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Invasive Fungal Disease in Solid Organ and Hematopoietic Cell Transplant Recipients, United States

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Abstract

Background: Updated benchmark data on invasive fungal disease (IFD) in solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT) recipients are necessary to increase clinical recognition and inform treatment and prevention strategies. We estimated IFD incidence and potential risk factors in transplant recipients in a large US commercial health insurance database.

Methods: We observed patients who received SOT or HCT during 2018–2022 until IFD development, disenrollment, or database end date (July 31, 2023). We calculated incidence

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Author Contributions

Jeremy A. W. Gold: conceptualization, investigation, writing – original draft, methodology, visualization, writing – review and editing, supervision, data curation, formal analysis. **Kaitlin Benedict:** conceptualization, methodology, writing – review and editing, formal analysis. **Elizabeth Sajewski:** methodology, validation, writing – review and editing. **Tom Chiller:** writing – review and editing, conceptualization. **Meghan Lyman:** conceptualization, writing – review and editing. **Mitsuru Toda:** conceptualization, writing – review and editing. **Jessica S. Little:** conceptualization, writing – review and editing. **Luis Ostrosky-Zeichner:** conceptualization, writing – review and editing, supervision.

Ethics Statement

This study used a fully deidentified dataset, which ensured that no personally identifiable information was present. As a result, Institutional Review Board (IRB) and Ethics Committee approvals were not required for this work.

This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

Consent

The authors have nothing to report.

Conflicts of Interest

Pertinent to this work, Luis Ostrosky-Zeichner has received research grants and/or consulting honoraria from the following companies: Scynexis, Melinta, GSK, Pulmocide, F2G, Basilea, Pfizer, Gilead, T2 Biosystems, and Eurofins Viracor. He is partially funded by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through UTHHealth-CCTS Grant Number UL1TR003167 and contract U01CK000692, Centers for Disease Control and Prevention. The other authors declare no conflicts of interest.

(per 1000 person-years) and time to IFD development, comparing demographic features and underlying conditions for IFD versus non-IFD patients.

Results: Overall, 9143 patients received an SOT (5667 kidney, 2025 liver, 759 heart, 650 lung, 39 pancreas, 3 intestine), and 5693 patients received an HCT (3519 autologous, 2114 allogeneic, 60 unspecified type). Among SOT patients, 360 developed an IFD (incidence: 21.0 [per 1000 person-years]). Mold infections had the highest incidence (7.1), followed by unspecified mycoses (3.9) and endemic mycoses (3.3). Among HCT patients, 292 developed an IFD (incidence: 28.5), with higher incidence among allogeneic (58.4) versus autologous (12.8) HCT recipients; among all HCT recipients, unspecified mycoses had the highest incidence (8.3), then pneumocystosis (7.6), and mold infections (6.7). Median time to IFD was 173.5 days for SOT recipients and 197.5 days for HCT recipients. IFD risk varied substantially by transplant type, region, and certain underlying conditions.

Conclusion: Our results suggest that IFDs remain an important cause of infection among SOT and HCT recipients, particularly later in the posttransplant period, and highlight the need for prevention strategies.

Keywords

aspergillosis; candidiasis; cryptococcosis; invasive fungal disease; pneumocystosis; solid organ transplantation; stem cell transplantation

1 | Introduction

In the United States, > 46 000 solid organ transplants (SOTs) and > 21 000 hematopoietic cell transplants (HCTs) are performed annually [1, 2]. Invasive fungal diseases (IFDs) cause substantial morbidity and mortality among SOT and HCT recipients [3]. Although novel approaches to prevention and management, as well as shifts in global IFD epidemiology, are transforming the clinical landscape, recent epidemiologic data remain limited [4-7]. During 2001–2006, researchers conducted the largest US surveillance effort for IFDs among SOT and HCT recipients at a network of 23 transplant centers called the Transplant-Associated Infection Surveillance Network (TRANSNET) [4, 5]. Among SOT recipients, 1-year cumulative incidences of the first IFD were 11.6%, 8.6%, 4.7%, 4.0%, 3.4%, and 1.3% for small bowel, lung, liver, heart, pancreas, and kidney transplant recipients, respectively, with invasive candidiasis as the most frequent IFD type, followed by aspergillosis [4]. Among HCT recipients, IFD incidence ranged from 5.8% to 8.1% for allogeneic transplant recipients and 1.2% for autologous transplant recipients, with aspergillosis the most common IFD type, followed by invasive candidiasis [5].

Updated benchmark data on the epidemiology and risk factors for IFDs in transplant recipients are critical to increasing clinical recognition and informing treatment and prevention strategies. Therefore, we analyzed a large US health insurance claims dataset to describe IFD incidence and potential risk factors in patients who received SOT or HCT.

2 | Methods

2.1 | Dataset

The 2018–2022 Merative MarketScan Commercial and Medicare Supplemental Research Databases (<https://www.merative.com/documents/brief/marketscan-explainer-general>) include deidentified data on outpatient visits, outpatient prescriptions, and hospitalizations for > 43 000 000 commercially insured employees, dependents, and retirees across the United States.

2.2 | Study Population

We identified patients who received an SOT or HCT during January 1, 2018–December 31, 2022 using the International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS) and the Current Procedural Terminology (CPT) codes. We excluded patients without continuous insurance enrollment during the 180 days preceding the date of first transplantation (~11%). For patients with multiple sequential transplants during the study period, analysis was relative to the first transplant. If SOT patients received multiple transplant types on the same day, we classified transplant type according to the highest IFD risk [4]. We used the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes to identify IFDs and other diagnoses of interest, excluding IFD diagnoses listed only on a laboratory or imaging claim (Table S1). To attempt to identify incident IFD diagnoses, we excluded patients who received IFD diagnoses during the 180 days before the first transplantation date (~1%).

2.3 | Study Design and Data Analysis

We followed patients from their first transplant until the first diagnosis of IFD. For patients who did not develop IFD, we followed them until the end date of the database (July 31, 2023) or until they were disenrolled from the database. Mortality data were unavailable; therefore, we could not calculate mortality rates or determine whether patients disenrolled because of death or change in insurance coverage. We calculated IFD incidence (per 1000 person-years) for each transplant type and IFD type and examined time between transplantation and IFD diagnosis.

Stratifying by transplant type, we compared IFD versus non-IFD patients, examining demographic characteristics, select conditions and outpatient immunosuppressive prescriptions that might increase IFD risk, and outpatient antifungal prescriptions. We included outpatient immunosuppressive medications and antifungal prescriptions with ≥ 21 days' supply filled from the date of transplantation until the day before IFD development (for IFD patients) or until the day before final follow-up date (for non-IFD patients). Information on inpatient medications, including antifungals, was unavailable in the dataset. We compared categorical variables using χ^2 or Fisher's exact tests for proportions and compared continuous variables using Student's *t*-tests ($\alpha = 0.05$). We conducted analyses using the MarketScan Treatment Pathways web-based analytic tool and SAS software (version 9.4; SAS Institute).

3 | Results

3.1 | Solid Organ Transplant Recipients

In total, 9143 patients received an SOT (5667 kidney, 2025 liver, 759 heart, 650 lung, 39 pancreas, 3 intestine) (Table 1). Median follow-up time was 567.0 days (interquartile range [IQR]: 285.0–1002.0). Overall, 360 SOT patients developed an IFD (incidence: 21.0 per 1000 person-years). Mold infections had the highest incidence (7.1) (aspergillosis: 6.7, mucormycosis: 0.4), followed by unspecified mycoses (3.9), endemic mycoses (3.3) (histoplasmosis: 1.8, coccidioidomycosis: 1.3, blastomycosis: 0.1), candidiasis (2.8), pneumocystosis (1.9), cryptococcosis (1.6), other specified mycoses (1.3), sporotrichosis (0.1), and eumycetoma (0.1); no patients had chromoblastomycosis or paracoccidioidomycosis.

Among SOT recipients, mold infection incidence was highest in the Northeast (overall 11.2; aspergillosis 10.8, mucormycosis 0.9) and lowest in the South (overall 4.8; aspergillosis 4.5, mucormycosis 0.4); candidiasis highest in the Midwest (3.1), lowest in the Northeast (1.3); endemics highest in the West (9.0), lowest in the Northeast (1.7); cryptococcosis highest in the South (1.9), lowest in the Northeast (0.4); and pneumocystosis highest in the Northeast (2.6), lowest in the West (1.3) (Table 2).

IFD incidence and types varied by SOT type. IFD incidence was highest in patients with lung transplantation (105.3), followed by pancreas (41.2), heart (24.8), liver (18.7), and kidney (12.6) transplantation. Among lung recipients with IFD ($n = 117$), most ($n = 66$, 56.4%) had a mold infection, followed by unspecified mycosis ($n = 17$, 14.5%) and candidiasis ($n = 15$, 12.8%). Among the three pancreas transplant recipients with IFD, one had candidal sepsis; two had an unspecified mycosis. Among heart transplantation recipients with IFD ($n = 35$), the most common IFD types were mold ($n = 11$, 31.4%), unspecified mycosis ($n = 11$, 31.4%), and endemic mycoses ($n = 7$, 20.0%). Among liver transplant recipients with IFD ($n = 67$), the most common IFD types were endemic mycoses ($n = 19$, 28.4%), followed by candidiasis ($n = 13$, 19.4%), mold ($n = 12$, 17.9%), pneumocystosis ($n = 9$, 13.4%), unspecified mycoses ($n = 9$, 13.4%), cryptococcosis ($n = 5$, 7.5%), and other specified mycoses ($n = 5$, 7.5%). Among kidney transplant recipients with IFD ($n = 138$), the most common IFD types were mold ($n = 32$, 23.2%), followed by unspecified mycoses ($n = 28$, 20.3%), endemic mycoses ($n = 25$, 18.1%), cryptococcosis ($n = 17$, 12.3%), candidiasis ($n = 16$, 11.6%), and pneumocystosis ($n = 16$, 11.6%).

For IFD patients, IFDs developed a median of 173.5 days (IQR: 66.0–407.5) after transplantation (Figure 1A,B). The median number of days from transplantation to IFD diagnosis was longer for pneumocystosis (372.5, IQR: 134.5–792.5) compared with cryptococcosis (210.0, 42.0–544.0), mold infections (178.0, IQR: 78.0–318.0), endemic mycoses (108.0, IQR: 53.5–492.0), and candidiasis (104.0, IQR: 50.0–315.0).

Across SOT recipients, the median age was 53.9 years (IQR: 43.5–61.1); 36.5% were female and 47.4% were Southern residents. For each SOT type, age group, sex, and regional distributions were generally similar regardless of IFD status (Table 3). The frequency of underlying conditions and outpatient immunosuppressive medications among patients with

IFD varied by SOT type. Chronic obstructive pulmonary disease was more frequent in liver transplant recipients with versus without IFD (17.9% vs. 6.9%, $p = 0.003$); pulmonary hypertension in kidney transplant recipients (10.1% vs. 4.6%, $p = 0.002$); diabetes in kidney (56.5% vs. 41.6%, $p < 0.001$), liver (53.7% vs. 34.6%, $p = 0.001$), and heart (57.1% vs. 38.1%, $p = 0.024$) transplant recipients; HIV in heart transplant recipients (2.9% vs. 0.0%, $p = 0.046$). Corticosteroid receipt was more frequent in lung transplant recipients with versus without IFD (82.1% vs. 63.6%, $p < 0.001$) and methotrexate in heart transplant recipients (5.7% vs. 0.8%, $p = 0.049$). Mycophenolate mofetil was less frequent in kidney transplant recipients with versus without IFD (47.1% vs. 55.6%, $p = 0.047$) (Table S2).

Outpatient antifungal prescriptions varied by SOT type and by IFD versus non-IFD status (Table S2). Overall, the most common prescriptions for SOT recipients were anti-*Pneumocystis* drugs (atovaquone, dapsone, pentamidine, or trimethoprim/sulfamethoxazole) (89.3%) and fluconazole (18.1%); itraconazole, isavuconazole, posaconazole, and voriconazole each were received by < 3% of patients.

3.2 | Hematopoietic Cell Transplant Recipients

A total of 5693 patients received an HCT (3519 autologous, 2114 allogeneic, 60 unspecified if allogeneic or autologous) (Table 1). Median follow-up time was 467.0 days (IQR: 232.0–870.0) for allogeneic and 573.0 days (IQR: 283.0–1016.0) for autologous transplant. Overall, 292 patients developed an IFD (incidence: 28.5 per 1000 person-years), with higher incidence among allogeneic (58.4) compared with autologous (12.8) HCT recipients. Among all HCT recipients, unspecified mycoses had the highest incidence (8.3), then pneumocystosis (7.6), and mold infections (6.7). Among allogeneic HCT recipients with IFD ($n = 205$), the most common IFD type was unspecified mycosis ($n = 64$, 31.2%), followed by mold ($n = 56$, 27.3%), aspergillosis ($n = 48$, 23.4%), mucormycosis ($n = 9$, 2.6%), pneumocystosis ($n = 46$, 22.4%), candidiasis ($n = 23$, 11.2%), other specified mycosis ($n = 18$, 8.8%), and cryptococcosis ($n = 1$, 0.5%). Among autologous HCT recipients with IFD ($n = 85$), the most common IFD type was pneumocystosis ($n = 31$, 36.5%), followed by unspecified mycosis ($n = 20$, 23.5%), mold ($n = 13$, 15.3%), candidiasis ($n = 10$, 11.8%), endemic mycoses ($n = 8$, 9.4%), and other specified mycosis ($n = 5$, 5.9%); no autologous HCT recipients developed cryptococcosis. Overall, no HCT patients developed chromoblastomycosis, eumycetoma, or sporotrichosis.

Among HCT recipients, mold infection incidence was highest in the West (overall 11.4; aspergillosis 9.4, mucormycosis 2.7) and lowest in the south (overall 4.6; aspergillosis 3.6, mucormycosis 1.0); candidiasis highest in the South (3.4), lowest in the Northeast (2.7); endemics highest in the South (1.7), lowest in the Northeast (0.7); and pneumocystosis highest in the Northeast (10.9), lowest in the Midwest (5.0) (Table 2).

For IFD patients, the number of days between transplant and IFD development was similar for allogeneic (197.5, IQR: 94.0–364.0) and autologous (193.0, IQR 64.0–541.0) transplant recipients (Figure 1C,D). Overall, this number was longest for mold infections 233.0 (107.0–439.0), followed by pneumocystosis (204.0, IQR 77.0–392.0), endemic mycoses (172.0, IQR: 123.0–687.5), and candidiasis (169.0, IQR: 97.0–486.0).

The median age (in years) comparing IFD patients versus non-IFD patients was lower for autologous HCT recipients (53.0, IQR: 29.9–59.7 vs. 58.0, IQR: 49.5–63.2; $p < 0.001$) and similar among allogeneic HCT recipients (51.6, IQR: 37.4–67.0 vs. 53.5, IQR: 37.4–61.6; $p = 0.571$) (Table 4). For both allogeneic and autologous HCT patients, the frequency of IFD development did not vary substantially by sex and region; overall, most HCT patients were male (autologous: 57.2%, allogeneic: 55.9%) and Southern residents (autologous: 42.6%, allogeneic: 39.8%).

In autologous HCT recipients, IFDs were more frequent in those with bronchiectasis (3.5% vs. 0.9%, $p = 0.044$), B-cell lymphoma (35.3% vs. 25.8%, $p = 0.048$), cytomegalovirus (9.4% vs. 2.0%, $p = 0.001$), corticosteroid receipt (16.5% vs. 8.8%, $p = 0.015$), and small molecule kinase inhibitor receipt (5.9% vs. 2.0%, $p = 0.034$) and less frequent in those with multiple myeloma/plasma cell neoplasms (42.4% vs. 64.4%, $p < 0.001$). In allogeneic HCT recipients, IFDs were more frequent in those with bronchiectasis (5.9% vs. 0.3%, $p = 0.005$), diabetes mellitus (21.5% vs. 15.6%, $p = 0.029$), myeloid leukemia (64.9% vs. 53.7%, $p = 0.002$), and tacrolimus receipt (81.0% vs. 69.8%, $p = 0.001$) (Table S3).

Outpatient antifungal prescriptions varied by HCT type and by IFD versus non-IFD status (Table S3). Overall, the most common prescriptions were for anti-*Pneumocystis* drugs (autologous: 52.5%, allogeneic: 73.7%), and fluconazole (autologous: 13.4%, allogeneic: 38.1%). Few (< 3%) autologous HCT recipients received mold-active azoles, and 56.5% of allogeneic received a mold-active azole, most frequently posaconazole (33.7%), followed by voriconazole (19.9%), isavuconazole (10.5%), and itraconazole (0.4%).

4 | Discussion

This study provides updated estimates of IFD epidemiology, including incidence, timing, and potential risk factors among large cohorts of transplant recipients (> 9000 SOT and > 5500 HCT) across the United States. The overall IFD incidence estimates (21.0 per 1000 person-years for SOT recipients, 58.4 for allogeneic HCT recipients, and 12.8 for autologous HCT recipients) are of the same order of magnitude as TRANSNET study estimates, in which the 12-month cumulative IFD incidence was 3.1% across SOT recipients, 5.8%–8.1% for allogeneic HCT recipients, and 1.2% for autologous HCT recipients [4, 5]. Similarly, in a prospective study of HCT recipients conducted during 2006–2011 at four US transplant centers, 11% of recipients developed an IFD [7]. Direct comparison of incidence estimates is difficult owing to differences in study design, and differences in IFD risk by transplant type are likely multifactorial, reflecting surgical technique, comorbidities, immunosuppressive regimens, and other factors. Overall, our findings underscore the ongoing substantial burden of IFD in transplant recipients and the continued importance of efforts to improve IFD prevention strategies.

IFD development in SOT recipients, regardless of IFD type, most often occurred > 90 days after transplantation, consistent with TRANSNET data [4]. In our study, IFDs in HCT patients generally occurred later (169 days for candidiasis and 172–349 days for other IFD types) compared with those in the TRANSNET study (61 days for candidiasis and ~100 to ~150 days for other IFD types) [4]. The reason for this difference is unclear but could

represent variations in the study populations and antifungal prophylaxis practices, a factor that we were not well-poised to assess given the dataset's lack of information on inpatient medications and indications for outpatient prescriptions.

Across each HCT and SOT type, mold infections composed a greater percentage of IFDs than did invasive candidiasis. This is consistent with TRANSNET data for HCTs but contrasts with TRANSNET data for SOTs, where candidiasis predominated over aspergillosis for each SOT type except lung transplant [4, 5]. Potential explanations for the predominance of mold infections over candidiasis in SOT recipients include the increasing use of galactomannan assays and PCR-based methods to diagnose certain mold infections, as well as challenges related to the coding for candidemia diagnosis. We suspect that our study underestimates the incidence of invasive candidiasis because of the insensitivity of diagnostic coding for this condition compared with TRANSNET, which involved review of electronic medical record data. Two large studies have found that candidemia is frequently coded as unspecified mycosis [8], a diagnosis assigned to 18.6% of SOT recipients and 29.1% of HCT recipients in our study. Despite a large nationally representative study suggesting increasing rates of mucormycosis-related hospitalizations among transplant recipients [9], mucormycosis frequency in our study (1.9% of IFDs in SOT recipients; 4.5% in HCT recipients) was similar to or slightly lower than in TRANSNET (2% of IFDs in SOT recipients; 8% in HCT recipients) [4, 5]. Regional variations in IFD incidence merit further study, particularly those observed for aspergillosis and mucormycosis (both highest in the Northeast among SOT recipients, highest in the West among HCT recipients, and lowest in the South for both groups), which might reflect differences in underlying patient populations, facility-level practices in diagnostic testing and prophylaxis, and regional differences in environmental spore counts [10, 11].

Endemic IFDs constituted a greater percentage of IFDs occurring in both SOT (15.6%) and HCT (4.1%) recipients in our study compared with TRANSNET data, wherein endemics constituted $\leq 5\%$ of IFDs in SOT recipients and $< 1\%$ of IFDs in HCT recipients [4, 5]. Several factors might explain this finding, including differences in study catchment areas, prophylaxis strategies, and testing practices. It is also possible that the higher incidence of endemic fungal infections in our study might also reflect expanding geography and increased national incidence of endemic fungal infections in general [12]. Pneumocystosis was also relatively frequent in our study (8.9% of IFDs in SOT recipients; 26.7% of IFDs in HCT recipients) compared with TRANSNET (1% of IFDs in SOT recipients; 2% of IFDs among HCT recipients) and generally occurred later than did most other IFDs [4, 5]. Potential explanations for this finding may be the longer duration of follow-up extending beyond the period of routine anti-*Pneumocystis* prophylaxis or the increasing use of polymerase chain reaction in diagnosing *Pneumocystis* pneumonia, as this tool is highly sensitive and might not distinguish colonization from infection [13, 14].

A specific diagnostic code for dematiaceous mold (eumycetoma, chromoblastomycosis, and phaeohyphomycosis) was assigned to only one patient (a lung transplant recipient with eumycetoma). In contrast, 56 patients with phaeohyphomycosis were identified during the TRANSNET study [15]. Although dematiaceous mold infections remain rare among SOT

and HCT recipients, continued clinical awareness is needed given the potential for climate change-related expansion of the geographic range [16].

To our knowledge, this is the largest observational cohort study to examine IFDs in transplant recipients; however, the study still only represents approximately 4% of all transplants performed in the United States during the study period and is subject to important limitations. Although MarketScan data are broadly representative of the commercially insured population, it is still a convenience sample and does not represent patients with other insurance types or those without insurance. The data also lack information on race and ethnicity, laboratory values that could help further stratify IFD risk (e.g., white blood cell counts) and identify fungal species, behavioral risk factors, inpatient medications, and patient mortality [17]. The data are not well-suited to examine trends over time, and no information was available on facility-level characteristics, which may influence practice patterns affecting IFD risk including prophylaxis, treatment, immunosuppressive regimens, or other practices [4]. Finally, ICD-10-CM codes are subject to potential undercoding and disease misclassification and may not always reflect proven or probable diagnoses made using consensus IFD definitions [18]. Given these substantial data limitations and the heterogeneity of transplantation types included in this analysis, multivariable analyses to disentangle risk factors were not performed; future studies using more granular information, such as electronic health record data, could elucidate IFD risk factors in transplant recipients and shape prophylaxis guidelines.

In conclusion, this study presents updated incidence estimates of IFDs among transplant recipients in the United States. Our results suggest that IFDs remain an important cause of infection, particularly later in the posttransplant period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

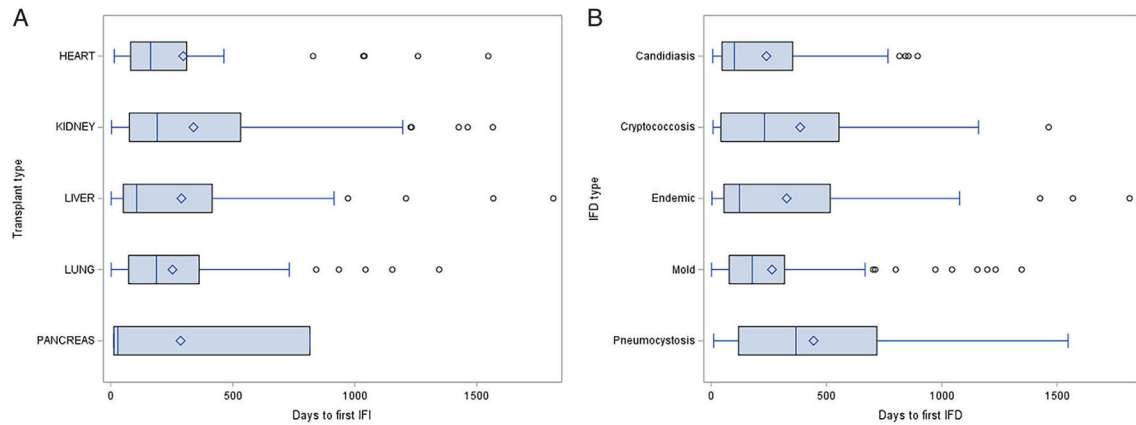
This study used third-party data that we cannot legally distribute. All relevant summary data are within the manuscript and the supporting files. The raw data underlying the results presented are available from the Merative MarketScan Research Databases: www.merative.com/documents/brief/marketscan-explainergeneral. Others can access the data by going to this website and contacting Merative. The authors did not have any special access privileges that others would not have.

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Solid organ transplant



Hematopoietic cell transplant

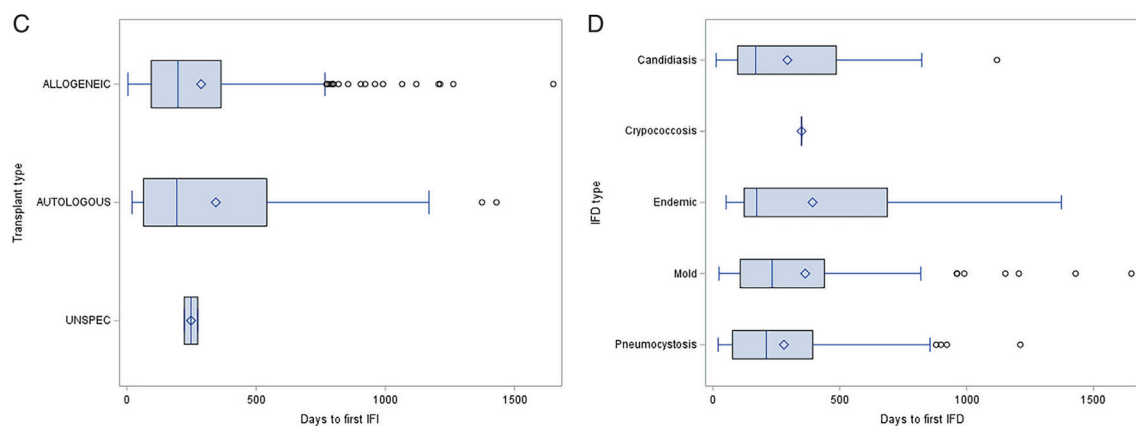


FIGURE 1 I.

Days between transplantation and invasive fungal disease (IFD) development among solid organ transplant recipients, by transplant type (A) and by IFD type (B), and among hematopoietic cell transplant recipients, by transplant type (C) and by IFD type (D). Box and whisker plots showing the number of days between transplantation and the development of invasive fungal disease (IFD) among solid organ transplant recipients categorized by transplant type (panel A) and IFD type (panel B). In addition, box and whisker plots for hematopoietic cell transplant recipients show the days to IFD development by transplant type (panel C) and IFD type (panel D). Each plot displays median values, interquartile ranges, and potential outliers.

TABLE 1 |

Number and incidence^a of invasive fungal diseases among solid organ or hematopoietic cell transplant recipients, by transplant type, United States, 2018–2022.

IFD type	Solid organ						Hematopoietic cell			
	Total (n = 9143)	Kidney ^b (n = 5667)	Liver ^c (n = 2025)	Heart (n = 759)	Lung ^d (n = 650)	Pancreas ^e (n = 39)	Total (n = 5693)	Autologous (n = 3519)	Allogeneic (n = 2114)	Unspecified allogeneic or autologous (n = 60)
Any IFD	360 (21.0)	138 (12.6)	67 (18.7)	35 (24.8)	117 (105.3)	3 (41.2)	292 (28.5)	85 (12.8)	205 (58.4)	2 (18.7)
Mold infections	121 (7.1)	32 (2.9)	12 (3.4)	11 (7.8)	66 (59.4)	0 (0)	69 (6.7)	13 (2.0)	56 (16.0)	0 (0)
Aspergillosis	115 (6.7)	28 (2.6)	11 (3.1)	10 (7.1)	66 (59.4)	0 (0)	57 (5.6)	9 (1.4)	48 (13.7)	0 (0)
Mucormycosis	7 (0.4)	4 (0.4)	2 (0.6)	1 (0.7)	0 (0)	0 (0)	13 (1.3)	4 (0.6)	9 (2.6)	0 (0)
Candidiasis	48 (2.8)	16 (1.5)	13 (3.6)	3 (2.1)	15 (13.5)	1 (13.7)	33 (3.2)	10 (1.5)	23 (6.6)	0 (0)
Endocarditis	2 (0.1)	1 (0.1)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Enteritis	3 (0.2)	1 (0.1)	2 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.3)	0 (0)
Meningitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary infection	19 (1.1)	4 (0.4)	1 (0.3)	3 (2.1)	11 (9.9)	0 (0)	12 (1.2)	4 (0.6)	8 (2.3)	0 (0)
Sepsis	26 (1.5)	11 (1.0)	10 (2.8)	0 (0)	4 (3.6)	1 (13.7)	21 (2.1)	6 (0.9)	15 (4.3)	0 (0)
Endemic mycoses	56 (3.3)	25 (2.3)	19 (5.3)	7 (5.0)	5 (4.5)	0 (0)	12 (1.2)	8 (1.2)	4 (1.1)	0 (0)
Blastomycosis	2 (0.1)	1 (0.1)	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.1)	1 (0.2)	0 (0)	0 (0)
Histoplasmosis	31 (1.8)	15 (1.4)	11 (3.1)	2 (1.4)	3 (2.7)	0 (0)	6 (0.6)	4 (0.6)	2 (0.6)	0 (0)
Coccidioidomycosis	23 (1.3)	9 (0.8)	8 (2.2)	4 (2.8)	2 (1.8)	0 (0)	5 (0.5)	3 (0.5)	2 (0.6)	0 (0)
Cryptococcosis	27 (1.6)	17 (1.6)	5 (1.4)	2 (1.4)	3 (2.7)	0 (0)	1 (0.1)	0 (0)	1 (0.3)	0 (0)
Pneumocystosis	32 (1.9)	16 (1.5)	9 (2.5)	3 (2.1)	4 (3.6)	0 (0)	78 (7.6)	31 (4.7)	46 (13.1)	1 (9.4)
Other specified	22 (1.3)	7 (0.6)	5 (1.4)	1 (0.7)	9 (8.1)	0 (0)	23 (2.2)	5 (0.8)	18 (5.1)	0 (0)
Unspecified	67 (3.9)	28 (2.6)	9 (2.5)	11 (7.8)	17 (15.3)	2 (27.5)	85 (8.3)	20 (3.0)	64 (18.3)	1 (9.4)

Abbreviation: IFD, invasive fungal disease.

^aIncidence displayed as the number of patients with IFD (incidence per 1000 person-years). Patients could have been diagnosed with more than one IFD type on the same day. In addition to IFDs displayed in the table, one case of sporotrichosis and one case of eumycetoma were identified, both in lung transplant patients. No patients had chromoblastomycosis or paracoccidioidomycosis. No IFDs were identified in 3 intestine transplant recipients.

^bIncludes 56 kidney/heart, 195 kidney/pancreas.

^cIncludes 14 liver/heart, 116 liver/kidney, 7 liver/lung, 4 liver/pancreas/intestine.

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^dIncludes 8 lung/heart, 5 lung/kidney.
^eIncludes 3 pancreas/intestine.

TABLE 2 |

Invasive fungal disease incidence^a among solid organ transplant and hematopoietic cell transplant recipients, by region, United States, 2018–2022.

Infection type	Solid organ					Hematopoietic cell				
	Midwest	Northeast	South	West	Missing	Midwest	Northeast	South	West	Missing
Mold	8.9	11.2	4.8	5.6	16.8	6.4	8.8	4.6	11.4	6.2
Aspergillosis	8.7	10.8	4.5	5.6	14.7	6.0	6.1	3.6	9.4	6.2
Mucormycosis	0.3	0.9	0.4	0.0	2.1	0.4	2.7	1.0	2.7	0.0
Candidiasis	3.1	1.3	2.9	3.0	6.3	2.8	2.7	3.4	3.4	6.2
Endemic	3.3	1.7	1.9	9.0	6.3	0.7	0.7	1.7	1.3	0.0
Blastomycosis	0.3	0.0	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.0
Coccidioidomycosis	0.0	0.4	0.2	8.1	2.1	0.4	0.0	0.5	1.3	0.0
Histoplasmosis	3.1	1.3	1.5	0.9	4.2	0.4	0.7	1.0	0.0	0.0
Cryptococcosis	1.8	0.4	1.9	1.3	2.1	0.0	0.7	0.0	0.0	0.0
Pneumocystosis	2.0	2.6	1.7	1.3	2.1	5.0	10.9	8.2	6.7	12.3
Unspecified	3.3	6.9	4.1	1.3	4.2	5.3	10.9	10.2	5.4	12.3

^aIncidence displayed as the number of patients with IFD (incidence per 1000 person-years). Patients could have been diagnosed with more than one IFD type on the same day. Region refers to the US census region of primary beneficiary's residence. Map of US census regions: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.

TABLE 3 |

Characteristics of patients with invasive fungal disease (IFD) development among solid organ transplant recipients, United States, 2018–2022^a.

Characteristics	Kidney				Liver				Heart				Lung			
	All (N = 5667)	IFD (n = 138)	No IFD (n = 5529)	P value	All (N = 2025)	IFD (n = 67)	No IFD (n = 1958)	P value	All (N = 759)	IFD (n = 35)	No IFD (n = 724)	P value	All (N = 650)	IFD (n = 117)	No IFD (n = 533)	P value
Demographic features																
Median age in years (IQR)	52.7 (42.4– 60.5)	54.9 (47.1– 62.0)	52.6 (42.4– 60.5)	0.031	55.1 (45.3– 61.1)	57.9 (48.7– 63.1)	54.9 (45.2– 61.1)	0.093	53.9 (41.3– 61.0)	57.9 (53.4– 62.5)	53.6 (41.1– 60.9)	0.046	57.9 (52.2– 63.9)	59.9 (53.3– 63.8)	59.7 (52.2– 63.9)	0.922
Age group (years)				0.084				0.647				0.080				0.460
0–17	144 (2.5)	1 (0.7)	143 (2.6)		81 (4.0)	2 (3.0)	79 (4.0)		71 (9.4)	3 (8.6)	68 (9.4)		13 (2.0)	1 (0.9)	12 (2.3)	
18–44	1545 (27.3)	29 (21.0)	1516 (27.4)		415 (20.5)	10 (14.9)	405 (20.7)		147 (19.4)	1 (2.9)	146 (20.2)		84 (12.9)	19 (16.2)	65 (12.2)	
45–64	3362 (59.3)	87 (63.0)	3275 (59.2)		1351 (66.7)	49 (73.1)	1302 (66.5)		467 (61.5)	27 (77.1)	440 (60.8)		429 (66.0)	73 (62.4)	356 (66.8)	
≥ 65	616 (10.9)	21 (15.2)	595 (10.8)		178 (8.8)	6 (9.0)	172 (8.8)		74 (9.7)	4 (11.4)	70 (9.7)		124 (19.1)	24 (20.5)	100 (18.8)	
Female	2139 (37.7)	49 (35.5)	2090 (37.8)	0.583	744 (36.7)	26 (38.8)	718 (36.7)	0.721	212 (27.9)	9 (25.7)	203 (28.0)	0.765	219 (33.7)	36 (30.8)	183 (34.3)	0.460
US census region ^b				0.993				0.215				0.927				0.186
Northeast	890 (16.4)	21 (15.8)	869 (16.4)		265 (13.6)	8 (12.7)	257 (13.6)		120 (16.6)	6 (19.4)	114 (16.5)		101 (16.4)	21 (18.9)	80 (15.9)	
South	2548 (47.0)	62 (46.6)	2486 (47.0)		981 (50.4)	27 (42.9)	954 (50.6)		333 (46.0)	13 (41.9)	320 (46.2)		260 (42.3)	41 (36.9)	219 (43.5)	
Midwest	1247 (23.0)	31 (23.3)	1216 (23.0)		415 (21.3)	13 (20.6)	402 (21.3)		165 (22.8)	8 (25.8)	157 (22.7)		165 (26.8)	37 (33.3)	128 (25.4)	
West	737 (13.6)	19 (14.3)	718 (13.6)		286 (14.7)	15 (23.8)	271 (14.4)		106 (14.6)	4 (12.9)	102 (14.7)		89 (14.5)	12 (10.8)	77 (15.3)	
Underlying medical conditions during 0–180 days before transplant^c																
Asthma	347 (6.1)	9 (6.5)	338 (6.1)	0.843	156 (7.7)	6 (9.0)	150 (7.7)	0.696	71 (9.4)	4 (11.4)	67 (9.3)	0.560	97 (14.9)	21 (17.9)	76 (14.3)	0.310
Bronchiectasis	22 (0.4)	1 (0.7)	21 (0.4)	0.419	21 (1.0)	2 (3.0)	19 (1.0)	0.152	10 (1.3)	1 (2.9)	9 (1.2)	0.378	177 (27.2)	43 (36.8)	134 (25.1)	0.011
Chronic obstructive	172 (3.0)	6 (4.3)	166 (3.0)	0.314	147 (7.3)	12 (17.9)	135 (6.9)	0.003	89 (11.7)	2 (5.7)	87 (12.0)	0.417	306 (47.1)	61 (52.1)	245 (46.0)	0.226

Characteristics	Kidney				Liver				Heart				Lung			
	All (N = 5667)	IFD (n = 138)	No IFD (n = 5529)	p value	All (N = 2025)	IFD (n = 67)	No IFD (n = 1958)	p value	All (N = 759)	IFD (n = 35)	No IFD (n = 724)	p value	All (N = 650)	IFD (n = 117)	No IFD (n = 533)	p value
pulmonary disease																
Dialysis	4467 (78.8)	115 (83.3)	4342 (78.5)	0.174	209 (10.3)	13 (19.4)	196 (10.0)	0.024	43 (5.7)	3 (8.6)	40 (5.5)	0.442	15 (2.3)	3 (2.6)	12 (2.3)	0.741
Interstitial lung disease	92 (1.6)	0 (0.0)	92 (1.7)	0.175	109 (5.4)	7 (10.4)	102 (5.2)	0.088	62 (8.2)	6 (17.1)	56 (7.7)	0.058	428 (65.8)	90 (76.9)	338 (63.4)	0.005
Pulmonary hypertension	266 (4.7)	14 (10.1)	252 (4.6)	0.002	243 (12.0)	10 (14.9)	233 (11.9)	0.454	381 (50.2)	18 (51.4)	363 (50.1)	0.882	331 (50.9)	64 (54.7)	267 (50.1)	0.367
Diabetes mellitus	2376 (41.9)	78 (56.5)	2298 (41.6)	< 0.001	713 (35.2)	36 (53.7)	677 (34.6)	0.001	296 (39.0)	20 (57.1)	276 (38.1)	0.024	229 (35.2)	41 (35.0)	188 (35.3)	0.963
Hematologic malignancy	171 (3.0)	4 (2.9)	167 (3.0)	> 0.999	52 (2.6)	1 (1.5)	51 (2.6)	> 0.999	32 (4.2)	0 (0.0)	32 (4.4)	0.392	13 (2.0)	5 (4.3)	8 (1.5)	0.066
HIV infection	57 (1.0)	3 (2.2)	54 (1.0)	0.161	11 (0.5)	2 (3.0)	9 (0.5)	0.489	1 (0.1)	1 (2.9)	0 (0.0)	0.046	5 (0.8)	0 (0.0)	5 (0.9)	0.591
Solid malignancy	309 (5.5)	10 (7.2)	299 (5.4)	0.347	581 (28.7)	18 (26.9)	563 (28.8)	0.737	48 (6.3)	3 (8.6)	45 (6.2)	0.480	43 (6.6)	7 (6.0)	36 (6.8)	0.761
Other conditions ^{c,d}																
Graft-versus-host disease	8 (0.1)	0 (0.0)	8 (0.1)	> 0.999	11 (0.5)	1 (1.5)	10 (0.5)	0.310	3 (0.4)	0 (0.0)	3 (0.4)	> 0.999	9 (1.4)	3 (2.6)	6 (1.1)	0.209
Cytomegalovirus	1264 (22.3)	25 (18.1)	1239 (22.4)	0.231	451 (22.3)	12 (17.9)	439 (22.4)	0.383	230 (30.3)	10 (28.6)	220 (30.4)	0.820	141 (21.7)	32 (27.4)	109 (20.5)	0.101
Neutropenia	879 (15.5)	23 (16.7)	856 (15.5)	0.704	333 (16.4)	9 (13.4)	324 (16.5)	0.499	119 (15.7)	1 (2.9)	118 (16.3)	0.033	102 (15.7)	14 (12)	88 (16.5)	0.221
Transplant rejection	1060 (18.7)	35 (25.4)	1025 (18.5)	0.042	455 (22.5)	16 (23.9)	439 (22.4)	0.778	597 (78.7)	29 (82.9)	568 (78.5)	0.535	276 (42.5)	54 (46.2)	222 (41.7)	0.372
Median follow-up time (IQR)	597 (296.0–1035.0)	724 (393.0–1241.0)	593 (295.0–1029.0)	0.001	521 (261.0–926.0)	735 (445.0–1094.0)	514 (260.0–917.0)	0.003	532 (281.0–999.0)	650 (347.0–1115.0)	523 (277.0–996.0)	0.437	507.5 (268.0–906.0)	665 (458.0–966.0)	459 (245.0–856.0)	< 0.001

Abbreviation: IQR, interquartile range.

^a *p* values were calculated using chi-square or Fisher's exact tests (for small cell sizes) for proportions.

^b US census region of primary beneficiary's residence. Map of US census regions: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.

^c Patients could have more than condition.

^d These conditions were either present between transplant date and date of incident IFD diagnosis or between the transplant date until the date of last follow-up, whichever occurred earliest.

TABLE 4 |
 Characteristics of patients with invasive fungal disease (IFD) among hematopoietic stem cell transplant recipients, United States, 2018–2022.^a

Characteristics	Autologous			p value	Allogeneic			p value
	All (N = 3519)	IFD (n = 85)	No IFD (n = 3434)		All (N = 2114)	IFD (n = 205)	No IFD (n = 1909)	
Demographic features								
Median age in years (IQR)	57.9 (49.2–63.1)	53 (29.9–59.7)	58 (49.5–63.2)	< 0.001	53.4 (37.4–61.4)	51.6 (37.4–67.0)	53.5 (37.4–61.6)	0.571
Age group (years)				< 0.001				0.043
0–17	166 (4.7)	14 (16.5)	152 (4.4)		226 (10.7)	18 (8.8)	208 (10.9)	
18–44	506 (14.4)	21 (24.7)	485 (14.1)		477 (22.6)	59 (28.8)	418 (21.9)	
45–64	2281 (64.8)	41 (48.2)	2240 (65.2)		1180 (55.8)	114 (55.6)	1066 (55.8)	
≥ 65	566 (16.1)	9 (10.6)	557 (16.2)		231 (10.9)	14 (6.8)	217 (11.4)	
Female	1506 (42.8)	26 (30.6)	1480 (43.1)	0.213	933 (44.1)	84 (41.0)	849 (44.5)	0.338
US census region ^b				0.588				0.241
Northeast	529 (15.9)	14 (17.3)	515 (15.8)		350 (17.4)	38 (19.3)	312 (17.2)	
South	1418 (42.6)	39 (48.1)	1379 (42.4)		801 (39.8)	85 (43.1)	716 (39.4)	
Midwest	906 (27.2)	17 (21.0)	889 (27.3)		542 (26.9)	41 (20.8)	501 (27.6)	
West	479 (14.4)	11 (13.6)	468 (14.4)		321 (15.9)	33 (16.8)	288 (15.9)	
Donor relatedness				NA				0.421
Related	NA	NA	NA		740 (35)	79 (38.5)	661 (34.6)	
Unrelated	NA	NA	NA		876 (41.4)	84 (41.0)	792 (41.5)	
Unspecified	NA	NA	NA		498 (23.6)	42 (20.5)	456 (23.9)	
Underlying medical conditions during 0–180 days before transplant ^c								
Asthma	280 (8.0)	9 (10.6)	271 (7.9)	0.364	154 (7.3)	21 (10.2)	175 (9.2)	0.282
Bronchiectasis	33 (0.9)	3 (3.5)	30 (0.9)	0.044	18 (0.9)	12 (5.9)	6 (0.3)	0.005
Chronic obstructive pulmonary disease	181 (5.1)	4 (4.7)	177 (5.2)	> 0.999	108 (5.1)	9 (4.4)	99 (5.2)	0.623
Dialysis	78 (2.2)	3 (3.5)	75 (2.2)	0.437	19 (0.9)	3 (1.5)	16 (0.8)	0.421
Interstitial lung disease	106 (3.0)	0 (0.0)	106 (3.1)	0.183	116 (5.5)	16 (7.8)	100 (5.2)	0.125
Pulmonary hypertension	123 (3.5)	2 (2.4)	121 (3.5)	0.769	88 (4.2)	8 (3.9)	80 (4.2)	0.844
Diabetes mellitus	604 (17.2)	8 (9.4)	596 (17.4)	0.055	341 (16.1)	44 (21.5)	297 (15.6)	0.029
Hematologic malignancies	3117 (88.6)	70 (82.4)	3047 (88.7)	0.068	1856 (87.8)	196 (95.6)	1660 (87.0)	< 0.001

Characteristics	Autologous				Allogeneic			
	All (N = 3519)	IFD (n = 85)	No IFD (n = 3434)	p value	All (N = 2114)	IFD (n = 205)	No IFD (n = 1909)	p value
B-cell lymphoma	915 (26.0)	30 (35.3)	885 (25.8)	0.048	387 (18.3)	43 (21.0)	344 (18.0)	0.298
Lymphoid leukemia	162 (4.6)	8 (9.4)	154 (4.5)	0.057	629 (29.8)	68 (33.2)	561 (29.4)	0.260
Myeloid leukemia	150 (4.3)	4 (4.7)	146 (4.3)	0.783	1158 (54.8)	133 (64.9)	1025 (53.7)	0.002
Other leukemia	55 (1.6)	2 (2.4)	53 (1.5)	0.386	887 (42.0)	99 (48.3)	788 (41.3)	0.053
Multiple myeloma/plasma cell neoplasms	2246 (63.8)	36 (42.4)	2210 (64.4)	< 0.001	239 (11.3)	29 (14.1)	210 (11.0)	0.177
Myelodysplastic syndromes	64 (1.8)	1 (1.2)	63 (1.8)	> 0.999	601 (28.4)	66 (32.2)	535 (28.0)	0.209
Myeloproliferative disorders	1146 (32.6)	22 (25.9)	1124 (32.7)	0.183	387 (18.3)	44 (21.5)	343 (18.0)	0.219
HIV infection	19 (0.5)	0 (0.0)	19 (0.6)	> 0.999	7 (0.3)	1 (0.5)	6 (0.3)	0.511
Solid malignancy	1233 (35.0)	37 (43.5)	1196 (34.8)	0.097	325 (15.4)	34 (16.6)	291 (15.2)	0.613
Other conditions^{c,d}								
Graft-versus-host disease	87 (2.5)	3 (3.5)	84 (2.4)	0.467	1418 (67.1)	148 (72.2)	1270 (66.5)	0.101
Cytomegalovirus	77 (2.2)	8 (9.4)	69 (2.0)	0.001	446 (21.1)	51 (24.9)	395 (20.7)	0.163
Neutropenia	1905 (54.1)	58 (68.2)	1847 (53.8)	0.008	1283 (60.7)	135 (65.9)	1148 (60.1)	0.111
Transplant rejection	11 (0.3)	0 (0.0)	11 (0.3)	> 0.999	54 (2.6)	4 (2)	50 (2.6)	0.565
Repeat transplantation	6 (0.2)	0 (0.0)	6 (0.2)	< 0.001	107 (5.1)	14 (6.8)	93 (4.9)	0.224
Median follow-up time (interquartile range)	573 (283.0–1016.0)	647 (332.0–1112.0)	570.5 (283.0–1012.0)	0.174	467 (232.0–870.0)	500 (297.0–870.0)	459 (224.0–869.0)	0.037

Abbreviation: IQR, interquartile range.

^a p values were calculated using chi-square or Fisher's exact tests (for small cell sizes) for proportions.

^b US census region of primary beneficiary's residence. Map of US census regions: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.

^c Patients could have more than condition.

^d These conditions were either present between transplant date and date of incident IFD diagnosis or between the transplant date until the date of last follow-up, whichever occurred earliest.