International Journal of Infectious Diseases 88 (2019) 154–158

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Incidence of and risk factors for cryptococcosis in kidney transplant recipients in Taiwan—A nationwide population-based study

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A R T I C L E I N F O

Article history:
Received 5 June 2019
Received in revised form 17 August 2019
Accepted 19 August 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Kidney transplant recipients
Cryptococcosis
Epidemiology

A B S T R A C T

Objectives: The aim of this study was to determine the long-term incidence of cryptococcosis in kidney transplant recipients (KTRs) and to analyze its risk factors.
Methods: This retrospective population-based cohort study analyzed data obtained from Taiwan's National Health Insurance Research Database for KTRs during 2000–2012 and matched cohorts. Both populations were followed until death, development of cryptococcosis, or December 2013.
Results: A total of 4,933 KTRs and 49,930 matched patients were included. The cryptococcosis incidence rates for the KTR cohort and matched cohort were 10.59 and 0.4 per 10,000 person-years, respectively. The hazard ratio for cryptococcosis among KTRs was 26.65 ($p < 0.001$); and 43.77 ($p < 0.001$) for cryptococcosis affecting the central nervous system (CNS). The Kaplan-Meier method confirmed an elevated cumulative incidence of cryptococcosis among KTRs (1.00% vs. 0.04%). Predictors for cryptococcosis were advanced age (OR 1.39, 95% CI 1.02–1.89, $P = 0.038$) and cancer (OR 2.63, 95% CI 1.22–5.67, $P = 0.013$), but not the use of any particular class of immunosuppressants.
Conclusions: KTRs are at dramatically higher risk of developing cryptococcosis, especially with CNS involvement, relative to a non-KTR matched cohort. Older KTRs and those with cancer are at even higher risk of developing cryptococcosis.

Introduction

Since the first documented kidney transplantation in the 1950s, advances in organ preservation, surgery, and immunosuppression have improved transplant success rates and long-term graft survival greatly (Linden, 2009). Kidney transplantation has become the favored treatment for end-stage kidney disease; indeed more than 73,000 kidney transplants were performed in 2010 alone according to the Global Observatory on Donation and Transplantation (Grinyo, 2013). Despite refinements in immunosuppressive regimens, diagnostic tools, and treatments, posttransplantation infection remains a major cause of morbidity and mortality in kidney transplant recipients (KTRs) (Karuthu and Blumberg, 2012).

Invasive fungal infections with *Cryptococcus* species are of particular concern in transplant patients (Snyder et al., 2009). The incidence of cryptococcosis, which had previously been a rare disease, rose as there came to be more patients living with defective cell-mediated immunity, including transplant recipients on immunosuppressant therapy and patients with AIDS (Sloan and Parris, 2014). In previous decades, cryptococcosis was diagnosed among approximately 5% to 8% of human immunodeficiency virus-infected patients (Aberg and Powderly, 2002). Under the ART era,

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https://doi.org/10.1016/j.ijid.2019.08.021
1201-9712/

the incidence of cryptococcosis in human immunodeficiency virus-infected patients has declined substantially from 66–23.6 cases per 1000 persons in 1992–1993 to 7–1.6 cases per 1000 persons in 2000 in the United States (Mirza et al., 2003). However, cryptococcosis has become the third most common cause of invasive fungal infections in solid organ transplant recipients (Pappas et al., 2010). It occurs in 0.2–5.0% of solid organ transplant recipients (2.4% in liver, 2.0% in lung and 2.8% in renal transplant recipients), with an overall mortality rate of 15–20%, and a grave mortality rate of 49% in patients with central nervous system (CNS) involvement (Husain et al., 2001; Pappas et al., 2010; Singh et al., 2007; Sloan and Parris, 2014).

Cryptococcosis clinical manifestations and outcomes, such as degrees of dissemination, CNS involvement, graft failure, and mortality, differ across transplant types, possibly due to differences in degree of immunosuppression and underlying diseases (Husain et al., 2001; Singh et al., 2007; Wu et al., 2002). Most solid organ transplant patients diagnosed with cryptococcosis are KTRs owing to kidney transplantations being performed successfully in relatively large numbers of patients. However, to date, few cryptococcosis epidemiology studies have been conducted in this population selectively (Husain et al., 2001; Singh et al., 2007). It has been suggested that cryptococcosis in transplant recipients may be the result, predominantly, of reactivation of a quiescent infection (Singh et al., 2008). If so, preventive strategies focused on preventing exposure are unlikely to be effective.

Elucidating cryptococcosis risk factors is important for developing prophylactic, diagnostic, and treatment strategies. However, most studies of cryptococcosis in transplant patients have included heterogenous populations of recipients of any organ transplant without delineating risk of cryptococcosis in KTRs specifically (Husain et al., 2001; Pappas et al., 2010; Singh et al., 2007). The aim of the present study was to determine the incidence and risk of cryptococcosis in KTRs. We employed the Taiwanese National Health Insurance Research Dataset (NHIRD), which provides a near universal representation of medical cases in Taiwan, to compare the incidence of cryptococcosis in KTRs versus that in the general population and to analyze the risk factors of developing cryptococcosis.

Methods

Data source

Taiwan's National Health Insurance program, launched in 1995, currently covers >99% of the 23 million residents of Taiwan (Cheng and Chiang, 1997). All patient data, including diagnoses, procedures, and prescriptions, are recorded in the NHIRD. Disease diagnoses are recorded using codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). KTRs were identified in Taiwan's registered catastrophic illness dataset, which includes a list of life-altering and debilitating diseases and is considered highly reliable owing to intense scrutiny (Li et al., 2012). Matched cohorts were extracted from the Longitudinal Health Insurance Database, which contains complete data for 1,000,000 randomly sampled beneficiaries in the NHIRD.

Study design and population

In this population-based, observational, retrospective cohort study, we compared the incidence of cryptococcosis (codes 321.0 and 117.5) in two adult (age > 20 years) cohorts—KTRs and a matched general population sample—during the period of January 2000–December 2012. The index date was the day when the catastrophic illness (kidney transplantation) was registered. We identified ten matched persons for each KTR in terms of year of diagnosis, age, sex, urbanization level, income level, Charlson Comorbidity Index score, diabetes, autoimmune disease, chronic pulmonary disease, chronic liver disease, and cancer. We extracted data on each identified individual for the period of January 1997–December 1999 to ensure that all individuals were followed for at least 3 years before study enrollment, thereby confirming the presence of any comorbidities (Deyo et al., 1992) and buttressing matching accuracy (Kuo et al., 2014). Patients in both cohorts were followed until a diagnosis of cryptococcosis was made, the patient was lost to follow up, the patient died, or December 31st, 2013. This study was approved by the Institution Review Board of Taipei Veterans General Hospital (2018-03-003BC), and informed consent was waived by Institutional Review Board.

Statistical analyses

Descriptive statistics were used to characterize the baseline data of both groups. Mean values are reported with standard deviations (SDs). The cumulative incidence of cryptococcosis was calculated by the Kaplan-Meier method and compared between the groups with a log-rank test. Cox proportional hazard models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs). We performed likelihood ratio testing of nested models and stratified subgroup analyses to determine whether associations between kidney transplantation and cryptococcosis were affected by the interaction of demographic characteristics, socioeconomic status, underlying conditions, and/or medications. P values < 0.05 were considered to be significant. Microsoft SQL Server 2008 R2 database management software (Microsoft Corporation, Redmond, WA) was used for data linkage, processing, and sampling. All analyses were conducted in STATA statistical software (version 12.0; StataCorp, College Station, TX).

Results

The characteristics of the KTR (N = 4,933) and matched cohorts (N = 49,330) are reported and compared in Table 1. Briefly, both groups had mean ages near 46 years old and a small-margin male majority. The clinical characteristics of the matched cohort were well-balanced with those of the KTR group. Multiple comorbidities were common in both groups, with the most common comorbidities being chronic pulmonary disease, diabetes, and chronic liver disease.

The mean number of follow-up years was 6.3 ± 3.4 for KTRs and 6.1 ± 3.4 for the matched cohort. As reported in detail in Table 2, the incidence rate for cryptococcosis in the KTR group was dramatically and very significantly higher (HR 26.65, 95% CI 13.76-51.60, $P < 0.001$) than that in the matched cohort. Analyzing cases with or without CNS involvement separately, we found that, relative to the matched cohort, KTRs had significantly higher incidence rates for cryptococcosis both with (HR 43.77, 95% CI 9.46-202.58, $P < 0.001$) and without (HR 23.20, 95% CI 1.09-48.51, $P < 0.001$) CNS involvement (Table 2).

Log-rank testing confirmed that the cumulative incidence of cryptococcosis was higher in the KTR group than in the matched cohort ($P < 0.001$, Figure 1). The Kaplan-Meier method showed the 13-year cumulative incidence of cryptococcosis in the KTR cohort (1.00%; 95% CI 0.69–1.44) was significantly higher (log rank $P < 0.001$) than that in the matched cohort (0.04%; 95% CI 0.02–0.07). The 1-year, 3-year, and 5-year cumulative incidences of cryptococcosis for KTRs and matched cohort were 0.17% versus 0.00%, 0.39% versus 0.02%, and 0.65% versus 0.02%, respectively (all $P < 0.001$).

Transplantation increased the risk of cryptococcosis in a diverse variety of population subgroups. Supplementary Table S1 demonstrated the comparison of the risk of cryptococcosis among different subgroups among KTRs stratified by age, sex, Charlson

Table 1
Baseline characteristics of KTRs and matched cohort.

Characteristic	KTRs N = 4,933	Matched cohort N = 49,330	*P*
Age, mean ± SD	46.4 ± 11.3	46.4 ± 16.6	0.892
Male, N (%)	2596 (52.6)	25684 (52.1)	0.453
Monthly income, N (%)			
Dependent	973 (19.7)	9637 (19.5)	0.989
NT$ <19,100	984 (19.9)	9836 (19.9)	
NT$ 19,100–42,000	2276 (46.1)	22859 (46.3)	
>NT$ 42,000	700 (14.2)	6998 (14.2)	
Urbanicity[a], N (%)			
Level 1 (urban)	2048 (41.5)	20509 (41.6)	0.990
Level 2	2656 (53.8)	26554 (53.8)	
Level 3	200 (4.1)	1995 (4)	
Level 4 (rural)	29 (0.6)	272 (0.6)	
Charlson comorbidity index score[b], mean ± SD	5.6 ± 2.6	5.6 ± 3.4	0.855
Comorbidity/history, N (%)			
Diabetes	1332 (27)	13407 (27.2)	0.791
Chronic pulmonary disease	1510 (30.6)	15050 (30.5)	0.883
Chronic liver disease	1528 (31)	15296 (31)	0.963
Autoimmune disease	340 (6.9)	3382 (6.9)	0.923
Cancer	572 (11.6)	5655 (11.5)	0.782

KTR, kidney transplant recipient; SD, standard deviation; NT$, new Taiwan dollars.
[a] Urbanicity levels divided into four strata according to the Taiwan National Health Research Institute publications.
[b] Index of overall systemic health. Increases in CCI score level are associated with stepwise increases in cumulative mortality.

Table 2
Comparison of cryptococcosis incidence between KTRs and matched cohort.

Diagnosis Parameter	KTRs	Matched cohort	*P*
Any cryptococcosis			
No. events/follow-up years	33/31,176	12/299,714	
Incidence rate[a]	10.59	0.40	
HR (95% CI)	26.65 (13.76–51.60)	Reference	<0.001
CNS cryptococcosis			
No. events	9	2	
Incidence rate[a]	2.89	0.067	
HR (95% CI)	43.77 (9.46–202.58)	Reference	<0.001
Non-CNS cryptococcosis			
No. events	24	10	
Incidence rate[a]	7.70	0.33	
HR (95% CI)	23.20 (1.09–48.51)	Reference	<0.001

KTR, kidney transplant recipient; HR, hazard ratio; CI, confidence interval; CNS, central nervous system.
[a] Cases per 10,000 person-years.

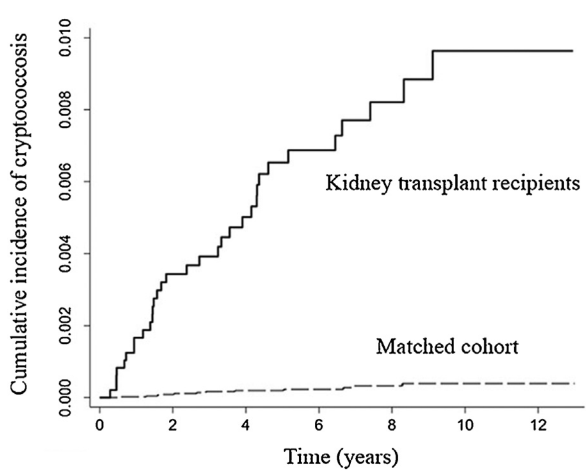

Figure 1. Cumulative incidence of cryptococcosis among kidney transplant recipients relative to a matched cohort.

comorbidity index score and comorbidities. In particular, chronic liver disease and chronic pulmonary disease comorbidities each elevated the risk of cryptococcosis in KTRs.

The risk factors for cryptococcosis in KTRs were further analyzed by using univariate and multivariate methods in Table 3. Advanced age and cancer comorbidity/history were found to be independent risk factors for cryptococcosis. Notably, no particular type of immunosuppressant therapy was found to be an independent risk factor for cryptococcosis (Table 3) and no immunosuppressant drug type was associated with the development of cryptococcosis (see Supplementary Table S2).

Discussion

In this study, we found that KTRs had an elevated risk (~26-fold) of cryptococcosis, especially cryptococcosis involving the CNS (~43-fold), relative to a matched cohort. Cumulative rates continued to increase steadily from 1-year to 3-years to 5-years postoperatively. Being older or having a cancer comorbidity/history were found to be independent risk factors for cryptococcosis. The incidences of cryptococcosis in the solid organ transplants remained relatively stable among all solid organ transplant patients over many decades; the incidence ranged from 0.27 to 5.3 per 100 solid-organ transplant recipients during 1950-2000 and 0.45–4.1 during 2001–2008 (Sun et al., 2009). For KTRs, Husain et al. in a review and meta-analysis of worldwide cryptococcosis incidence reports through 1998 showed the incidence of cryptococcosis was 2.8 per 100 patients (Husain et al., 2001). A large study of 2,122 KTRs in the USA (University of Pittsburgh Medical Center) involving a cohort of 5,521 organ transplant recipients (January 1989–July 1999) revealed an incidence of 0.33 per 100 patients (Wu et al., 2002). The cryptococcosis incidence rate obtained in this study for KTRs in the period of January 2000 to December 2012 in Taiwan was 0.7 per 100 KTRs. Similar to other organ transplant recipients, no dramatic increase was observed in the incidence of cryptococcosis in KTRs.

Our finding of progressively greater cumulative incidence rates from 1-year to 5-years postoperatively fits well with prior studies showing relatively late onset of cryptococcosis in solid organ transplant recipients (range of median onset times, 16–21 months after transplantation) (Husain et al., 2001; Kontoyiannis et al., 2010; Singh et al., 2007). Notwithstanding, many patients do develop cryptococcosis within a year of transplantation. Indeed, Singh et al. (2007) and Husain et al. (2001) observed within-1-year cryptococcosis incidence rates of 31.5% and 41%, respectively. When

Table 3
Risk factors for cryptococcosis in KTRs.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, per 10 years	1.43 (1.05–1.96)	0.024	1.39 (1.02–1.89)	0.038
Male sex	1.19 (0.60–2.33)	0.621		
Comorbidity/history				
Diabetes	1.45 (0.71–2.98)	0.311		
Autoimmune disease	1.29 (0.39–4.22)	0.675		
Chronic pulmonary disease	1.29 (0.39–4.22)	0.675		
Liver cirrhosis	0.99 (0.47–2.08)	0.985		
Cancer	2.85 (1.33–6.11)	0.007	2.63 (1.22–5.67)	0.013
HBV	–			
HCV	–			
Immunosuppressant drugs[a]				
Steroids	1.11 (0.57–2.18)	0.753		
Calcineurin inhibitors	0.97 (0.13–7.11)	0.977		
Purine antagonists	5.34 (0.73–39.08)	0.099		
mTOR inhibitors	0.89 (0.31–2.52)	0.822		

KTR, kidney transplant recipients; CI, confidence interval; OR, odds ratio; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection.
[a] Calcineurin inhibitors include cyclosporine and tacrolimus; purine antagonists include azathioprine, mycophenolate mofetil, and mycophenolic acid; mTOR inhibitors include sirolimus and everolimus.

considering onset data, it is important to remember that the mean onset datum reported for any particular cohort will depend upon the follow-up duration of the study as well as the survival rate of the patients. That is, with improving survival rates, longer follow-up would surely identify more cases, making median time of cryptococcosis onset longer. Although immunosuppression per se is a major risk factor for the development of cryptococcosis (Snyder et al., 2009), linking cryptococcosis risk in solid organ transplant patients with particular types of immunosuppressant drugs has been elusive (Husain et al., 2001; Singh et al., 2007). This lack of differentiation may be attributed to difficulties with measuring immunosuppressant effects due to small numbers of cases as well as complex clinical scenarios such as transplantation type, comorbidities, and the use of various doses and courses of multiple immunosuppressants. The use of steroids has been associated with cryptococcosis in the patients without HIV, but not selectively in organ transplant recipients (Baddley et al., 2008). Multi-dose regimens of immunotherapeutics (the anti-CD52 antibody alemtuzumab or anti-thymocyte globulin) have been associated with the development of cryptococcosis, though the clinical characteristics differed significantly between the analyzed groups (Silveira et al., 2007). Finally, it is noteworthy that calcineurin inhibitors have been shown to affect the clinical manifestation of cryptococcosis (i.e., dissemination and mortality), but not its incidence rate (Singh et al., 2007). In the present cohort, our multivariate analysis did not reveal any particular immunosuppressant drug type to be associated with a higher cryptococcosis risk.

Elucidation of cryptococcosis risk factors should help medical professionals with disease prevention and treatment planning. In addition to immunosuppressive therapy, old age, malignancy, autoimmune diseases, and diabetes mellitus have been associated with cryptococcosis incidence in non-HIV-positive patients (Lin et al., 2016; Lin et al., 2015; MacDougall et al., 2011; Pappas, 2013). The present findings of advanced age and cancer being independent factors of developing cryptococcosis replicate, partially, those prior findings. Old age is associated with more comorbidities and decreased cellular and humoral immunity (Haynes and Maue, 2009), and an underlying immunoinsufficiency that would predispose patients to cancers may also contribute to the development of cryptococcosis.

A major strength of this study was the use of a population-based database, which enabled us to include all transplant patients in Taiwan with a long follow-up time. However, the NHIRD contains ICD-9-CM coding without differentiation between *Cryptococcus* pathogen species, especially differentiation between the most common, geographically widespread pathogenic species *C. neoformans* and the more rare and tropical-region limited, but also much more virulent, species *C. gattii*. The relatively low prevalence of *C. gattii*, which was reported to account for only 4.1% of cryptococcosis cases in Taiwan (1997–2010), with most patients not being transplant recipients (Tseng et al., 2013), may mitigate the effect of the lack of species identification in our study. Furthermore, some risk factors can be missed by using Big Data sources–for instance, serum creatinine level at diagnosis, rejection treatment, induction therapy and immunosuppressants at the time of diagnosis or at transplantation as well as its change are unable to be clearly identified. A second limitation of this study is that only the aspects disease comorbidity/history and medication use that involved the national health administration are recorded in the database. Thus, any self-funded health care consultations and treatments are omitted. Third, cryptococcosis diagnoses can sometimes be missed. Because transplant patients are subjected to closer medical monitoring than the general public, the results may be subject to a surveillance bias in favor of KTRs not having missed diagnoses. Notwithstanding, meningitis due to cryptococcosis affecting the CNS is not easily ignored or overlooked.

In conclusion, this matched cohort study showed that KTRs have a dramatically elevated incidence of cryptococcosis, especially cryptococcosis of the CNS, relative to the general population. Older KTRs and those with a history or comorbidity of cancer are at especially high risk.

Contributions

YTC, WSL and FDW participated in the design, led the analysis, and drafted the manuscript. CAT and WCF participated in the analysis and interpretation and drafted the Tables and Figures of the manuscript. PFW participated in the data collection. FDW commented and revised drafts of the manuscript. All authors approved the final manuscript.

Funding source

This work was supported by a research grant from Taipei Veterans General Hospital, Taipei, Taiwan (grant number V106C-183).

Ethical approval

This study was approved by the Institution Review Board of Taipei Veterans General Hospital, and informed consent was waived by Institutional Review Board.

Conflicts of interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.021.

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