

EPIDEMIOLOGY OF CRYPTOCOCCOSIS AND CRYPTOCOCCAL
MENINGITIS IN A LARGE RETROSPECTIVE COHORT OF PATIENTS
FOLLOWING SOLID ORGAN TRANSPLANTATION

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE, OF
MASTER OF SCIENCE

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MAY 2017

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Acknowledgements

I wish to express my sincere gratitude to all those who have supported me during the Master's program and my research. I especially want to thank:

My advisers, Professors **Daniel Weisdorf** and **Jo-Anne Young** for their excellent guidance, generosity of their time and expertise and above all for giving me a chance to do a Masters at University of Minnesota.

My mentors at Washington University in St. Louis, Professors **Margaret A. Olsen**, **Bill Powderly** and **Carlos A. Santos** for outstanding mentorship and advice.

Professor **Jim Johnson** for being gracious to be on my thesis committee.

Shelley Cooksey together with **Andrea Kish** for their advice and making the impossible possible;

and

Most importantly, **Preeti**, my wife for her unconditional support and my daughter **Diya** who makes me wonder every day and are the best part of my life.

This study used the services of the Center for Administrative Data Research, supported in part by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR000448 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH), Grant Number R24 HS19455 through the Agency for Healthcare Research and Quality (AHRQ), and Grant Number KM1CA156708 through the National Cancer Institute (NCI) at the National Institutes of Health (NIH).

Abstract

Background: Cryptococcosis is the third most common invasive fungal infection in solid organ transplant (SOT) recipients. There are no nationally representative data describing the incidence, risk factors and outcomes of cryptococcosis after SOT.

Methods: We assembled a large cohort of adult SOT recipients using ICD-9 CM billing data from HCUP State Inpatient Databases of Florida (2006-2012), New York (2006-2011) and California (2004-2010). Demographics, comorbidities, death, and cryptococcal infections coded during hospitalization were identified.

Results: 42,634 adults with SOT were identified during the study period. Cryptococcal disease was identified in 0.37 % (n=158), of which 44% had meningitis (n=69). Median time to diagnosis of cryptococcosis was 464 days (range 4 – 2,393). The median time to onset of cryptococcosis was earlier for lung (191 days; range 7.5 – 1,816), heart (195 days; range 4 – 1,061) and liver (200 days; range 4 – 1,581) compared to kidney transplant recipients (616 days; range 12 – 2,393); $P < 0.001$ log rank test. Very early-onset disease (< 30 days after transplantation) more frequently occurred in liver and lung transplant recipients. Lung transplant recipients had the highest risk of cryptococcosis (HR 2.10; CI 1.21 – 3.60). Cryptococcosis was associated with death (HR 2.29; CI 1.68 – 3.11), after adjusting for age, type of SOT, prior transplant failure/rejection, diabetes, and other comorbidities.

Conclusion: Cryptococcosis is rare after SOT but associated with significantly increased risk of death. Lung transplant recipients are at highest risk for cryptococcosis among SOT's. Non-kidney transplants have earlier onset of cryptococcosis and higher risk of death compared to kidney transplant recipients.

Table of Contents

List of Tables	vi
List of Figures	vii
Introduction.....	1
Methods.....	4
Study design and patient populaton.....	4
Demographic data, comorbidities and follow-up.....	5
Statistical analysis.....	5
Results	7
Patient characteristics.....	7
Cryptococcal Infections	7
Very early versus later onset cryptococcosis.....	8
Inpatient Mortality in patients with cryptococcosis.....	9
Discussion	10
Bibliography	14
Table 1 Univariable risk factors for cryptococcosis.....	16
Table 2 Multivariable risk factors for cryptococcosis.....	19
Table 3 Cox proportional hazard model of risk factors for death	20
Figure 1 Time to onset of cryptococcosis in days, stratified by type of transplant.....	23
Figure 2 Time to death in days stratified by cryptococcosis.....	24
Appendix.....	25

List of Tables

Table 1	Univariable risk factors for Cryptococcosis in patients with and without Cryptococcosis among 42,634 solid organ transplant recipients.
Table 2	Multivariable Cox proportional hazard model of risk factors for Cryptococcosis
Table 3	Cox proportional hazard model of risk factors for death in 42,634 solid organ transplant recipients.

List of Figures

Figure 1: Time to onset of cryptococcosis in days, stratified by type of transplant.

Figure 2: Time to death in days, in a cohort of adult solid organ transplant recipients, stratified by the presence or absence of cryptococcosis.

Introduction

Cryptococcosis is an important opportunistic fungal infection that causes significant mortality and morbidity among solid organ transplant (SOT) recipients (1-3).

Traditionally cryptococcosis is most often associated with human immunodeficiency virus (HIV) infection; however, with the advent of effective antiretroviral therapy, the majority of cases in developed nations occur among non-HIV infected patients, especially organ transplant recipients (4, 5). Among 302 cases of cryptococcosis identified over a 14-year period from an academic medical center in the southern United States, 28% occurred in SOT recipients (4). Results from the Transplant-Associated Infection Surveillance Network (TRANSNET), a consortium of 23 U.S. transplant centers and data from Prospective Antifungal Therapy Alliance (PATH Alliance), showed that cryptococcosis is the third most common invasive fungal infection in SOT recipients, after invasive candidiasis and aspergillosis, comprising 8-10% of all invasive fungal infections identified in SOT recipients (1, 6). Overall incidence rates of cryptococcosis in cohorts of SOT recipients range from 0.2% to 4.1%, depending on the type of organ transplanted and the duration of follow-up and has remained stable over the years (1, 3).

Organ transplantation is a rapidly evolving field with rapid strides in surgical techniques, immunosuppression and prophylactic antifungal therapy. Although the incidence of invasive candidiasis and aspergillosis in SOT has decreased significantly over years the incidence of cryptococcosis has remained stable [median incidence of cryptococcosis was 1.52% (range, 0.27% – 5.3%) among a prior cohort (1950-2000) and

1.56% (range, 0.45% – 4.1%) among more recent cohort of SOT recipients (2001 - 2008)] (3).

Cryptococcosis typically occurs late in the post-transplant period, with a median of 575 days from transplant in the TRANSNET study and 21 months in a multinational prospective study among all types of SOT recipients by Singh et al (1, 7) . The time to onset of disease was earlier (< 12 months) for the majority of lung and liver transplant compared to kidney and heart transplant recipients in a review of published cases of cryptococcosis in SOT recipients (8). Mortality rates among all types of SOT recipients with cryptococcosis range from 14-19.6% and may approach 50% in SOT recipients with meningitis (3, 6, 9). Independent risk factors for death in all types of SOT recipients were cryptococemia, high intracranial pressure and renal failure, while calcineurin-inhibitor based immunosuppressive regimens were associated with lower mortality (7) .

Studies from academic medical centers contribute to our understanding of epidemiology of cryptococcosis and its outcomes in SOT recipients, however they have limited generalizability. Cryptococcosis identified and managed in community hospitals after patients have transitioned away from transplant centers may have been missed, especially with the prolonged time to onset after transplant. There are no population-level data describing the epidemiology of cryptococcosis and cryptococcal meningitis post-transplantation. We assembled a large and more representative cohort of SOT recipients from multiple hospitals using the longitudinal Agency for Healthcare Research and Quality (AHRQ), Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases (SID) to study the epidemiology of cryptococcosis and cryptococcal

meningitis. The SID contain demographic and billing data that capture inpatient diagnoses and procedures through *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding. This approach allowed us to follow a large number of patients over a long period of time and identify cryptococcosis and cryptococcal meningitis regardless of whether patients were treated in the index transplant hospital or a different hospital.

Methods:

Study design and patient population. We performed a retrospective cohort study of adults aged 18 years and older who underwent kidney, lung, liver, heart, pancreas, or intestine SOT, identified by ICD-9-CM procedure codes (55.69, 50.59, 37.51, 33.50, 33.51, 33.52, 33.6, 52.80, 52.86, 46.97) from 2004 to 2010 in California, 2006 to 2012 in Florida, and 2006 to 2011 in New York. These states and years were chosen based on the availability of patient-level encrypted identifiers to link admissions within and across hospitals over time and the population diversity of these states. We chose the cohort inception years to allow one year of prior data to identify comorbidities. Only the first transplant during the study period was included for all patients. We excluded patients who lived in states other than the one where transplantation was performed, were coded for cryptococcosis and cryptococcal meningitis within 1 year before transplantation, or died on the day of transplant. This study was considered exempt by the Washington University School of Medicine Human Research Protection Office.

Demographic data, comorbidities and follow-up. Demographic characteristics of the study population were determined during the transplant admission. Comorbidities were identified using the Elixhauser classification and ICD-9-CM diagnosis codes within one year before and during the transplant hospitalization (10). Comorbidities that were the primary reason leading to transplant were excluded (e.g., renal failure in kidney transplant, liver disease in liver transplants). Transplant failure or rejection episodes were identified during readmissions but considered a potential risk factor for cryptococcosis

only if it was identified prior to its onset. Inpatient readmissions were identified using the encrypted patient-level identifier. Dates of onset of cryptococcosis, cryptococcal meningitis and transplant failure or rejections were estimated to be midpoint of the stay if they were coded during the initial transplant hospitalization. For events identified during readmissions the date of admission was considered the date of onset. Prior transplantation was identified by a procedure code for SOT in the year prior to transplantation (only in the year reserved for comorbidities) or by a V-code to indicate prior transplant (V42.0, V42.7, V42.1, V42.6, V42.83, and V42.84). Transplant failure or rejection was not considered if it was coded during the transplant hospitalization in an individual with a history of SOT. Outcomes identified during the SOT hospitalization and during hospital readmissions were newly-coded cryptococcosis (ICD-9-CM diagnosis code 117.5) and cryptococcal meningitis (ICD-9-CM diagnosis code 321.0). ICD-9-CM diagnosis codes for septicemia, pneumonia, surgical site, and skin and soft tissue infection assigned during the admission coded for cryptococcosis were used to characterize the site of cryptococcal infection (codes listed in the Appendix).

Statistical analysis. Descriptive statistics were used to describe the demographic and clinical characteristics of the study population. Potential risk factors for cryptococcosis and inpatient death were analyzed using univariable and multivariable Cox proportional hazards models. To create a censor date, the transplant date was estimated as the 15th day of the admission month for CA and NY, and the midpoint of the discharge quarter for FL (FL SID does not provide an admission month). In the risk factor analysis for

cryptococcosis, patients were censored at inpatient death, or maximum follow-up. The proportional hazards assumption was evaluated for each variable using visual inspection of log-log survival curves and the correlation between Schoenfeld residuals and ranking of individual failure times (11). Variables were specified by selecting clinically meaningful factors that could potentially be associated with cryptococcosis and we sequentially eliminated variables with highest *P* values to arrive at a parsimonious model, followed by assessment of confounding to arrive at the final model. To evaluate whether the risk of death with and without cryptococcosis varied with time we used a heavy-side function to assess differential risk within one year and after one year of transplant (12). Statistical significance was set at $p < 0.05$. All analyses were performed using SAS Enterprise Guide 5.1 (Cary, North Carolina).

Results:**Patient characteristics**

The final study population consisted of 42,634 adult SOT recipients. A total of 63.7% had kidney transplantation, followed by 21.1% liver, 7.2% heart, and 5.2% lung transplants. Other or multiple organs were transplanted in 2.4% of the SOT patients (pancreas, intestine or multi-organ). The mean age at the time of transplant was 51.7 years; 62.6% were males, 51.2% were white, 21.1% were Hispanic, 76.3% lived in large metropolitan areas, and 15.8% had Medicaid or self-pay listed as primary insurance. Commonly identified comorbidities were, diabetes mellitus (37.5%), renal failure (12.0%) and chronic lung disease (10.1%). 1,492 patients (3.5%) had history of a prior organ transplant(s). The median duration of follow-up after SOT was 1295 days (range 1-3075 days).

Cryptococcal Infections

One hundred fifty-eight patients were coded for cryptococcosis (0.37%) after SOT. There was no significant difference in the incidence of cryptococcosis identified between the three states (0.35% in CA, 0.37% in FL and 0.41% in NY; $P = 0.661$). Sixteen of 158 patients were coded for cryptococcosis during the index transplant hospitalization. A total of 69 (44%) patients were identified with meningitis. Of the remaining patients with non-meningeal cryptococcosis, 41 (46.06%) were coded for pneumonia and 19 (21.34%) additional patients were coded for septicemia, skin and soft tissue or surgical site infection. Eighty-nine (0.32%) patients with cryptococcosis were identified after kidney transplant, 40 (0.44%) after liver, 15 (0.66%) after lung, and 13 (0.42%) after heart

transplantation. Twenty-six percent (38/158) of patients with cryptococcosis identified at readmission were treated at a hospital different from the index transplant surgery hospital. Eighty-three percent (57/69) of patients with cryptococcal meningitis had a procedure code for a lumbar puncture during the admission compared to 41% (36/89) of patients coded for cryptococcosis without meningitis ($P < 0.001$).

Lung transplant recipients had the highest risk of cryptococcosis compared to other organ transplant recipients, with a HR of 2.10 after adjusting for age and underlying comorbidities (**Table 1**). Increasing age, diabetes and having Medicaid or no health insurance were also risk factors for cryptococcosis in the multivariable Cox model (**Table 2**).

The median time to diagnosis of cryptococcosis from the date of transplant was 464 days (range 4 – 2,393). The median time to onset of disease was earlier after lung (191 days; range 7.5 – 1816), heart (195 days; range 4-1,061) and liver (200 days; range 4-1,581) than kidney transplant (616 days; range 12 – 2,393) ($P < 0.001$, Kruskal-Wallis test, **Figure 1**).

Very early versus later onset cryptococcosis

Very early-onset disease (cryptococcosis occurring within 30 days after transplantation) developed in 16 (10.1%) of 158 patients (median 10.7 days, range 4 - 23) after transplant while later onset cryptococcosis more than 30 days after transplant occurred in the remaining 142 patients (median 515 days, range 32 – 2,393). The proportion of patients with very early onset disease among liver or lung transplants was significantly higher than other transplants ($P < 0.001$, Fischer's exact test). However inpatient mortality did

not differ between the patients with very early onset vs. later-onset cryptococcosis ($P = 1.000$; Fischer's exact test).

Inpatient Mortality in patients with cryptococcosis

Forty-one of 158 (26.0%) patients with cryptococcosis died during the study period in-hospital versus 3,879 of 42,476 (9.1%) without cryptococcosis (HR 2.57; $P < 0.001$, **Table 3 and Figure 2**). Eighteen of 69 (26.1%) patients with cryptococcal meningitis died (HR 2.54, $P < 0.001$ compared to uninfected SOT recipients). In multivariable analysis cryptococcosis was associated with 2.3-fold increased risk of inpatient mortality ($P < 0.001$), adjusting for age, type of transplant, prior graft rejection/failure and several comorbidities (**Table 3**). There was no increased mortality risk with cryptococcosis during the first year after transplant (HR 1.39; $P = 0.257$); but there was a 3.2-fold increased risk of mortality more than one year after transplant ($P < 0.001$, **Figure 2**). The risk of death was highest for lung, followed by liver, heart and other transplants compared to renal transplant. Increasing age, prior transplant failure/rejection, congestive heart failure, liver disease, having Medicaid or no health insurance, and several other comorbidities were independent risk factors for in-hospital death (**Table 3**). The median time to death from diagnosis of cryptococcosis was 87.5 days (range 3 – 2,792). The median time to death from transplant was 637 days (range 32 – 2807) in patients with cryptococcosis and 359 days (range 1 – 2,858) in patients without cryptococcosis ($P < 0.001$, log rank test).

Discussion

We found that cryptococcal infections were rare, but associated with significant mortality in a large diverse population of SOT recipients from three U.S. states. The overall incidence of cryptococcosis was 0.37%, similar to the 12-month incidence of 0.2% reported in the TRANSNET study (1). Prior studies have found that 44 – 60% of SOT recipients with cryptococcosis developed CNS involvement (2,7,13). We found that meningitis was coded in 44% of the SOT recipients with cryptococcosis. The Infectious Diseases Society of America guidelines recommend evaluating for meningitis by lumbar puncture in SOT recipients with positive cryptococcal antigen test and in all immunosuppressed patients with pulmonary cryptococcosis (14). The proportion of patients coded for a lumbar puncture was significantly lower among the patients with cryptococcosis without meningitis compared to those patients coded for cryptococcal meningitis. The slightly higher proportion of patients without cryptococcal meningitis when compared to previous studies could be due to an error in additional coding for meningitis, or an error in ascertainment wherein an active search for CNS disease was not done in these patients (2,7). Among patients with non-meningeal cryptococcosis, the commonest site of involvement was pulmonary followed by septicemia and skin / soft tissue involvement, similar to the clinical presentations reported in prior cohorts of SOT recipients (2,3).

The majority of cases of cryptococcosis are late infections and considered to represent reactivation of latent infection in the recipient (15). The median time to cryptococcal disease from transplantation in our study (464 days) was consistent with the findings of

TRANSNET study (575 days) (1). Very early onset of cryptococcosis (within one month after transplant) is rare, and was reported in 5% of 175 SOT recipients with cryptococcosis by Sun et al (16). We found 10% of SOT recipients were coded for very early onset disease. Similar to the finding in the study by Sun et al., the majority of very early onset cryptococcal infection in our study occurred in liver and lung transplant recipients (16). These very early onset infections may reflect either undetected pre-transplant or donor-derived infections. Albeit rare, this should prompt clinicians to consider cryptococcosis in the evaluation of very early onset infections.

In this study lung transplant recipients had the highest risk for cryptococcosis, followed by liver and heart transplant recipients. Kidney transplant recipients had the lowest risk. This has not been reported previously in the literature. The median time to onset of cryptococcosis after transplant was earlier for lung, heart and liver (<1 year) compared to kidney transplant recipients (1.7 years). This was similar to the findings by Husain et al., where the median time to onset of cryptococcosis was 35 months for kidney and 25 months for heart, compared to 8.8 and 3 months for liver and lung transplant recipients (8). The higher risk and earlier onset of disease may reflect the greater intensity of immunosuppression with a higher risk of reactivation disease in the non-kidney transplant populations.

Twenty-six percent of patients with cryptococcosis died in-hospital versus 9.1% without disease over a median follow up time of 3.5 years in this large cohort of SOT recipients. The 90-day mortality rate (13.3%) in our study was very similar to that reported in a multicenter study of 111 SOT recipients with cryptococcosis by Singh et al in the modern

era of effective antifungal therapy (14%) (7). In our multivariable model, cryptococcosis was significantly associated with over a 2-fold increase risk of death. Lung, liver and heart transplant recipients were at higher risk for death compared to renal transplant recipients after adjusting for age, cryptococcosis and other comorbidities. Insurance coverage affected risk of death with patients with Medicaid or no health insurance at higher mortality risk.

The strengths of this study are the large cohort size, the long duration of follow up that allowed capture of late occurring infections, and identification of cryptococcosis treated in a hospital other than the transplant center. Twenty-six percent of infections were diagnosed in a hospital other than the patient's primary transplant center. Use of large administrative databases, such as the SID adds to our understanding of outcomes of rare diseases among hospitalized patients and supplements detailed single- and multi-center studies. However, there are several limitations. The ICD-9-CM diagnosis codes used to identify cryptococcosis in this study have not been validated, although the code for cryptococcal meningitis has been used to describe the epidemiology of disease (17). A validation study of ICD-9 diagnosis codes for several severe infections report positive predictive values >80% (18). Another limitation is that the data source used in this study contains only demographic and inpatient hospital ICD-9-CM billing data and does not have microbiology or other laboratory test results or data on antifungal or immune suppressive medications.

In summary, this is the first study that provides population-level information on the epidemiology of cryptococcosis after SOT in the current era. Cryptococcosis though rare,

was associated with significant mortality in this population. Lung, liver and heart transplant recipients were at higher risk for cryptococcosis compared to kidney transplant recipients. Cryptococcosis remains an important threat in SOT recipients and we need better management strategies and prophylactic and screening algorithms especially in liver and lung transplant recipients at risk of very early onset disease as subject of future research.

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Table 1. Univariable risk factors for Cryptococcosis in patients with and without Cryptococcosis among 42,634 solid organ transplant recipients.

	No. (%) of patients		HR (95% CI)	p
	With Cryptococcosis (n = 158)	Without Cryptococcosis (n= 42,476)		
Age				
18-40 years	16 (10.1)	8456 (19.9)	1	
41-50 years	35 (22.2)	8925 (21.0)	2.07 (1.14 – 3.74)	0.016
51-60 years	50 (31.6)	13119 (30.9)	2.04 (1.16 – 3.58)	0.013
60-70 years	48 (30.4)	9969 (23.5)	2.67 (1.52 – 4.71)	0.007
>70 years	<11	2007 (4.7)	2.50 (1.10 – 5.65)	0.028
Race				
White	74 (46.8)	20926 (49.3)	1	
Black	17 (10.7)	6363 (14.9)	0.78 (0.46- 1.34)	0.359
Hispanic	42 (26.6)	8981 (21.1)	1.36 (0.93 – 1.98)	0.114
Asian or Pacific Islander	13 (8.2)	3364 (7.9)	1.11 (0.62- 2.02)	0.728
Other or missing	12 (7.6)	2842 (6.7)	1.31 (0.71-2.42)	0.382
Female Sex	54 (34.1)	15882 (37.4)	0.95 (0.89 – 1.01)	0.596

Type of Insurance					
Private/Medicare/Others	133 (84.2)	38489 (90.6)	1		
Medicaid/Self-pay	25 (15.8)	3987 (9.4)	1.80 (1.17 – 2.75)		0.007
Income quartile					
0-25 th	73 (46.2)	13081 (30.8)	2.10 (1.30 -3.33)		0.002
51-75 th	26 (16.5)	10115 (23.8)	1.05 (0.60 -1.83)		0.857
76 -100 th	24 (15.2)	9913 (23.3)	1		
Type of transplant					
Kidney	89 (56.3)	27129 (63.9)	1		
Liver	40 (25.3)	8970 (21.1)	1.32 (0.91 – 1.92)		0.142
Lung	15 (9.5)	2223 (5.2)	2.06 (1.19 – 3.57)		0.009
Heart	13 (8.2)	3059 (7.2)	1.29 (0.72 – 2.30)		0.397
Others (multi-organ)	<11	1095 (2.6)	0.27 (0.04 – 1.93)		0.191
Prior transplant failure / rejection	85 (53.8)	22475 (52.9)	0.50 (0.16 – 1.59)		0.244
Other comorbidities					
Diabetes mellitus	86 (54.4)	15898 (37.4)	2.03 (1.48 – 2.78)		0.001
Renal failure	16(10.1)	5110 (12.0)	0.84 (0.52 – 1.41)		0.512
Chronic pulmonary disease	19 (12.0)	4308 (10.1)	1.20 (0.74 – 1.93)		0.421

Congestive Heart Failure	16 (10.1)	4127 (9.7)	1.02 (0.63 – 1.71)	0.930
Liver disease	10 (6.3)	2243 (5.3)	1.22 (0.65 – 2.33)	0.532
Connective tissue disorder	<11	1923 (4.5)	0.56 (0.20 – 1.51)	0.252
Prior transplantation	<11	1489 (3.5)	0.51 (0.16 – 1.59)	0.243

Table 2. Multivariable Cox proportional hazard model of risk factors for cryptococcosis

Risk factor	HR (95% CI)	p
Age		
18-40 years	1.00	
41-50 years	1.92 (1.06 – 3.48)	0.030
51-60 years	1.78 (1.01 – 3.13)	0.046
60-70 years	2.28 (1.22 – 3.86)	0.007
>70 years	2.41 (1.03 – 4.95)	0.041
Type of transplant		
Kidney	1.00	
Liver	1.16 (0.78 – 1.71)	0.466
Lung	2.10 (1.21 – 3.60)	0.009
Heart	1.15 (0.63 – 2.07)	0.645
Others (multi-organ)	0.23 (0.03 – 1.64)	0.142
Diabetes mellitus	1.95 (1.41 – 2.69)	<0.001
Medicaid/Self pay	1.99 (1.27 – 3.11)	0.002

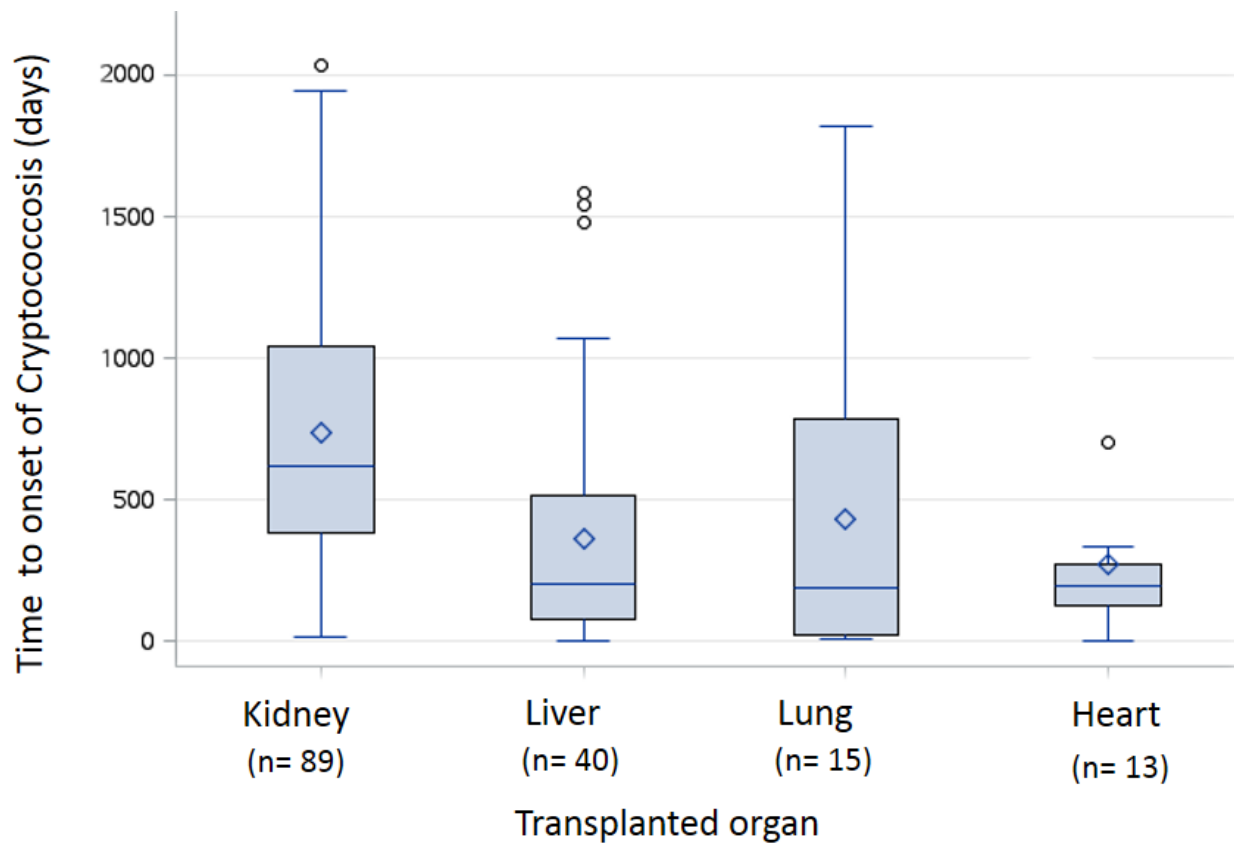
Table 3. Cox proportional hazard model of risk factors for death in 42,634 solid organ transplant recipients.

Risk factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p
Cryptococcosis	2.57 (1.89 – 3.50)	<0.001	2.29 (1.68 – 3.11)	<0.001
Cryptococcal Meningitis	2.54 (1.60 – 4.04)	<0.001		
Age				
18-40 years	1.00			
41-50 years	1.46 (1.30 – 1.65)	<0.001	1.36 (1.19 – 1.53)	<0.001
51-60 years	2.01(1.81 – 2.24)	<0.001	1.60 (1.43 – 1.80)	<0.001
60-70 years	2.77 (2.48 – 3.09)	<0.001	2.29 (2.04 – 2.57)	<0.001
>70 years	3.32 (2.87 – 3.85)	<0.001	3.70 (3.14 – 4.30)	<0.001
Female sex	0.95 (0.89 – 1.01)	0.596		
Type of transplant				
Kidney	1.00		1.00	
Liver	2.67 (2.47 – 2.87)	<0.001	2.47 (2.26 – 2.71)	<0.001
Lung	4.86 (4.41 – 5.37)	<0.001	3.68 (3.28 – 4.12)	<0.001
Heart	2.47 (2.21 – 2.76)	<0.001	2.32 (2.11 – 2.65)	<0.001
Others (multi-organ)	3.35 (2.88 – 3.89)	<0.001	2.21 (1.86 – 2.65)	<0.001
Type of Insurance				
Medicaid/Self-pay	1.46 (1.28 – 1.56)	<0.001	1.24 (1.13 - 1.37)	<0.001
Prior transplant failure / rejection	2.66 (2.46 – 2.86)	<0.001	2.53 (2.38 – 2.77)	<0.001

Other comorbidities				
Diabetes mellitus	1.27 (1.20 – 1.36)	<0.001	1.14 (1.07 – 1.21)	0.001
Renal failure	1.66 (1.53 – 1.80)	<0.001		
Chronic pulmonary disease	1.31 (1.20 – 1.44)	<0.001		
Obesity	1.04 (0.94 – 1.15)	0.484		
Congestive heart failure	1.68 (1.54 – 1.83)	<0.001	1.58 (1.47 – 1.73)	<0.001
Liver disease	1.41 (1.24 – 1.60)	<0.001	1.22 (1.05 – 1.42)	0.007
Connective tissue disorder	0.83 (0.70 – 0.98)	0.020		
Solid tumors	1.51 (1.12 – 2.04)	0.006		
Hypertension	0.52 (0.49 - 0.56)	<0.001	0.87 (0.80 – 0.94)	<0.001
Hematological malignancies	1.65 (1.11 – 2.48)	0.013		
Cancer with metastasis	1.95 (1.27 – 2.99)	0.002		
Valvular heart disease	1.52 (1.39 – 1.66)	<0.001		
Depression	1.38 (1.26 – 1.52)	<0.001		
Pulmonary circulation disorder	2.12 (1.95 – 2.31)	<0.001		
Weight loss	2.07(1.90 – 2.27)	<0.001	1.22 (1.11 – 1.34)	<0.001
Peripheral vascular disease	1.34 (1.38 – 1.69)	<0.001	1.46 (1.32 – 1.62)	<0.001
Electrolyte disorders	1.51 (1.42 – 1.62)	<0.001	1.18 (1.11 – 1.26)	<0.001
Psychoses	1.48 (1.26 – 1.75)	<0.001	1.21 (1.02 – 1.42)	0.022
Drug abuse	1.57(1.33 – 1.81)	<0.001	1.20 (1.05 – 1.39)	0.006
Neurological disorders	1.20 (1.06 – 1.36)	0.002		

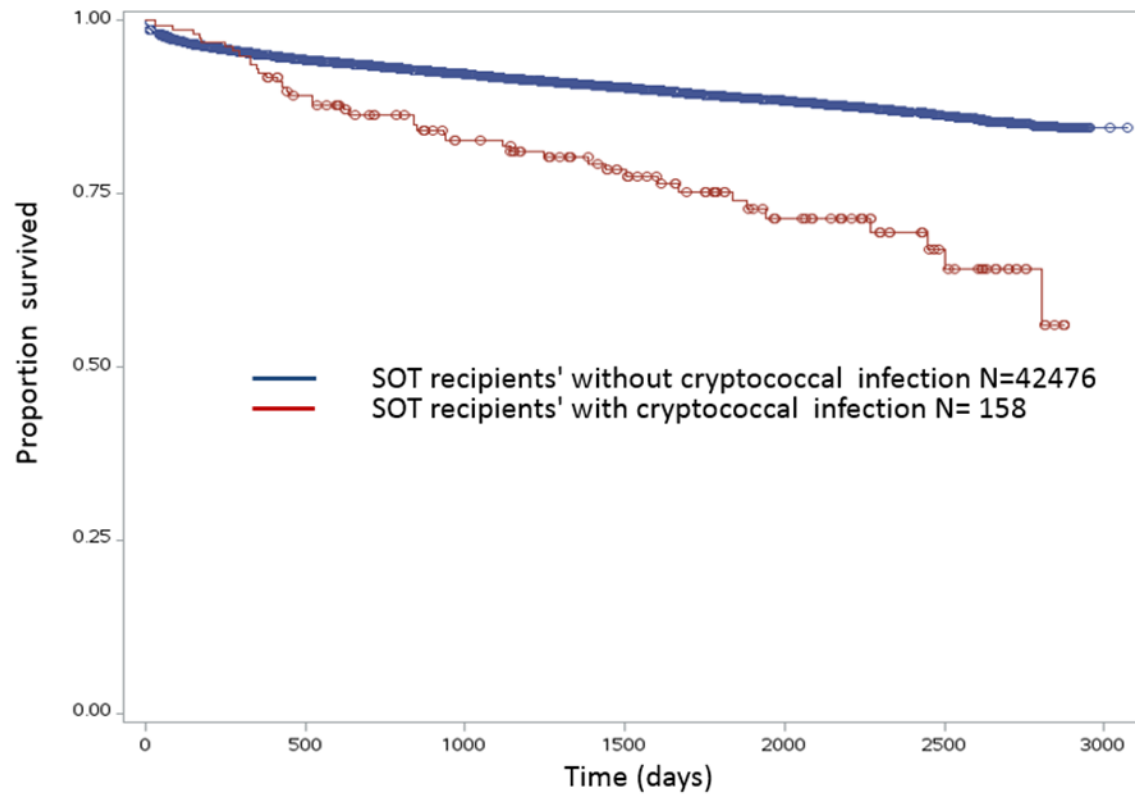
Prior transplantation	1.23 (1.05 – 1.43)	0.008
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Figure 1: Time to onset of cryptococcosis in days, stratified by type of transplant.



Boxes represent values within the 25th–75th percentiles (interquartile range), and horizontal lines represent the median and the diamonds the mean values. Error bars indicate the maximum and minimum observation below the upper and lower fences (1.5 IQR) and circles the maximum observations.

Figure 2: Time to death in days, in a cohort of adult solid organ transplant recipients, stratified by the presence or absence of cryptococcosis.



APPENDIX. Diagnosis Codes Used in Combination to Identify Septicemia, Pneumonia, Surgical Site Infection, and Skin and Soft Tissue Infections

Diagnosis	ICD-9-CM Diagnosis Code
Septicemia	038.8, 038.9, 790.7
Pneumonia	483.8, 484.7, 484.8, 485, 486, 510, 510.9, 513.0
Surgical Site Infection	998.5, 998.51, 998.59
Skin and Soft Tissue Infection	5673.1, 680.0 -680.9, 681.00 – 681.02, 681.10, 681.11, 681.9, 682.0- 682.9, 683, 684, 685.0, 686.0, 686.00, 686.01, 686.09, 686.1, 686.8, 686.9, 675.00- 675.04, 675.10 – 675.14, 675.80 – 675.84, 675.90 – 675.94, 705.83, 727.89, 728.0, 728.86