal failure | 3201 (70.4) | 119 (58) | 8 (80) | 57 (98.3) | 37 (44) | 4 (10.3) | 13 (92.9) |
| Serologies | | | | | | | |
| CMV[a] | | | | | | | |
| D−/R− | 940 (20.8) | 27 (13.2) | 4 (40) | 5 (8.6) | 12 (14.3) | 5 (13.2) | 1 (7.1) |
| R+ | 2713 (60) | 140 (68.6) | 5 (50) | 41 (70.7) | 58 (69) | 26 (68.4) | 10 (71.4) |
| D+/R− | 869 (19.2) | 37 (18.1) | 1 (10) | 12 (20.7) | 14 (16.7) | 7 (18.4) | 3 (21.4) |
| EBV[a] | | | | | | | |
| D−/R− | 51 (1.1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| R+ | 4264 (94.9) | 190 (96) | 9 (100) | 57 (98.3) | 74 (93.7) | 36 (94.7) | 14 (100) |
| D+/R− | 176 (3.9) | 8 (4) | 0 (0) | 1 (1.7) | 5 (6.3) | 2 (5.3) | 0 (0) |
| Transplant characteristics | | | | | | | |
| Donor, deceased | 3415 (75.1) | 178 (86.8) | 10 (100) | 43 (74.1) | 72 (85.7) | 39 (100) | 14 (100) |
| Blood group compatibility | 4374 (96.1) | 204 (99.5) | 10 (100) | 57 (98.3) | 84 (100) | 39 (100) | 14 (100) |
| Maximal CIT, minutes (median, IQR)[a] | 356 (150, 520) | 381 (272.5, 523.5) | 176 (123, 186) | 475 (258, 656) | 385 (310, 484) | 339 (275, 380) | 600.5 (526, 666) |
| Induction IS[b] | | | | | | | |
| Basiliximab | 3394 (74.6) | 152 (74.1) | 3 (30) | 44 (75.9) | 65 (77.4) | 38 (97.4) | 2 (14.3) |
| Thymoglobulin | 910 (20) | 38 (18.5) | 8 (80) | 18 (31) | 0 (0) | 0 (0) | 12 (85.7) |
| Other | 64 (1.4) | 3 (1.5) | 0 (0) | 1 (1.7) | 2 (2.4) | 0 (0) | 0 (0) |
| First maintenance IS[c] | | | | | | | |
| Antimetabolites | 4330 (95.2) | 189 (92.2) | 10 (100) | 58 (100) | 68 (81) | 39 (100) | 14 (100) |
| Calcineurin inhibitors | 4494 (98.8) | 205 (100) | 10 (100) | 58 (100) | 84 (100) | 39 (100) | 14 (100) |
| Corticosteroids | 4491 (98.7) | 204 (99.5) | 9 (90) | 58 (100) | 84 (100) | 39 (100) | 14 (100) |
| mTORi | 608 (13.4) | 37 (18) | 2 (20) | 1 (1.7) | 26 (31) | 7 (17.9) | 1 (7.1) |
| Antifungal prophylaxis[d] | 520 (11.4) | 48 (23.4) | 1 (10) | 2 (3.4) | 7 (8.3) | 36 (92.3) | 2 (14.3) |

CIT, cold ischemia time; CMV, cytomegalovirus; D, donor; EBV, Epstein-Barr virus; IC, invasive candidiasis; IQR, interquartile range; IS, immunosuppression; mTORi, mammalian target of rapamycin inhibitors; R, recipient; SOTr, solid organ transplant recipients; TPX, transplantation.

[a] Missing values for SOTr with IC: Ethnicity (N:1), CMV (N:1), EBV (N:7), and maximal CIT (N:5).

[b] Induction immunosuppression was reported within ±7 days from the day of transplant.

[c] Maintenance immunosuppressive treatment was reported from the day of transplant until the end of follow-up.

[d] Antifungal prophylaxis at baseline was reported from the day of transplant until 14 days posttransplant.

### 3.2. Incidence of IC

The 1-year cumulative incidence of IC was 2.8% (95% confidence interval [CI], 2.4, 3.3) for all SOTr: 1.8% (95% CI, 0.82, 3.6) for heart, 5.4% (95% CI, 4.2, 6.8) for liver, 5.9% (95% CI, 4.1, 8.3) for lung, 1% (95% CI, 0.69, 1.5) for kidney, and 8.4% (95% CI, 4.3, 14) for pancreas/pancreas-kidney transplant recipients (Gray's test 90.5; $P < .001$) (Fig. 1A, B). Candidemia appeared to be less frequently encountered, when compared with intra-abdominal and all other site IC (Fig. 1C-E). When looked separately by SOT type, 1-year cumulative incidence for candidemia was 0.67% (95% CI, 0.47, 0.94) for all SOT recipients: 1.3% (95% CI, 0.5, 2.9) for heart, 1.3% (95% CI, 0.79, 2.2) for liver, 1.8% (95% CI, 0.91, 3.4) for lung, and 0.11% (95% CI, 0.03, 0.32) for kidney transplant recipients (Gray's test 32.9; $P < .001$); in pancreas/pancreas-kidney transplant recipients no candidemia events were observed (Supplementary Fig. S2A). One-year cumulative incidence of intra-abdominal IC and all other IC was 1.4% (95% CI, 1.1, 1.7) and 0.93% (95% CI, 0.68, 1.2), respectively (data by SOT type are presented in Supplementary Fig. S2B, C). The 1-year cumulative incidence of IC due to *C. albicans* was 2% (95% CI, 1.7, 2.5) versus 1.1% (95% CI, 0.79, 1.4) for non-*albicans Candida* spp. (Fig. 1F, G; data by SOT type are shown in Supplementary Fig. S2D, E). The 1-year cumulative incidence of IC significantly decreased during the study period from 3.4% (95% CI, 2.6, 4.4), to 3.1% (95% CI, 2.3, 4.1), and 2% (95% CI, 1.4, 2.7) for patients transplanted in 2008-2012, 2013-2016, and 2017-2020, respectively (Gray's test stratified by SOTr 6.1; $P = .046$; Fig. 2A). In contrast, there was no statistically significant decline in 1-year cumulative incidence during the study period by SOT type (Fig. 2B).

### 3.3. Characteristics of IC

Among the 262 episodes of IC, 80.2% (210/262) and 19.8% (52/262) were proven and probable, respectively (Table 2). None of the 262 episodes of IC was diagnosed with b-D-glucan. The majority of infections (65.3%, 171/262) occurred in the first year posttransplant: 137/171 (80.1%) proven infections and 34/171 (19.9%) probable infections (Supplementary Fig. S1). The median time between transplantation and IC was 136 days (IQR, 20.5, 598.5): 146 days (IQR, 23, 617) and 104 days (IQR, 17, 547.8) for *C. albicans* and *C.* non-*albicans*, respectively ($P = .25$; Supplementary Fig. S3). Infection was predominantly monomicrobial (96.2%, 252/262), with *C. albicans* being the causative species in more than 2/3 of all episodes (69.6%, 181/262). Among the 117 isolated non-*albicans Candida* spp., *C. glabrata* was the most frequent species (27.4%, 32/117), followed by *C. krusei* (18.8%, 22/117) and *C. tropicalis* (9.4%, 11/117) (Fig. 3). There were no IC cases due to *C. auris* during the study period. For 24.8% (29/117) non-*albicans Candida* spp., there was no additional species identification available. *Candida glabrata* was the predominant causative species in all organ transplants, except in heart transplants with *C. krusei* and *C. parapsilosis* prevailing (Fig. 3). The most frequently affected SOT types were liver (40.8%, 107/262) and kidney (27.5%, 72/262). The predominant infection site was the GIT (41.2%, 108/262), followed by candidemia (23.3%, 61/262), SSIs (19.8%, 52/262), liver/biliary tract (9.9%, 26/262), and respiratory tract (5.7%, 15/262). More than 1 infection site was observed in 14.9% (39/262) cases. Antifungal prophylaxis prior to and antifungal treatment after diagnosis of IC were administered in 18.3% (48/262) and 95.4% (250/262) of all episodes of IC, respectively.

### 3.4. Outcome of IC

All-cause 12-week mortality in SOTr with IC was 23.5% (95% CI, 17.5, 29.2). The highest mortality was observed in liver (34.5%, 95% CI, 23.5, 43.9), closely followed by heart (30%, 95% CI, 0, 53.3) SOTr, whereas no pancreas/pancreas-kidney SOTr with IC died by 12 weeks post-diagnosis (log-rank test $P < .011$; Fig. 4A, B). Candidemia was associated with higher 12-week all-cause mortality (51.1%, 95% CI, 34.5, 63.5), compared with intra-abdominal (14%, 95% CI, 6.63, 20.7) and other IC sites (17.3%, 95% CI, 7.46, 26.1; log-rank test, $P < .001$; Fig. 4C). Mortality after infection with *C.albicans* and non-*albicans Candida* spp. was 17.2% (95% CI, 10.4, 23.5) and 35.1% (95% CI, 21.4, 46.4), respectively (log-rank test, $P = .002$; Fig. 4D). The 12-week mortality according to SOT type based on the site of infection and *Candida* spp. is shown in Supplementary Figure S4.

IC diagnosed during the first year posttransplant had an important impact on 1-year mortality in all SOTr (Fig. 5). The impact of candidemia on 1-year mortality was highest if it occurred in the first 3 months posttransplant (hazard ratio [HR], 26; 95% CI, 14.2, 47.4; $P < .001$), compared with candidemia diagnosed between 3 and 6 months (HR, 13.4; 95% CI, 3.1, 57.7; $P < .001$), and 6- and 12-month posttransplant (HR, 7.93; 95% CI, 2.45, 25.6; $P < .001$). Intra-abdominal IC was significantly associated with 1-year mortality if it occurred in the first 3 months (HR, 6.19; 95% CI; 1.92, 20; $P = .002$) or between 6 and 12 months posttransplant (HR, 9.75; 95% CI, 4.57, 20.8; $P < .001$). The impact of IC at other infection sites on mortality was significant if it was diagnosed in the first 3 months posttransplant (HR, 5.85; 95% CI, 1.83, 18.6; $P = .003$; Supplementary Table 2). Mortality did not significantly differ between monomicrobial and polymicrobial IC (log-rank test 0.9; $P = .35$; Supplementary Fig. S5).

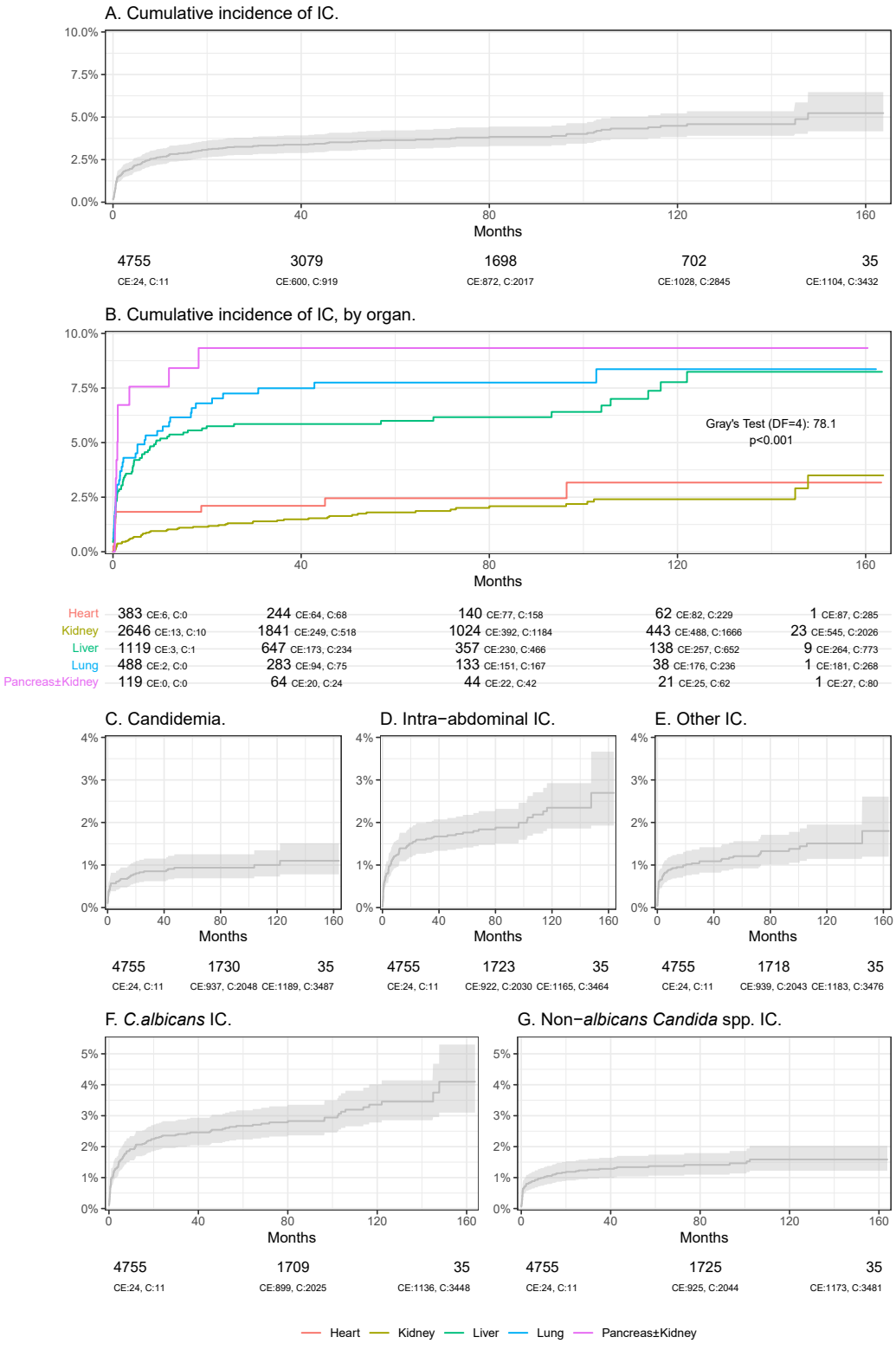


**Figure 1.** Cumulative incidence of invasive *Candida* infections overall (A), by solid organ transplant type (B), site of infection (C-E; candidemia, intra-abdominal, other), and *Candida* spp. (F, G; *C. albicans*, non-*albicans Candida* spp.). C, censored; CE, competing event; IC, invasive candidiasis; DF, degree of freedom.

## 4. Discussion

This large retrospective multicenter cohort study over a 13-year period informs on the epidemiology and outcomes of IC in SOTr, reporting 1-year cumulative incidence of IC higher than previously described with decreasing rates observed in the course of the study period and associated with substantial mortality, especially among patients with candidemia.

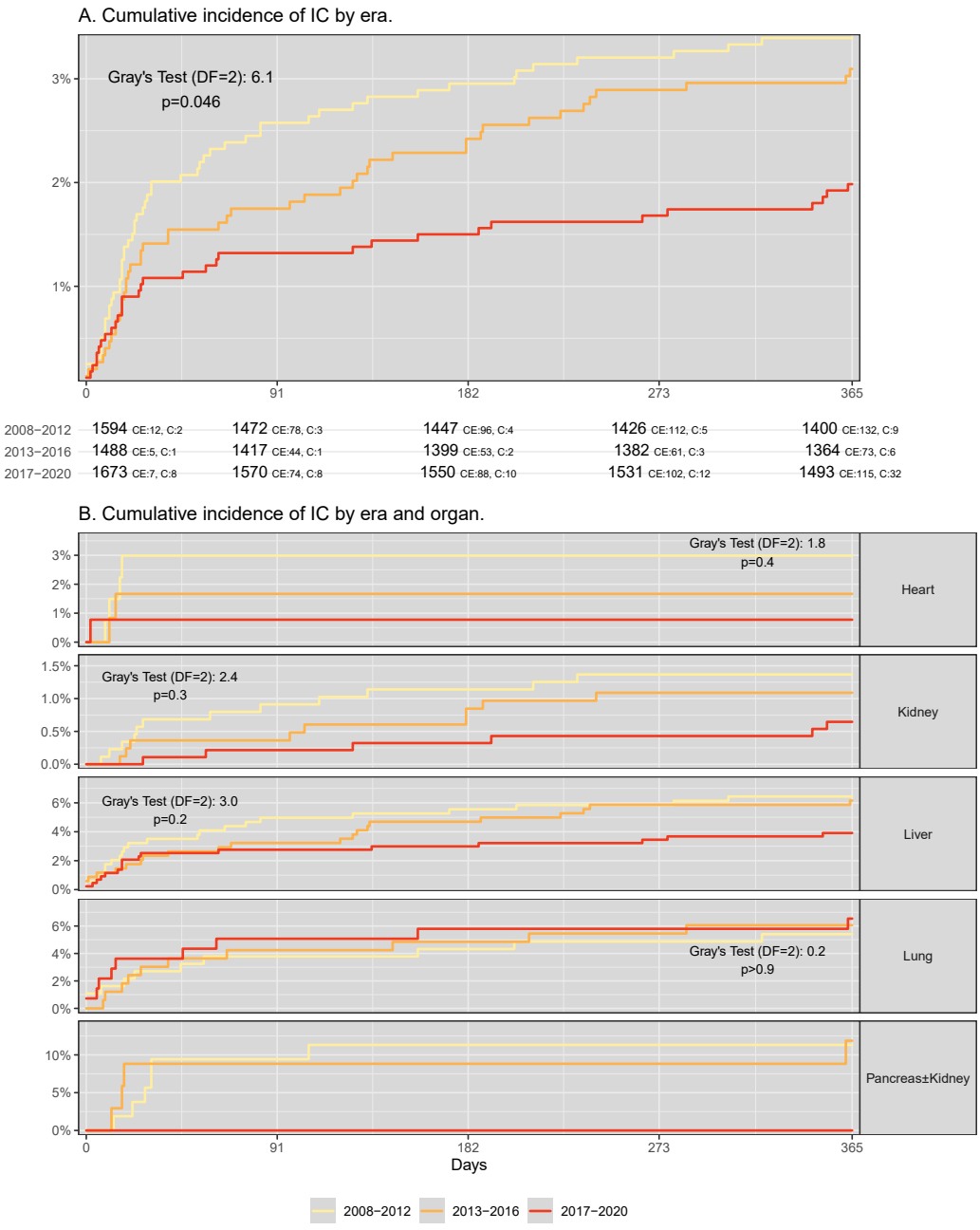


**Figure 2.** One-year cumulative incidence of invasive *Candida* infections by transplant period from 2008 to 2020 overall (A) and by solid organ transplant (SOT) type (B). For the period 2017-2020, no events were observed in pancreas/pancreas-kidney transplant recipients. C, censored; CE, competing event; IC, invasive candidiasis; DF, degree of freedom.

The 1-year cumulative incidence of IC in our study was 2.8%, which is higher than previously reported.[1,24] This may be attributed to a study period expanding over 13 years, an extensive medical network in Switzerland, which allows for close medical follow-up, and to the fact that the STCS prospectively monitors all SOTr consistently and with a median follow-up time of 4.4 years posttransplant.[11,12] The 1-year cumulative incidence of IC significantly decreased during the study period from 3.4% to 2% for patients transplanted in 2008-2012 versus 2017-2020. This likely points to improvements in diagnostics and treatment of IC. There were no relevant differences in prophylactic strategies in our study population over time. In contrast to the declining 1-year cumulative incidence, the overall cumulative incidence of IC continuously increased even after the first year posttransplant and during the 13-year follow-up period, suggesting that the risk for IC continues beyond the first year posttransplant. A previous study on IC found a similar trend, but for a shorter surveillance period.[1] In line with our findings, a recent Canadian study showed an increasing cumulative incidence of invasive fungal infection until 10 years posttransplant.[24] The above suggests that clinicians should consider this diagnosis even late posttransplant in the appropriate clinical context.

**Table 2**
Characteristics of invasive *Candida* infections.

| Characteristics | Overall | Heart | Kidney | Liver | Lung | Pancreas ± kidney |
|---|---|---|---|---|---|---|
| | N = 262 (%) | N = 12 (%) | N = 72 (%) | N = 107 (%) | N = 55 (%) | N = 16 (%) |
| **Certainty of diagnosis** | | | | | | |
| Proven | 210 (80.2) | 11 (91.7) | 54 (75) | 87 (81.3) | 47 (85.5) | 11 (68.8) |
| Probable | 52 (19.8) | 1 (8.3) | 18 (25) | 20 (18.7) | 8 (14.5) | 5 (31.3) |
| **Infection type** | | | | | | |
| Single pathogen | 252 (96.2) | 12 (100) | 70 (97.2) | 100 (93.5) | 54 (98.2) | 16 (100) |
| ***Candida* species**[a] | | | | | | |
| *Candida albicans* | 181 (69.6) | 10 (83.3) | 46 (64.8) | 76 (71) | 38 (69.1) | 11 (73.3) |
| Non-*albicans Candida* spp. | 98 (37.7) | 2 (16.7) | 29 (40.8) | 43 (40.2) | 19 (34.5) | 5 (33.3) |
| **Infection site**[b] | | | | | | |
| Candidemia | 61 (23.3) | 5 (41.7) | 10 (13.9) | 29 (27.1) | 16 (29.1) | 1 (6.3) |
| GIT | 108 (41.2) | 2 (16.7) | 31 (43.1) | 47 (43.9) | 21 (38.2) | 7 (43.8) |
| Liver/biliary tract | 26 (9.9) | 0 (0) | 0 (0) | 26 (24.3) | 0 (0) | 0 (0) |
| Respiratory tract[c] | 15 (5.7) | 0 (0) | 3 (4.2) | 2 (1.9) | 10 (18.2) | 0 (0) |
| SSI | 52 (19.8) | 5 (41.7) | 9 (12.5) | 21 (19.6) | 12 (21.8) | 5 (31.3) |
| Other[d] | 45 (17.2) | 3 (25) | 24 (33.3) | 9 (8.4) | 6 (10.9) | 3 (18.8) |
| **Antifungal prophylaxis**[e] | 48 (18.3) | 1 (8.3) | 1 (1.4) | 7 (6.5) | 37 (67.3) | 2 (12.5) |
| **Antifungal treatment** | 250 (95.4) | 11 (91.7) | 68 (94.4) | 100 (93.5) | 55 (100) | 16 (100) |

CNS, central nervous system; GIT, gastrointestinal tract; IC, invasive candidiasis; SSI, surgical site infection.

[a] In 2/262 (0.8%) episodes of IC, the *Candida* species was unknown.

[b] In 39/262 (14.9%) episodes of IC, more than 1 infection site was affected.

[c] Only proven respiratory tract infections were analyzed, including 9/15 (60%) empyema, 2/15 (13.3%) tracheobronchitis, 2/15 (13.3%) parenchymal/endo-/peribronchial invasive infection, and 1/15 (6.7%) lung abscess; 1/15 (6.7%) was diagnosed at an outside hospital, and no further information was available.

[d] Other infection sites included urinary tract (N:25), bone and joint (N:10), site not identified (N:3), CNS, conservation liquid, eye, genital tract, heart, mediastinal, and sinus (N:1 each).

[e] Antifungal prophylaxis was reported from the day of transplant until the occurrence of IC.

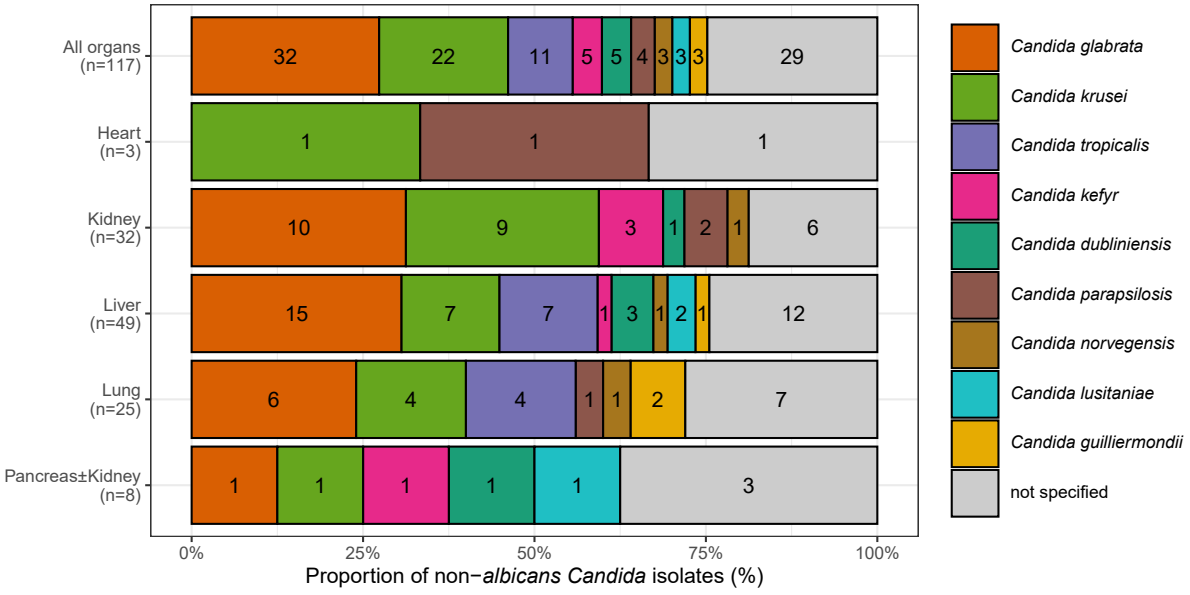


**Figure 3.** Species distribution of non-albicans *Candida* spp. in invasive *Candida* infections. Total numbers of *Candida* isolates are indicated on the *y*-axis and for each *Candida* spp.

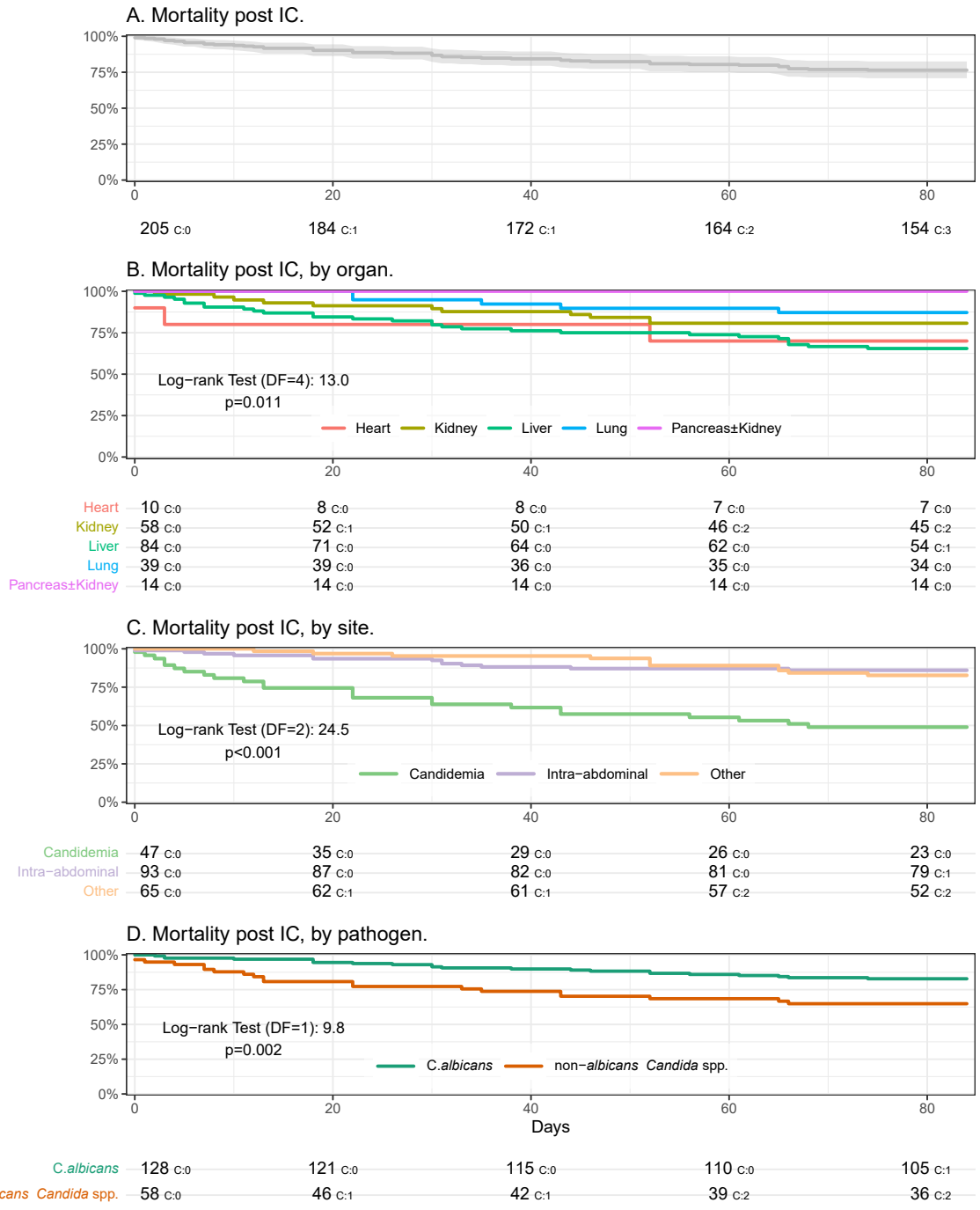


**Figure 4.** All-cause 12-week mortality of solid organ transplant recipients with invasive *Candida* infections overall (A), by solid organ transplant type (B), site of infection (C; candidemia, intra-abdominal, other), and *Candida* spp. (D; *C. albicans*, non-*albicans Candida* spp.). C, censored; IC, invasive candidiasis; DF, degree of freedom.

As previously reported, liver and kidney recipients were the predominant SOT population with IC, as they represent the most common transplanted organs in Switzerland.[11,12] However, cumulative incidence was highest after pancreas/pancreas-kidney, lung, and liver transplantation, with comparably lower incidence rates in heart and kidney SOTr. Intra-abdominal infections represented the most frequent IC manifestation in our study, followed by candidemia and SSIs. This is in contrast to previously published data with candidemia being the most frequent infection site, followed by intra-abdominal infections.[3,4] We hypothesized that an increased use of fungal biomarkers, in contrast to previous older series, could have been a potential reason for the higher numbers of intra-abdominal infections observed in our study, but surprisingly b-D-glucan was rarely used in this cohort. However, the assay was not available in many centers until very recently, which may, in part, explain the infrequent use of the test

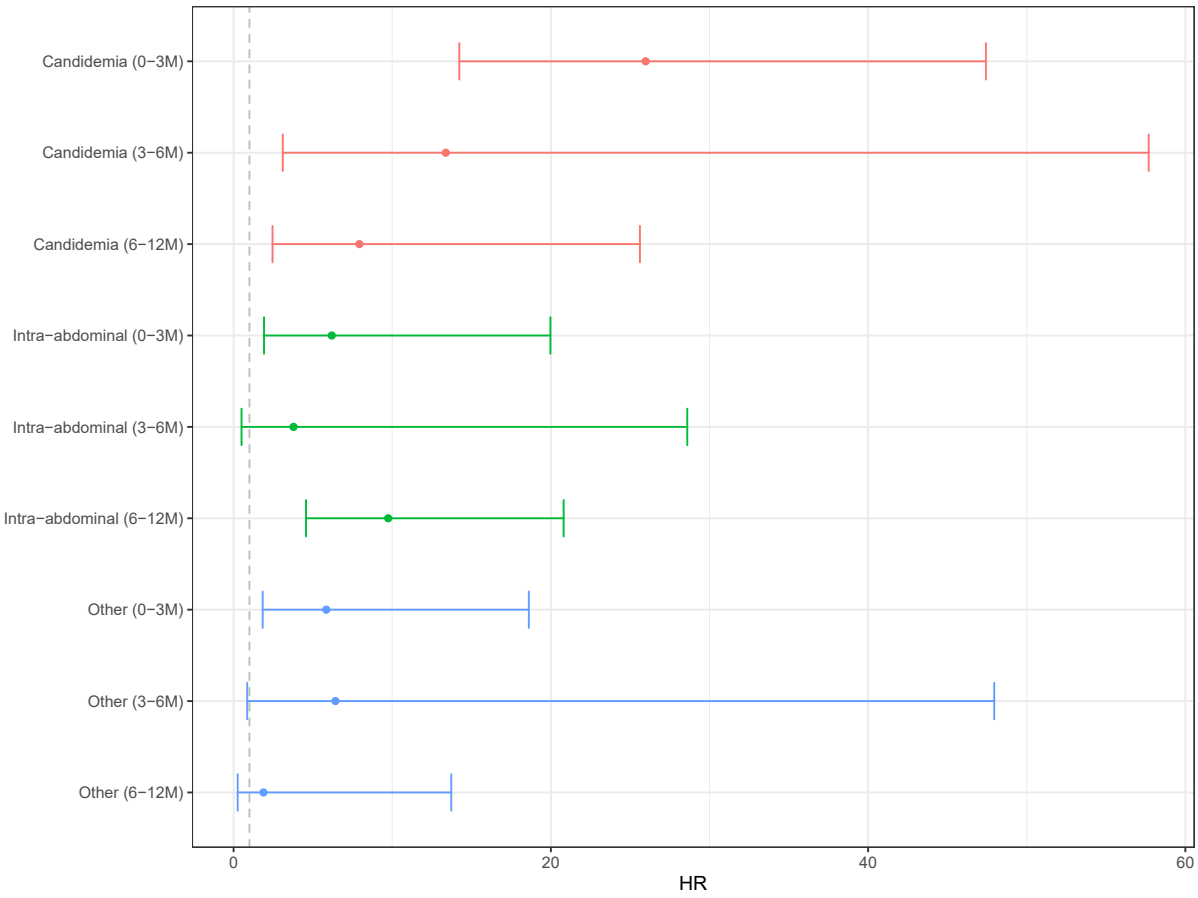


**Figure 5.** Impact of invasive *Candida* infections on 1-year mortality, using a time-varying model, stratified by organs.

during the study period. In addition, only positive b-D-glucan results are reported in the STCS database; hence, we cannot draw any conclusions on the overall performance of b-D-glucan. The considerable progress in the field, with the identification of intra-abdominal IC as a significant proportion of *Candida* infections diagnosed in clinical practice, particularly in high-risk surgical patients, might have contributed to more diagnoses of noncandidemic IC in the contemporary era.[25,26] In line with prior studies, *Candida albicans* was the single most common cause of IC, although at a relatively higher rate than previously reported.[2-4,6,8] This is consistent with other data in Switzerland as reported by the FUNGINOS group, suggesting that although non-*albicans Candida* spp. have increased from 2004 to 2018, *C. albicans* remains the predominant candidemia pathogen in Switzerland.[5] In line with other contemporary data, *C. glabrata* was the predominant non-*albicans Candida* spp. isolated in our cohort.[2,5,6] Interestingly, the proportion of *C. krusei* was higher than previously reported in SOTr with comparably lower rates of *C. parapsilosis*.[2,4] Prior data of the Prospective Antifungal Therapy (PATH) Alliance showed an association between prior antifungal therapy and isolation of *C. glabrata* or *C. krusei*, which might in part explain our findings.[3]

All-cause 12-week mortality of patients with IC in our study was 23.5%, which is in the same range as 26.5% reported in the TRANSNET study more than 2 decades ago.[4] Mortality after IC was highest among liver and heart transplant recipients, consistent with previously reported high 30-day mortality rates after liver transplantation and poor outcomes among heart recipients after IC.[3,8,27,28] Patients with intra-abdominal IC had the lowest mortality in this study. This may, in part, be due to the localized, nondisseminated infection, and the earlier diagnosis and management of those infections, with patients frequently undergoing exploratory and drainage procedures postoperatively. Although the use of b-D-glucan and molecular diagnostics has been associated with improved diagnosis of intra-abdominal IC, due to a lack of relevant data, we cannot make any further conclusions on this topic.[25,26] In contrast to the rather low mortality rates observed in patients with intra-abdominal infections, more than half of patients with candidemia died by 12 weeks, which is higher than 21%-25% described in the general population, likely reflecting the severity of this infection in high-risk, immunocompromised patients, such as SOTr.[29,30] For instance, liver transplant recipients, a particularly fragile patient population, with candidemia had the highest mortality observed in this series, further underscoring the importance of the host in driving clinical outcomes. Finally, candidemia, particularly when diagnosed early posttransplant, had an important impact on 1-year posttransplant mortality, further pointing to the clinical significance of this complication. Similar to what has already been reported, we observed higher mortality in patients with non-*albicans Candida* spp. IC compared with *Candida albicans*.[4] This may reflect selection

biases, as more severely ill patients are more likely to have been exposed to antifungal agents, hence selecting for more resistant species.

Our study has numerous limitations. Despite using international guidelines for the definition of IC, incorrect reporting of IC events in the STCS cannot be fully excluded. However, data are thoroughly reviewed and confirmed by transplant infectious disease specialists before they are validated and entered into the STCS database. Data on antifungal susceptibility are not available in the STCS database, and thus, we were not able to provide more detailed information on relevant susceptibility profiles. Antifungal prophylaxis and treatment data were available for the whole surveillance period in a dichotomic variable (yes/no) only; therefore, we cannot draw firm conclusions regarding specific treatment regimens. As detection of colonization is highly dependent on screening of asymptomatic individuals and a uniform definition and standard screening strategy for *Candida* colonization are missing in the STCS, we did not include nor analyze data on *Candida* spp. colonization in this study. Lack of standardized definition of renal failure in the STCS is an important limitation of the registry and of this manuscript, which does not allow to make more definitive conclusions as to the degree of renal insufficiency and its impact on clinical outcomes. Finally, the restriction of the study sites to Switzerland precludes generalizability to other settings.

In conclusion, this multicenter cohort study constitutes one of the largest contemporary series of IC in SOTr investigating the incidence and mortality of IC with results spanning a 13-year study period reporting on >4000 SOTr. We demonstrate a high 1-year cumulative incidence of IC in SOTr, albeit with decreasing rates over the study period, pointing to improved clinical practices and patient care of SOTr over time. Although candidemia remains the least frequent form of IC in SOTr, associated mortality remains high with significant impact on 1-year posttransplant survival. Considering the overall dismal clinical outcomes in SOTr with IC, future efforts to optimize antifungal prophylactic strategies, diagnostics, and treatment are urgently needed.

## Acknowledgments

The authors would like to thank all our patients for their trust in and support of the Swiss Transplant Cohort Study. Furthermore, the authors would like to sincerely thank all the study nurses, the central and local data managers, the investigators involved in the Swiss Transplant Cohort Study, and other staff who care for all solid organ transplant recipients in the Swiss transplant centers.

Members of the Swiss Transplant Cohort Study

Patrizia Amico, Adrian Bachofner, Vanessa Banz, Sonja Beckmann, Guido Beldi, Christoph Berger, Ekaterine Berishvili, Annalisa Berzigotti, Françoise-Isabelle Binet, Pierre-Yves Bochud, Petra Borner, Sanda Branca, Anne Cairoli, Emmanuelle Catana, Yves Chalandon, Philippe Compagnon, Sabina De Geest, Sophie De Seigneux, Michael Dickenmann, Joëlle Lynn Dreifuss, Michel Duchosal, Thomas Fehr, Sylvie Ferrari-Lacraz, Andreas Flammer, Jaromil Frossard, Déla Golshayan, Nicolas Goossens, Fadi Haidar, Jürg Halter, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Linard Hoessly, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Nina Khanna, Michael Koller, Andreas Kremer, Thorsten Krueger, Christian Kuhn, Bettina Laesser, Frédéric Lamoth, Roger Lehmann, Alexander Leichtle, Arnaud L'Huillier, Oriol Manuel, Hans-Peter Marti, Michele Martinelli, Valérie McLin, Katell Mellac, Aurélia Merçay, Karin Mettler, Nicolas Müller, Jelena Müller, Ulrike Müller-Arndt, Mirjam Nägeli, Dionysios Neofytos, Jakob Nilsson, Manuel Pascual, Rosmarie Pazeller, David Reineke, Juliane Rick, Fabian Rössler, Silvia Rothlin, Thomas Schachtner, Stefan Schaub, Dominik Schneidawind, Macé Schuurmans, Simon Schwab, Thierry Sengstag, Daniel Sidler, Federico Simonetta, Jürg Steiger, Guido Stirnimann, Ueli Stürzinger, Christian Van Delden, Jean-Pierre Venetz, Jean Villard, Julien Vionnet, Caroline Wehmeier, Markus Wilhelm, and Patrick Yerly.

## Funding

The Swiss Transplant Cohort Study is supported by the Swiss National Science Foundation (SNSF, http://www.snf.ch; grant number: 33CS30_177522/2), Unimedsuisse (https://www.unimedsuisse.ch), and the Transplant Centers.

## Author contributions

L.M., O.M., N.J.M., and D.N. participated in the study design. L.M., J.F., and D.N. participated in the analysis of data and writing of the manuscript. J.F. provided the statistical analysis. P. W.S., O.M., N.K., K.B., L.W., C.v.D., N.J.M., and D.N. participated in the data collection. All authors participated in critically reviewing the manuscript and have given final approval of the version to be published.

## Declaration of competing interest

The authors of this manuscript have conflicts of interest to disclose as described by *American Journal of Transplantation*. O. Manuel reports participating in advisory boards of MSD, Takeda, and Biotest. N.J. Mueller reports travel grants from Pfizer, MSD, and Biotest. D. Neofytos reports research support and consulting fees from MSD, Pfizer, Takeda, and Gilead. The other authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

## Data availability

All data included in the present study belong to the Swiss Transplant Cohort Study. Data can be requested for specified purposes after approval of a proposal by the Scientific Committee of the Swiss Transplant Cohort Study and approval by the responsible ethics committees.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2025.07.2480.

**ORCiD**

Lilly Meyer https://orcid.org/0009-0003-3012-1890
Oriol Manuel https://orcid.org/0000-0001-7607-0943
Dionysios Neofytos https://orcid.org/0000-0001-6970-2869

## References

1. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis*. 2010;50 (8):1101–1111. https://doi.org/10.1086/651262.
2. Fernández-Ruiz M, Cardozo C, Salavert M, et al. Candidemia in solid organ transplant recipients in Spain: epidemiological trends and determinants of outcome. *Transpl Infect Dis*. 2019;21(6):e13195. https://doi.org/10.1111/tid.13195.
3. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis*. 2010;12(3):220–229. https://doi.org/10.1111/j.1399-3062.2010.00492.x.
4. Andes DR, Safdar N, Baddley JW, et al. The epidemiology and outcomes of invasive Candida infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Transpl Infect Dis*. 2016; 18(6):921–931. https://doi.org/10.1111/tid.12613.
5. Adam KM, Osthoff M, Lamoth F, et al. Trends of the epidemiology of candidemia in Switzerland: a 15-year FUNGINOS survey. *Open Forum Infect Dis*. 2021;8(10):ofab471. https://doi.org/10.1093/ofid/ofab471.
6. Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN. Twenty years of the SENTRY antifungal surveillance program: results for *Candida* species from 1997-2016. *Open Forum Infect Dis*. 2019;6 (suppl 1):S79–S94. https://doi.org/10.1093/ofid/ofy358.
7. Puig-Asensio M, Padilla B, Garnacho-Montero J, 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–O254. https://doi.org/10.1111/1469-0691.12380.
8. Bassetti M, Peghin M, Carnelutti A, et al. Invasive *Candida* infections in liver transplant recipients: clinical features and risk factors for mortality. *Transplant Direct*. 2017;3(5):e156. https://doi.org/10.1097/TXD.0000000000000673.
9. van Hal SJ, Marriott DJ, Chen SC, et al. Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience. *Transpl Infect Dis*. 2009;11(2):122–127. https://doi.org/10.1111/j.1399-3062.2009.00371.x.
10. Koller MT, van Delden C, Müller NJ, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *Eur J Epidemiol*. 2013;28(4):347–355. https://doi.org/10.1007/s10654-012-9754-y.
11. Stampf S, Mueller NJ, van Delden C, et al. Cohort profile: the Swiss Transplant Cohort Study (STCS): a nationwide longitudinal cohort study of all solid organ recipients in Switzerland. *BMJ Open*. 2021;11(12): e051176. https://doi.org/10.1136/bmjopen-2021-051176.
12. van Delden C, Stampf S, Hirsch HH, et al. Burden and timeline of infectious diseases in the first year after solid organ transplantation in the Swiss Transplant Cohort Study. *Clin Infect Dis*. 2020;71(7): e159–e169. https://doi.org/10.1093/cid/ciz1113.
13. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2020;71(6):1367–1376. https://doi.org/10.1093/cid/ciz1008.
14. Humar A, Michaels M, AST ID Working Group on Infectious Disease Monitoring. American Society of Transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. *Am J Transplant*. 2006;6(2):262–274. https://doi.org/10.1111/j.1600-6143.2005.01207.x.
15. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6(2):65–70.
16. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16(3):1141–1154.
17. Rosner B, Glynn RJ, Lee ML. The Wilcoxon signed rank test for paired comparisons of clustered data. *Biometrics*. 2006;62(1):185–192. https://doi.org/10.1111/j.1541-0420.2005.00389.x.
18. Jiang Y, Lee M-LT, He X, Rosner B, Yan J. Wilcoxon rank-based tests for clustered data with R package clusrank. *J Stat Softw*. 2020;96(6): 1–26. https://doi.org/10.18637/jss.v096.i06.
19. R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021.
20. Sjoberg DD, Whiting K, Curry M, Lavery JA, Larmarange J. Reproducible summary tables with the gtsummary Package. *R J*. 2021; 13:570. https://doi.org/10.32614/RJ-2021-053.
21. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *J Open Source Softw*. 2019;4:1686. https://doi.org/10.21105/joss.01686.
22. Therneau TM, Grambsch PM. *Modeling survival data: extending the Cox model*. 1 ed. New York, NY: Springer; 2000 (Statistics for Biology and Health).
23. Sjoberg DD, Fei T. tidycmprsk: competing risks estimation. R package version 1.0.0; 2023. https://CRAN.R-project.org/package=tidycmprsk.
24. Hosseini-Moghaddam SM, Ouédraogo A, Naylor KL, et al. Incidence and outcomes of invasive fungal infection among solid organ transplant recipients: a population-based cohort study. *Transpl Infect Dis*. 2020;22 (2):e13250. https://doi.org/10.1111/tid.13250.
25. Clancy CJ, Shields RK, Nguyen MH. Invasive candidiasis in various patient populations: incorporating non-culture diagnostic tests into rational management strategies. *J Fungi (Basel)*. 2016;2(1):10. https://doi.org/10.3390/jof2010010.typ^{11502}}"1]>
26. Nguyen MH, Wissel MC, Shields RK, et al. Performance of *Candida* real-time polymerase chain reaction, beta-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. *Clin Infect Dis*. 2012; 54(9):1240–1248. https://doi.org/10.1093/cid/cis200.
27. Schaenman JM, Rosso F, Austin JM, et al. Trends in invasive disease due to *Candida* species following heart and lung transplantation. *Transpl Infect Dis*. 2009;11(2):112–121. https://doi.org/10.1111/j.1399-3062.2009.00364.x.
28. Eichenberger EM, Satola S, Neujahr D, et al. Candidemia in thoracic solid organ transplant recipients: characteristics and outcomes relative to matched uninfected and bacteremic thoracic organ transplant recipients. *Clin Transplant*. 2023;37(9):e15038. https://doi.org/10.1111/ctr.15038.
29. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med*. 2007;356(24): 2472–2482. https://doi.org/10.1056/NEJMoa066906.
30. Thompson 3rd GR, Soriano A, Cornely OA, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. *Lancet*. 2023;401(10370):49–59. https://doi.org/10.1016/S0140-6736(22)02324-8.