ORIGINAL ARTICLE

History of psychosis and mania, and outcomes after kidney transplantation - a retrospective study

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SUMMARY

History of psychosis or mania, if uncontrolled, both represent relative contraindications for kidney transplantation. We examined 3680 US veterans who underwent kidney transplantation. The diagnosis of history of psychosis/mania was based on a validated algorithm. Measured confounders were used to create a propensity score-matched cohort (n = 442). Associations between pretransplantation psychosis/mania and death with functioning graft, all-cause death, graft loss, and rejection were examined in survival models and logistic regression models. Post-transplant medication nonadherence was assessed using proportion of days covered (PDC) for tacrolimus and mycophenolic acid in both groups. The mean ± SD age of the cohort at baseline was 61 ± 11 years, 92% were male, and 66% and 27% of patients were white and African-American, respectively. Compared to patients without history of psychosis/mania, patients with a history of psychosis/mania had similar risk of death with functioning graft [subhazard ratio (SHR) (95% confidence interval (CI)): 0.94(0.42–2.09)], all-cause death [hazard ratio (95% CI): 1.04 (0.51–2.14)], graft loss [SHR (95% CI): 1.07 (0.45–2.57)], and rejection [odds ratio(95% CI): 1.23(0.60–2.53)]. Moreover, there was no difference in immunosuppressive drug PDC in patients with and without history of psychosis/mania (PDC: 76 ± 21% vs. 78 ± 19%, P = 0.529 for tacrolimus; PDC: 78 ± 17% vs. 79 ± 18%, P = 0.666 for mycophenolic acid). After careful selection, pretransplantation psychosis/mania is not associated with adverse outcomes in kidney transplant recipients.

Transplant International 2018; 31: 554–565

Key words
bipolar disorder, kidney transplantation, mortality, schizophrenia, survival

Received: 3 December 2017; Revision requested: 11 January 2018; Accepted: 29 January 2018;
Published online: 27 February 2018

doi:10.1111/tri.13127

Introduction

The prevalence of bipolar disorder is around 3% and schizophrenia is around 1% in the general population [1,2]. These disorders are more frequently found in US veterans compared to the general population [3]. Both schizophrenia and bipolar disorder showed associations with common and strong risk factors of chronic kidney disease (CKD) such as diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease [4]. In addition, treatment of bipolar disorder with lithium has a strong association with the development and worsening of CKD [5].

There are very few absolute contraindications for kidney transplantation. Psychiatric disorders, especially a history of psychosis and/or mania, which are the cardinal symptoms of schizophrenia and bipolar disorder, remain a relative contraindication endorsed by most organ transplant societies [6–9]. There are several reasons for this, including concerns about relapse of psychiatric illness, medication and other post-transplant treatment adherence, inadequate social support, emotional and cognitive capability, and potential drug interactions between psychotropic and immunosuppressant medications [10,11]. However, there are very few data to support these concerns and most of them stem from assessment during the post-transplant period [12].

Published data on post-transplant outcomes in patients with history of pretransplant history of psychosis/mania are extremely limited and consists mainly of case reports and very small observational studies [13–19]. These observational studies [11,13,16,17,19] have shown the feasibility of transplantation in patients with history of psychiatric disorders with an excellent patient and allograft survival rate. One of the largest studies examined 164 veteran organ transplant recipients (40 with a kidney graft) and reported excellent outcomes in the first 3 years after transplantation [17]. Similar results were reported from the Irish National Renal Transplant Programme [11]. Comparing 15 patients with diagnosis of bipolar affective disorder and six patients with schizophrenia with the rest of the recipients, there were no significant differences in patient survival, graft survival, and graft function [11]. Well-known risk factors of allograft loss were antisocial behavior, associated depression, medical noncompliance, history of psychotic episodes more than 1 year before transplantation, homelessness, and isolation [4,20]. A recent study from Europe included 47 patients with history of bipolar disorder and schizophrenia, and found similar graft and patient survival in recipients with history of this disorder versus others [13,21]. All of these previous studies are small, focusing primarily on patient and allograft survival, and have severe methodological limitations such as low number of events, lack of considering competing risks in transplant outcomes, and unmeasured confounders such as medical comorbidities, medications, and laboratory data and none of these studies assessed medication adherence in these patients. Consequently, the association between history of pretransplantation psychosis/mania and graft and patient outcomes post-transplantation is still uncertain. In addition, these studies did not assess associations between the history of psychosis/mania and risk of rejection or medication nonadherence after transplantation.

To address this knowledge gap, we aimed to investigate the association of history of pretransplantation psychosis/mania with post-transplant all-cause mortality and death with functioning graft, graft loss, rejection, and medication adherence using a large nationally representative cohort of US veterans with pre- and post-transplantation data. We hypothesized that the history of pretransplantation psychosis/mania is associated with higher risk of death, graft loss, rejection, and medication nonadherence.

Materials and methods

Data source and cohort definition

We analyzed longitudinal data of kidney transplant recipients from the Transition of Care in CKD (TC-CKD) study, a retrospective cohort study examining US veterans with late-stage nondialysis-dependent chronic kidney disease (NDD-CKD) transitioning to renal replacement therapy from October 1, 2007 through March 31, 2014 [22–24]. A total of 85 505 US veterans were identified from the US Renal Data System as a source population. Only individuals who received preemptive kidney transplantation or transitioned to receive renal replacement therapy and then subsequently received kidney transplantation were included in the source population. The algorithm for the cohort definition is shown in Fig. 1. We excluded patients, who were never transplanted (n = 81 294) and those without any available information on comorbid conditions including history of psychosis/mania (n = 531), which resulted in a study population of 3680 patients. From these 3680 patients, a propensity score-matched cohort was created including 442 kidney transplant recipients.

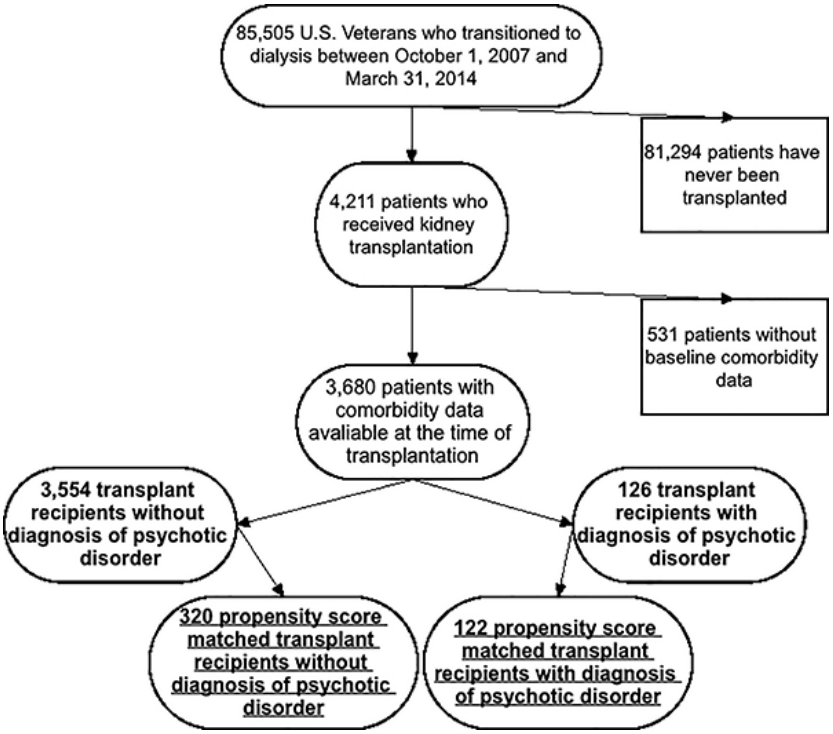

Figure 1 Flowchart of selection of the patients.

Exposure variable

Information on history of psychosis/mania before transplantation was extracted from Veterans Affairs (VA) Inpatient and Outpatient Medical SAS Datasets, using the ICD-9-CM diagnostic codes as well as from VA/Centers for Medicare and Medicaid Services data. We used the validated algorithm described by Frayne *et al.* [25] to define history of psychosis/mania using outpatient or inpatient medical records prior to kidney transplantation.

Covariates

Data from the United States Renal Data System (USRDS) Patient and Medical Evidence files were used to determine patients' baseline demographic characteristics at the time of kidney transplantation. Information on comorbidities at the time of kidney transplantation was extracted from VA Inpatient and Outpatient Medical SAS Datasets, using the ICD-9-CM diagnostic and Current Procedural Terminology codes, as well as from VA/Centers for Medicare and Medicaid Services data. Medication data were collected from both Centers for Medicare and Medicaid Services Data (Medicare Part D) and VA pharmacy dispensation records. Patients who received at least one dispensation of medication within the 12 months pretransplantation period were recorded as having been treated with these medications. Laboratory data were obtained from VA research databases as previously described [26,27], and their baseline values were defined as the average of each covariate during the 12 months pretransplantation period.

Assessment of medication adherence and persistence

Detailed information about each tacrolimus and mycophenolic acid prescription was collected during the first year after kidney transplantation in a subcohort of propensity score-matched patients (n = 149 for tacrolimus and n = 144 for mycophenolic acid), who received these prescriptions through a VA pharmacy. Only seven patients received cyclosporin in the propensity-matched cohort, and hence, this data have not been analyzed. Proportion of days covered (PDC) and medication persistence were calculated. The detailed description of PDC has been published previously [24]. Figure S1 shows the graphical description of the calculations for the different adherence methods.

Briefly, PDC was defined as the proportion of days when the drug was available in the measurement period, capped at 100% [28,29]. The index date was the date of the first available prescription after transplantation. The last prescription had to be dispensed before the first-year transplantation anniversary, and the full prescription period was included in the denominator, regardless

whether the supply lasted until after the date of the first-year transplantation anniversary. Only outpatient prescriptions were taken into account. Any inpatient time period was added to the denominator. For medication persistence, the following algorithm was used: persistence was coded as being 1 (present) if a patient refilled each subsequent prescription with gaps not exceeding 30 or 60 days; otherwise, it was coded as 0 (absent or nonpersistent) [29].

Outcome assessment

The primary outcomes of interest were death, graft loss, rejection, and adherence to immunosuppressive drugs after kidney transplantation. All-cause mortality data, censoring events, and associated dates were obtained from VA and USRDS data sources.

These outcomes were defined as follows:

1 For the all-cause death analysis, the start of the follow-up period was the date of kidney transplantation, and patients were followed up until death or other censoring events including loss to follow-up or end of follow-up period [22–24]. For this analysis, we used Cox proportional hazards regression.

2 For the death with functioning graft analysis, the start of the follow-up period was the date of kidney transplantation, and patients were followed up until death or other events including graft loss, loss to follow-up, or end of follow-up period (September 30, 2014) [22–24]. For this analysis, we used competing risks regression, where the primary outcome was death and the competing outcome was graft loss. Data were censored for loss to follow-up or end of follow-up period.

3 For the graft loss analysis, the start of the follow-up period was the date of kidney transplantation, and patients were followed up until graft loss or other events including death, loss to follow-up, or end of follow-up period [22–24]. For this analysis, we used competing risks regression, where the primary outcome was graft loss and the competing outcome was death. Data were censored for loss to follow-up or end of follow-up period.

4 For rejection analyses unfortunately, we did not have data about the time of rejection, and hence, we were not able to run any type of time-to-event analysis for this outcome. For the rejection data derived from USRDS, we used logistic regression analyses.

5 Finally for immunosuppressive medication adherence, we calculated PDC and medication persistence for tacrolimus and mycophenolic acid. The detailed description of the PDC calculations is described above.

Statistical analysis

Baseline patient characteristics were summarized according to the presence or absence of history of psychosis/mania prior to kidney transplantation and presented as percent for categorical variables and mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Differences between patients with and without history of psychosis and mania were assessed using standardized differences before and after propensity score matching.

The propensity score method was used to account for baseline differences arising from dissimilarities in clinical and demographic characteristics of patients with and without history of psychosis/mania. Variables associated with history of psychosis/mania were identified using logistic regression and were used to calculate propensity scores. STATA's "psmatch2" command suite was used to generate the propensity score-matched cohorts by 1–4 nearest neighbor matching with replacement. The following variables were included in the logistic regression model to create the propensity score: age, gender, race/ethnicity, postal code of the patient's address, preemptive transplantation, type of transplant donor (deceased versus living), type of dialysis modality, duration of dialysis before transplantation, the presence of comorbidities (myocardial infarction, diabetes, hypertension, heart failure, ischemic heart disease, cerebrovascular disease, paraplegia/hemiplegia, renal disease, peripheral vascular disease, lung disease, peptic ulcer disease, connective tissue disease, anemia, hyperlipidemia, liver disease, malignancy, and depression) and medication use (phosphorous binders, active vitamin D (native or active), renin-angiotensin-aldosterone system inhibitors, alpha-blockers, β-blockers, calcium channel blockers, vasodilators, insulin, diuretics, statins, antianginals, anticoagulants, thrombolytics, aspirin, digitalis, and erythropoietin stimulating agents). Figure S2 shows the distribution of the propensity score in the two groups pre- and postmatching.

The associations between pretransplantation history of psychosis/mania and post-transplantation outcomes were assessed in the propensity-matched cohort using competing risks regression (Fine and Gray) [30] for death with functioning graft and graft loss, and Kaplan–Meier method and Cox proportional hazard models for all-cause mortality. Logistic regression analysis was used for rejection risk assessment. The SD of PDC for immunosuppressive drugs was compared using *t*-test, while chi-squared tests were used to compare medication nonpersistance and categorical PDC (group 1: PDC = 100% vs. group 2: PDC <100%) for different immunosuppressive drugs.

We conducted several sensitivity analyses to evaluate the robustness of our main findings. Associations were examined in subgroups of patients stratified by sex, race, marital status and the presence or absence of diabetes, the presence or absence of ischemic heart disease, and preemptive transplantation. Potential interactions were formally tested by including relevant interaction terms. We adjusted for income and marital status as sensitivity analysis to assess whether these variables have any effect on the examined association. These variables have not been selected in the main model due to significant missingness (19% for income and 10% for marital status). Finally, we also performed all analyses in the entire cohort after adjustment for propensity score.

Reported *P* values were two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP Version 15 (STATA Corporation, College Station, TX, USA). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

Results

Baseline characteristics

The mean ± SD age of the cohort at baseline was 61 ± 11 years, 92% were male, and 66% and 27% of patients were white and African-American, respectively. Nineteen percent of the transplants were preemptive, 72% were married, and 48% of the patients were diabetic. In the entire cohort, we identified 126 and 3554 patients with and without a history of psychosis/mania, respectively. Twenty-four (0.65%) patients had a history of mania, 106 (2.88%) patients had a history of psychosis, and four (0.11%) patients had a history of both. Baseline characteristics of patients categorized by history of psychosis/mania status are shown in Table 1. In the original cohort (n = 3680), patients with history of psychosis/mania were more likely to be African-American and unmarried, had higher prevalence of diabetes mellitus, peripheral vascular disease, chronic lung disease, liver disease, depression, hypertension, and were more likely to receive antihypertensive medications. These differences disappeared after matching by propensity score (Table 1).

Predictors of psychotic disorders

In our multivariable logistic regression model, the presence of chronic lung disease, depression, as well as aspirin and statin usage were associated with history of psychosis/mania (Table S1).

Death with functioning graft

During a median follow-up period of 2 years, a total of 39 (9%) deaths occurred [crude incidence rate, 38 per 1000 patient-years; 95% confidence interval (CI): 28–52]. The crude mortality rate was similar in patients with history of psychosis/mania [10 (8%) deaths, 37 per 1000 patient-years, 95% CI: 20–70] versus patients without history of psychosis/mania [29 (9%) deaths, 38 per 1000 patient-years, 95% CI: 26–54] as shown in Fig. 2a. Compared to patients without history of psychosis/mania, patients with history of psychosis/mania had similar risk of death with functioning graft in competing risks regression [subhazard ratio (SHR) (95% CI): 0.94 (0.42–2.09)] (Table 2). Similar results were found after further adjustment for marital status and income [SHR (95% CI): 0.82 (0.36–1.85)] in our sensitivity analysis. Moreover, there was no association between history of psychosis [SHR (95% CI): 1.23 (0.29–5.27)], history of mania [SHR (95% CI): 0.83 (0.34–2.00)], and risk of death with functioning graft when the two disorders were analyzed separately. Additionally, there was a lack of association between history of psychosis/mania and risk of death with functioning graft in different subgroups (Fig. 3a). Moreover, similar results were found in the entire cohort after adjustment for propensity score [SHR (95% CI): 0.53 (0.19–1.45)] in our sensitivity analysis.

All-cause death

The survival probability was similar in patients with and without history of psychosis/mania as shown in Fig. S3. Compared to patients without history of psychosis/mania, patients with history of psychosis/mania had similar all-cause mortality risk [HR (95% CI): 1.04 (0.51–2.14)] (Table 2). Similar results were found after additional adjustment for marital status and income [HR (95% CI): 0.89 (0.43–1.86)]. Moreover, there was no association of history of psychosis [HR (95% CI): 0.82 (0.36–1.87)] and history of mania [HR (95% CI): 1.70 (0.52–5.52)] with all-cause death when the two disorders were analyzed separately. Additionally, there was a lack of association between history of psychosis/mania and all-cause mortality risk in different subgroups (Fig. 3b). Moreover, similar results were found in the entire cohort after adjustment for propensity scores [HR (95% CI): 0.60 (0.23–1.54)] in our sensitivity analysis.

Table 1. Baseline characteristics of the study population.

	Before matching			After matching		
	No history of psychosis/mania (n = 3554)	History of psychosis/ mania (n = 126)	SD	No history of psychosis/mania (n = 320)	History of psychosis/mania (n = 122)	SD
Demographics						
Age (years)	61 ± 11	59 ± 9	0.072	59 ± 10	59 ± 9	−0.007
Gender (male), n (%)	3262 (92)	114 (90)	0.334	291 (91)	110 (90)	0.026
Race, n (%)						
White	2343 (66)	75 (60)	−0.615	212 (66)	73 (60)	0.056
African–American	933 (26)	47 (37)		92 (29)	45 (37)	
Others	58 (2)	0 (0)		3 (1)	0 (0)	
Unknown	220 (6)	4 (3)		13 (4)	4 (3)	
Comorbidities						
Myocardial infarction, n (%)	234 (7)	13 (10)	0.334	25 (8)	12 (10)	0.071
Congestive heart failure, n (%)	540 (15)	23 (18)	0.083	56 (18)	23 (19)	0.035
Peripheral vascular disease, n (%)	370 (10)	19 (15)	−0.112	38 (12)	16 (13)	0.037
Cerebrovascular disease, n (%)	273 (8)	12 (10)	0.160	32 (10)	12 (10)	−0.005
Chronic pulmonary disease, n (%)	457 (13)	33 (26)	0.432	74 (23)	30 (25)	0.034
Connective tissue disease, n (%)	71 (2)	4 (3)	0.147	7 (2)	4 (3)	0.067
Peptic ulcer disease, n (%)	40 (1)	4 (3)	0.230	7 (2)	4 (3)	0.067
Paraplegia and hemiplegia, n (%)	19 (0.5)	1 (0.8)	0.000	1 (0)	1 (1)	0.067
Diabetes, n (%)	1681 (47)	78 (62)	0.080	175 (55)	74 (61)	0.121
Liver disease, n (%)	394 (11)	24 (19)	0.366	63 (20)	22 (18)	−0.042
Malignancy, n (%)	221 (6)	12 (10)	0.291	32 (10)	12 (10)	−0.005
Anemia, n (%)	1764 (50)	72 (57)	0.195	183 (57)	71 (58)	0.020
Depression, n (%)	182 (5)	71 (56)	1.353	104 (33)	67 (55)	0.463
Hyperlipidemia, n (%)	1403 (40)	54 (43)	−0.020	136 (43)	53 (43)	0.019
Hypertension, n (%)	2823 (79)	113 (90)	−0.160	273 (85)	109 (89)	0.121
Ischemic heart disease, n (%)	863 (24)	40 (32)	0.480	95 (30)	38 (31)	0.032
Pre-emptive transplantation, n (%)	696 (20)	21 (17)	0.144	59 (18)	20 (16)	−0.054
Living donor transplantation, n (%)	1160 (33)	33 (26)	−0.301	84 (26)	32 (26)	0
Dialysis modality: hemodialysis, n (%)	2253 (82)	89 (87)	0.212	209 (65)	86 (70)	−0.078
Duration of dialysis (days), median (IQR)	551 (145–1062)	690 (298–1335)	−0.157	630 (174–1209)	670 (298–1335)	0.110
Medications						
ESAs, n (%)	252 (7)	16 (13)	−0.228	40 (13)	15 (12)	−0.006
Native vitamin D, n (%)	295 (8)	25 (20)	0.051	65 (20)	24 (20)	−0.016
Active vitamin D, n (%)	505 (14)	33 (26)	0.110	73 (23)	30 (25)	0.042
Sevelamer, n (%)	771 (22)	45 (36)	−0.207	113 (35)	43 (35)	−0.001
Lanthanum, n (%)	210 (6)	11 (9)	0.065	19 (6)	11 (9)	0.117
Calcium acetate, n (%)	660 (19)	33 (26)	−0.729	87 (27)	32 (26)	−0.022

Table 1. Continued.

	Before matching			After matching		
	No history of psychosis/mania (n = 3554)	History of psychosis/ mania (n = 126)	SD	No history of psychosis/mania (n = 320)	History of psychosis/mania (n = 122)	SD
Anticoagulants, n (%)	260 (7)	24 (19)	0.272	53 (17)	20 (16)	−0.005
Thrombolytics, n (%)	19 (0.5)	1 (0.8)	0.284	6 (2)	1 (1)	−0.091
Aspirin, n (%)	385 (11)	47 (37)	0.233	96 (30)	44 (36)	0.129
Digitalis, n (%)	29 (1)	1 (0.8)	−0.162	3 (1)	1 (1)	−0.013
β-blockers, n (%)	1343 (38)	80 (64)	0.115	187 (58)	77 (63)	0.096
α-blockers, n (%)	458 (13)	27 (21)	0.069	57 (18)	26 (21)	0.088
Calcium channel blockers, n (%)	1187 (33)	68 (54)	0.283	163 (51)	64 (52)	0.030
Antianginals, n (%)	209 (6)	16 (13)	0.088	39 (12)	15 (12)	0.003
Statins, n (%)	1220 (34)	77 (61)	0.063	185 (58)	74 (61)	0.058
Vasodilators, n (%)	477 (13)	26 (21)	−0.637	63 (20)	25 (20)	0.020
Thiazides diuretics, n (%)	128 (4)	7 (6)	−0.088	17 (5)	7 (6)	0.019
Loop diuretics, n (%)	855 (24)	42 (330)	0.020	109 (34)	40 (33)	−0.027
Potassium sparing diuretics, n (%)	93 (3)	4 (3)	0.077	12 (4)	4 (3)	−0.026
RAASi, n (%)	994 (28)	55 (44)	−0.044	139 (43)	51 (42)	−0.033
Insulin, n (%)	765 (22)	47 (37)	0.025	114 (36)	45 (37)	0.026
Other variables NOT included propensity score						
Marital status, n (%)						
Married	2328 (72)	77 (61)	0.485	210 (71)	75 (62)	0.500
Single	246 (8)	5 (4)		17 (6)	5 (4)	
Divorced	550 (17)	39 (31)		58 (20)	38 (31)	
Widowed	100 (3)	5 (4)		10 (3)	4 (3)	
Income (USD), median (IQR)	20 874 (1585–38 646)	19 626 (4524–34 260)	−0.030	22 020 (5040–35 028)	19 626 (3435–35 028)	0.389
Service connection, %	90 (30–100)	100 (60–100)	0.161	100 (60–100)	100 (60–100)	0.096
Charlson Comorbidity Index, median (IQR)	2 (0–3)	2 (1–4)	0.474	2 (1–3)	2 (1–4)	0.268
Serum albumin (g/dl), mean ± SD	3.7 ± 0.5	3.7 ± 0.5	−0.394	3.7 ± 0.6	3.8 ± 0.5	−0.213
Serum AST, (g/dl), median (IQR)	20 (16–26)	19 (15–26)	0.237	21 (17–28)	19 (15–26)	0.621
Serum ALT, (g/dl), median (IQR)	20 (15–28)	20 (15–29)	0.297	21 (15–29)	19 (15–29)	0.235
Blood hemoglobin, (g/dl), mean ± SD	11.5 ± 1.3	11.5 ± 1.4	0.156	11.4 ± 1.3	11.5 ± 1.4	0.418
Serum phosphorus, (g/dl), mean ± SD	4.9 ± 1.2	4.9 ± 1.9	−0.282	4.9 ± 1.2	5.0 ± 1.1	−0.410
Serum PTH, (g/dl), median (IQR)	260 (184–428)	303 (152–419)	−0.142	253 (152–401)	296 (150–404)	−0.143
Systolic BP (mmHg), mean ± SD	137 ± 18	133 ± 17	−0.374	138 ± 17	132 ± 18	−0.652
Diastolic BP (mmHg), mean ± SD	75 ± 11	74 ± 9	−0.381	75 ± 10	74 ± 10	−0.549
Body mass index (kg/m^2), mean ± SD	28 ± 4	29 ± 4	−0.481	28 ± 4	29 ± 4	−0.372

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; ESAs, erythropoietin-stimulating agents; IQR, interquartile range; PTH, parathyroid hormone; RAASi, renin–angiotensin–aldosterone system inhibitors; SD, standard deviation; Std. Diff., standardized differences; USD, United States dollar.

Graft loss

A total of 56 (13%) graft losses occurred (crude incidence rate, 54 per 1000 patient-years; 95% CI: 41–70). The crude graft loss rate was similar in patients with history of psychosis/mania [14 (11%) graft loss, 52 per 1000 patient-years, 95% CI: 31–88] versus patients without history of psychosis/mania [42 (13%) graft loss, 55 per 1000 patient-years, 95% CI: 40–74] as shown in Fig. 2b. Compared to patients without a history of psychosis/mania, patients with history of psychosis/mania had similar graft loss risk in competing risks regression (SHR [95% CI]: 1.07 [0.45–2.57]) (Table 2). Similar result was found after additional adjustment for marital status and income [SHR (95% CI): 0.84 (0.36–1.98)]. Moreover, there was no association of history of psychosis [SHR (95% CI): 0.87 (0.33–2.32)] and history of mania [SHR (95% CI): 1.64 (0.37–7.20)] with risk of graft loss when the two disorders were analyzed separately. Additionally, there was a lack of association between history of psychosis/mania and graft loss risk in different subgroups (Fig. 3c). Moreover, similar results were found in the entire cohort after adjustment for propensity score [SHR (95% CI): 1.33 (0.43–4.09)] in our sensitivity analysis.

Risk of rejection

Compared to patients without history of psychosis/mania, patients with history of psychosis/mania had similar risk of rejection [odds ratio (OR) (95% CI): 1.23 (0.60–2.53)] (Table 2). Similar results were found after additional adjustment for marital status and income [OR (95% CI): 1.30 (0.62–2.75)]. Moreover, there was no association of history of psychosis [OR (95% CI): 1.04 (0.47–2.27)] and history of mania [OR (95% CI): 2.26 (0.73–6.99)] with risk of rejection when the two disorders have been analyzed separately. Additionally, there was a lack of association between history of psychosis/mania and risk for rejection in different subgroups (Fig. 3d). Moreover, similar results were found in the entire cohort after adjustment for propensity score [OR (95% CI): 1.31 (0.60–2.88)] in our sensitivity analysis.

Medication nonadherence

Of the 442 patients in the propensity-matched cohort, 149 patients received tacrolimus prescriptions from a VA pharmacy after transplantation. The average PDC for tacrolimus in the first-year after transplantation was 77 ± 20. There was no difference in PDC in patients with and without history of psychosis/mania (PDC: 76 ± 21 vs. 78 ± 19, $P = 0.529$). In addition, the proportion of patients with PDC <100% was also similar between these groups (89% with history of psychosis/mania vs. 87% without history of psychosis/mania, $P = 0.762$). Finally, the 30- and 60-day persistence with drug therapy (duration of time from initial drug dispensation to "unauthorized" discontinuation) was also similar in patients with and without history of psychosis/mania (30 days: 54% vs. 54%, $P = 0.998$; 60 days: 39% vs. 28%, $P = 0.183$).

Of the 442 patients in the propensity-matched cohort, 144 patients received mycophenolic acid prescriptions from a VA pharmacy after transplantation. The average PDC for mycophenolic acid in the first-year after transplantation was 79 ± 17%. There was no difference in PDC in patients with and without history of psychosis/mania (PDC: 78 ± 17% vs. 79 ± 18%, $P = 0.666$). In addition, the proportion of patients with PDC <100% was also similar between these groups (96% with history of psychosis/mania vs. 93% without history of psychosis/mania, $P = 0.440$). Finally, the 30- and 60-day persistence with drug therapy was also similar in patients with and without history of psychosis/mania (30 days: 49% vs. 48%, $P = 0.949$; 60 days: 20% vs. 20%, $P = 0.954$).

Discussion

In this large national cohort of incident kidney transplant US veterans, we found that recipients with history of psychosis/mania have similar survival, graft loss, and rejection risk compared to recipients without these diagnoses. In addition, we showed that these selected recipients with history of psychosis/mania have similar post-transplantation immunosuppressive medication adherence compared to their counterparts without these diagnoses.

Very few previous studies assessed the association between history of psychosis/mania and post-transplant outcomes. Most of them are small observational trials with very few patients and have several methodological flaws [13–19]. There are many potential reasons why these studies, including our own, have not shown any differences in outcome. A main reason is good medication adherence after transplantation. Our results show that the adherence to antirejection medications in the post-transplant period was similar in recipients with history of psychosis/mania versus the ones without. A previous study involving USRDS patients showed that medication nonadherence is associated with higher risk

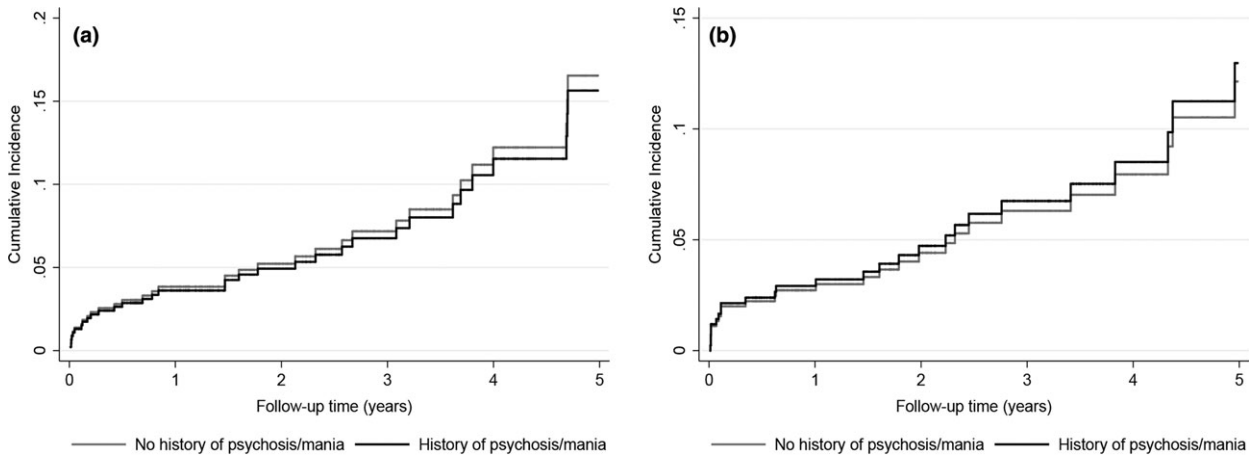

Figure 2 Cumulative incidence of death with functioning graft (panel a) and graft loss (panel b) using competing risks regression models in the propensity-matched cohort.

of graft loss and death in transplant recipients who were hospitalized with a diagnosis of psychosis after transplantation [12]. Some of these patients might have had new psychotic diagnoses after transplantation secondary to several factors such as high dose steroid use, drug interactions, or surgery. Another potential explanation is the free access to health care in the VA system. A recent study showed that the quality of care of mental disorders was better in the VA healthcare system compared to the private sector [31], which could explain

Table 2. Association between history of psychosis and/or mania and post-transplantation outcomes using Cox proportional regression, competing risks regression, and logistic regression models in the propensity-matched cohort (n = 442).

History of psychosis and/or mania versus no. of history of psychosis and/or mania (ref.)	Hazard ratios (HRs)	95% confidence interval of HRs	*P*-value
All-cause death	1.04	0.51–2.14	0.913
History of psychosis and/or mania versus no. of history of psychosis and/or mania (ref.)	**Subhazard ratios (SHRs)**	**95% confidence interval of SHRs**	***P*-value**
Death with functioning graft	0.94	0.42–2.09	0.881
Graft loss	1.07	0.45–2.57	0.874
History of psychosis and/or mania versus no. of history of psychosis and/or mania (ref.)	**Odds ratios (ORs)**	**95% confidence interval of ORs**	***P*-value**
Rejection	1.23	0.60–2.53	0.567
	History of psychosis and/or mania	**No of history of psychosis and/or mania**	***P*-value***
Immunosuppressive adherence: proportion of days covered for			
Tacrolimus (%) (mean ± SD)	76 ± 21	78 ± 19	0.529
Mycophenolic acid (%) (mean ± SD)	78 ± 17	79 ± 18	0.666
Immunosuppressive persistence: 30 days gap			
Tacrolimus	54%	54%	0.998
Mycophenolic acid	49%	48%	0.949

HR, hazard ratio; OR, odds ratio; SHR, subhazard ratio.

**P* values for adherence are result of *t*-test and chi-squared test.

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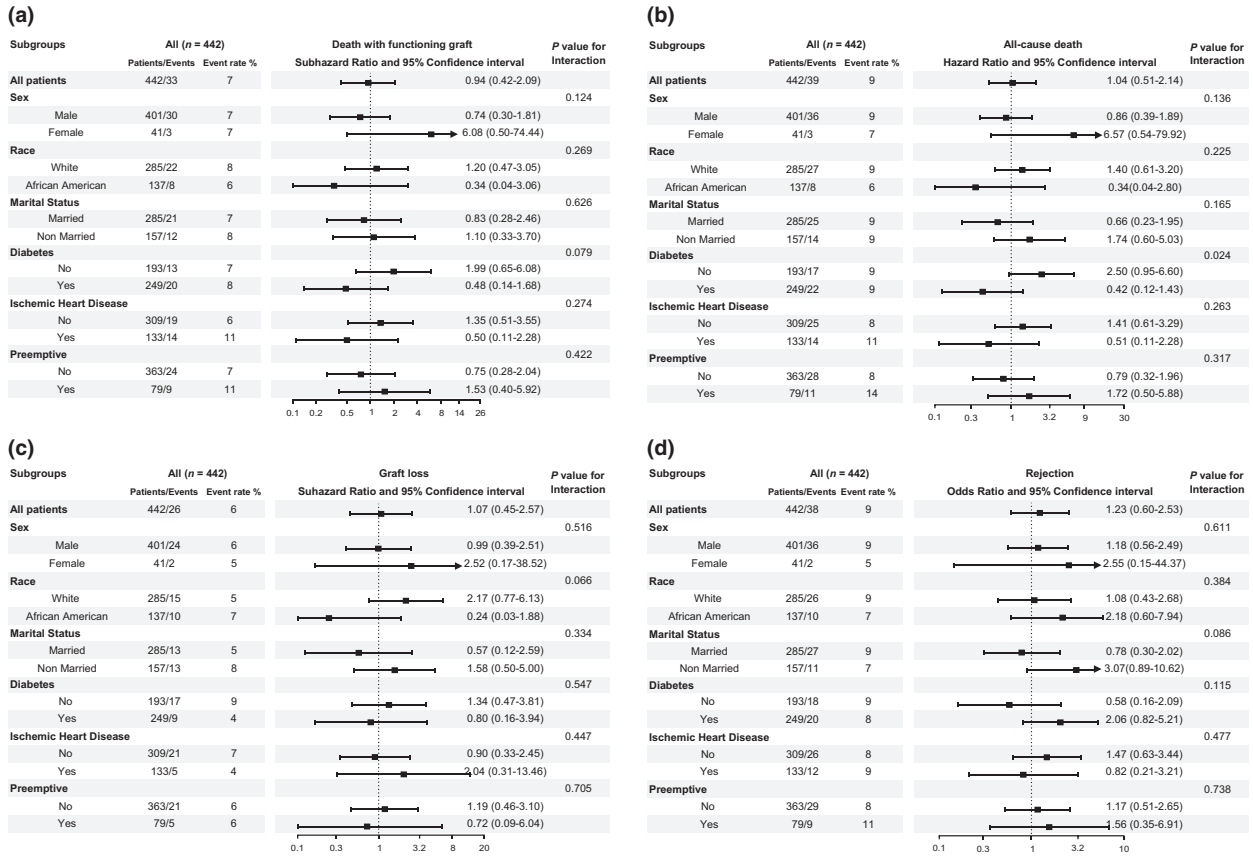

Figure 3 Association between history of psychosis or mania and death with functioning graft (panel a), all-cause death (panel b), graft loss (panel c), and rejection (panel d) in the propensity-matched cohort in different subgroups.

both a better selection process and also better quality of care after transplantation.

Our study suggests that transplantation can be safe even in patients with a history of psychosis/mania. However, it is important to note that while all these recipients have been transplanted, they likely underwent very careful selection prior to being listed for transplantation. Our study does not suggest that all end-stage renal disease (ESRD) patients with history of psychosis/mania should be eligible for transplantation. Almost 9% of dialysis patients are hospitalized with a mental disorder in a year [32], but only 3.5% of kidney transplant recipients have history of psychosis/mania, which might suggest that many ESRD patients with history of psychosis/mania are not transplanted. Our study demonstrates that the selection process in VA medical centers is successful and results in similar graft and patient outcomes. While these results are encouraging, we need more data from outside the VA system and from other countries confirming our results.

Our study is notable for its relatively large sample size and event numbers, and for being representative of veterans who received care in the VA system across the entire United States. In addition, we used a validated method to diagnose the history of psychosis/mania from an administrative dataset [25]. To our knowledge, this is the largest study to assess the association of history of psychosis/mania before kidney transplantation with transplantation outcomes. In addition, this is the first study which assessed medication adherence after kidney transplantation in recipients with these diagnoses.

This study also has several limitations that need to be acknowledged. Patients were mostly male US veterans; hence, the results may not be generalizable to women or other patient populations, in particular to those outside the United States. Our study is also limited by the use of an administrative database and by diagnoses being based on ICD codes instead of clinical evaluation. We did not have details about the clinical care and evaluation of patients pre- and post-transplantation, or

about any special care of guidance they may have received pre- and post-transplantation from medical professionals or caretakers. Additionally, we do not have data about the type of rejection; therefore, more granular analyses cannot be performed in our dataset. However, we used a definition based on a validated algorithm [25] to eliminate this potential bias. We did not include other psychiatric problems in our analyses as the reliability of the ICD codes for these problems is questionable. Moreover, we did not have information listing and transplantation data for patients who did not undergo kidney transplantation; hence, we do not know how many of them were assessed for transplantation and found to be eligible or ineligible. Finally, as with all observational studies, we cannot eliminate the effect of unmeasured confounders.

Conclusion

In conclusion, this large national cohort of US transplant recipients with history of psychosis/mania shows similar medication adherence and survival, graft loss and rejection risk compared to recipients without these diagnoses. This demonstrates that the transplant candidate selection process can be successful. Further studies are needed to define how we can safely select even more transplant candidates from the dialysis patient population with history of psychosis/mania.

Authorship

MZM: contributed to research design, analysis of the data, interpretation of data and writing the manuscript, reviewed and accepted the final version of the manuscript. JDE: contributed to reviewed and accepted the final version of the manuscript. AG: contributed to interpretation of data, research design, reviewed and accepted the final version of the manuscript. MT: contributed to reviewed and accepted the final version of the manuscript. PKP: contributed to analysis of the data, reviewed and accepted the final version of the manuscript. KJ: contributed to reviewed and accepted the final version of the manuscript. AR: contributed to reviewed and accepted the final version of the manuscript. ZM: contributed to reviewed and accepted the final version of the manuscript. IM: contributed to reviewed and accepted the final version of the manuscript. MN: contributed to reviewed and accepted the final version of the manuscript. KK-Z: contributed to reviewed and accepted the final version of the manuscript. CPK: contributed to research design, interpretation of data and writing the manuscript, reviewed and accepted the final version of the manuscript.

Funding

This study is supported by grant 5U01DK102163 from the National Institute of Health (NIH) to KKZ and CPK, and by resources from the US Department of Veterans Affairs. The data reported here have been supplied in part by the United States Renal Data System (USRDS). Support for VA/CMS data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, and VA Information Resource Center (Project Numbers SDR 02-237 and 98-004).

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

CPK and KKZ are employees of the Department of Veterans Affairs. Opinions expressed in this paper are those of the author's and do not necessarily represent the opinion of the Department of Veterans Affairs. The results of this paper have not been published previously in whole or part.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Graphical presentation of calculation of proportion of days covered.

Figure S2. Histogram of the propensity score before and after matching in recipients with and without history of psychosis/mania.

Figure S3. Probability of all-cause death using Kaplan-Meier methods in the propensity-matched cohort.

Table S1. Predictors of history of psychosis/mania using logistic regression analysis in the entire cohort (n = 3663).

REFERENCES

1. Belmaker RH. Bipolar disorder. *N Engl J Med* 2004; **351**: 476.
2. Freedman R. Schizophrenia. *N Engl J Med* 2003; **349**: 1738.
3. Trivedi RB, Post EP, Sun H, *et al.* Prevalence, comorbidity, and prognosis of mental health among US veterans. *Am J Public Health* 2015; **105**: 2564.
4. Price A, Whitwell S, Henderson M. Impact of psychotic disorder on transplant eligibility and outcomes. *Curr Opin Organ Transplant* 2014; **19**: 196.
5. Alsady M, Baumgarten R, Deen PM, de Groot T. Lithium in the kidney: friend and foe? *J Am Soc Nephrol* 2016; **27**: 1587.
6. Dudley C, Harden P. Renal Association Clinical Practice Guideline on the assessment of the potential kidney transplant recipient. *Nephron Clin Pract* 2011; **118**(Suppl. 1): c209.
7. Ebpg, European Renal A, European Society for Organ T. European best practice guidelines for renal transplantation (part 1). *Nephrol Dial Transplant* 2000; **15**(Suppl. 7): 1.
8. Kalble T, Lucan M, Nicita G, *et al.* EAU guidelines on renal transplantation. *Eur Urol* 2005; **47**: 156.
9. Kasiske BL, Cangro CB, Hariharan S, *et al.* The evaluation of renal transplantation candidates: clinical practice guidelines. *Am J Transplant* 2001; **1**(Suppl. 2): 3.
10. Klapheke MM. The role of the psychiatrist in organ transplantation. *Bull Menninger Clin* 1999; **63**: 13.
11. Butler MI, McCartan D, Cooney A, *et al.* Outcomes of renal transplantation in patients with bipolar affective disorder and schizophrenia: a national retrospective cohort study. *Psychosomatics* 2017; **58**: 69.
12. Abbott KC, Agodoa LY, O'Malley PG. Hospitalized psychoses after renal transplantation in the United States: incidence, risk factors, and prognosis. *J Am Soc Nephrol* 2003; **14**: 1628.
13. Kofman T, Pourcine F, Canoui-Poitrine F, *et al.* Safety of renal transplantation in patients with bipolar or psychotic disorders: a retrospective study. *Transpl Int* 2018; **31**: 377.
14. Dave V, Mulley W, Kanellis J, Summers S. Managing psychosis in a renal transplant recipient with bipolar affective disorder and allograft rejection. *Nephrology* 2015; **20**(Suppl. 1): 2.
15. Power RE, Hayanga AJ, Little DM, Hickey DP. Outcome of cadaveric renal transplantation in patients with psychiatric disorders. *Ir Med J* 2002; **95**: 172.
16. Carrasco FR, Moreno A, Ridao N, *et al.* Kidney transplantation complications related to psychiatric or neurological disorders. *Transplant Proc* 2009; **41**: 2430.
17. Evans LD, Stock EM, Zeber JE, *et al.* Posttransplantation outcomes in veterans with serious mental illness. *Transplantation* 2015; **99**: e57.
18. DiMartini A, Twillman R. Organ transplantation and paranoid schizophrenia. *Psychosomatics* 1994; **35**: 159.
19. Zimbrean P, Emre S. Patients with psychotic disorders in solid-organ transplant. *Prog Transplant* 2015; **25**: 289.
20. Corbett C, Armstrong MJ, Parker R, Webb K, Neuberger JM. Mental health disorders and solid-organ transplant recipients. *Transplantation* 2013; **96**: 593.
21. Molnar MZ. Is kidney transplantation safe after careful selection of the recipients with a history of psychotic disorder? *Transpl Int* 2018; **31**: 364.
22. Sumida K, Molnar MZ, Potukuchi PK, *et al.* Association of slopes of estimated glomerular filtration rate with post-end-stage renal disease mortality in patients with advanced chronic kidney disease transitioning to dialysis. *Mayo Clin Proc* 2016; **91**: 196.
23. Sumida K, Molnar MZ, Potukuchi PK, *et al.* Association between vascular access creation and deceleration of estimated glomerular filtration rate decline in late-stage chronic kidney disease patients transitioning to end-stage renal disease. *Nephrol Dial Transplant* 2016; **32**: 1330.
24. Molnar MZ, Gosmanova EO, Sumida K, *et al.* Predialysis cardiovascular disease medication adherence and mortality after transition to dialysis. *Am J Kidney Dis* 2016; **68**: 609.
25. Frayne SM, Berg E, Holmes TH, *et al.* Mental illness-related disparities in length of stay: algorithm choice influences results. *J Rehabil Res Dev* 2010; **47**: 709.
26. Kovesdy CP, Norris KC, Boulware LE, *et al.* Association of race with mortality and cardiovascular events in a large cohort of US veterans. *Circulation* 2015; **132**: 1538.
27. Kovesdy CP, Alrifai A, Gosmanova EO, *et al.* Age and outcomes associated with BP in patients with incident CKD. *Clin J Am Soc Nephrol* 2016; **11**: 821.
28. Choudhry NK, Shrank WH, Levin RL, *et al.* Measuring concurrent adherence to multiple related medications. *Am J Manag Care* 2009; **15**: 457.
29. Cramer JA, Roy A, Burrell A, *et al.* Medication compliance and persistence: terminology and definitions. *Value Health* 2008; **11**: 44.
30. Fine J, Gray R. A proportional hazards model for subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496.
31. Watkins KE, Smith B, Akincigil A, *et al.* The quality of medication treatment for mental disorders in the department of veterans affairs and in private-sector plans. *Psychiatr Serv* 2016; **67**: 391.
32. Kimmel PL, Thamer M, Richard CM, Ray NF. Psychiatric illness in patients with end-stage renal disease. *Am J Med* 1998; **105**: 214.