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ORIGINAL ARTICLE

History of posttraumatic stress disorder and outcomes after kidney transplantation

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A history of posttraumatic stress disorder (PTSD), if uncontrolled, represents a contraindication for kidney transplantation. However, no previous large study has assessed the association between pretransplant history of PTSD and posttransplantation outcomes. We examined 4479 US veterans who had undergone transplantation. The diagnosis of history of PTSD was based on a validated algorithm. Measured covariates were used to create a matched cohort (n = 560). Associations between pretransplant PTSD and death with functioning graft, all-cause death, and graft loss were examined in survival models. Posttransplant medication nonadherence was assessed using proportion of days covered (PDC). From among 4479 veterans, 282 (6.3%) had a history of PTSD. The mean age ± standard deviation (SD) of the cohort at baseline was 61 ± 11 years, 91% were male, and 66% and 28% of patients were white and African American, respectively. Compared to patients without a history of PTSD, patients with a history of PTSD had a similar risk of death with a functioning graft (subhazard ratio [SHR] 0.97, 95% confidence interval [CI] 0.61-1.54), all-cause death (1.05, 0.69-1.58), and graft loss (1.09, 0.53-2.26). Moreover, there was no difference in

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CCI, Charlson Comorbidity Index; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ESA, erythropoietin-stimulating agent; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; NDD-CKD, nondialysis-dependent chronic kidney disease; NIH, National Institutes of Health; PDC, proportion of days covered; PTH, parathyroid hormone; PTSD, posttraumatic stress disorder; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; SHR, subhazard ratio; Std., Diff., standardized differences; TC-CKD, Transition of Care in Chronic Kidney Disease; USD, United States Dollar; USRDS, United States Renal Data System; VA/CMS, Veterans Affairs/Centers for Medicare & Medicaid Services.

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immunosuppressive drug PDC in patients with and without a history of PTSD (PDC: 98 ± 4% vs 99 ± 3%, *P* = .733 for tacrolimus; PDC: 99 ± 4% vs 98 ± 7%, *P* = .369 for mycophenolic acid). A history of PTSD in US veterans with end-stage renal disease should not on its own preclude a veteran from being considered for transplantation.

KEYWORDS
clinical research/practice, epidemiology, graft survival, health services and outcomes research, kidney transplantation/nephrology, patient survival

1 | INTRODUCTION

Renal transplantation is the treatment of choice for patients with end-stage renal disease.[1] However, there continues to be a huge disparity between the availability of organs and the number of patients on the waiting list. As per the Organ Procurement and Transplantation Network, there are currently (8/2018) 94 893 patients on the waiting list for renal transplantation, whereas the number of donors available for renal transplants is 9356.[2] To try to prevent waste of any available organs as well as to ensure a good posttransplant outcome, thorough medical, surgical, financial, and psychosocial evaluation is done to determine whether a patient will be an appropriate transplant candidate.

Coexisting psychiatric disorders have been suggested as a contributor to poor transplant outcomes due in part to behavioral factors such as nonadherence to medical therapy as well as physiologic factors such as modification of immunologic and stress responses.[3,4] Specific guidance for mental health disorders in the transplant assessment process is hampered by the lack of robust quality evidence. Transplant programs commonly include some form of assessment of mental health problems, but there is a lack of consensus on both how best to assess mental health and what constitutes an absolute contraindication to transplantation.[5-7] Multiple guidelines list active psychiatric illness as an absolute contraindication without a very clear definition of what constitutes an active psychiatric illness. In addition, active substance abuse and medication nonadherence have been listed as absolute contraindications,[5,6,8] both of which are highly prevalent in patients with psychiatric illness.

Posttraumatic distress syndrome (PTSD) as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is a stress-related disorder that occurs after exposure to a serious/life-threatening traumatic event, which is associated with intrusion symptoms related to the event (eg, nightmares, flashbacks), as well as avoidance of stimuli associated with the event, negative alterations in cognition and mood, and marked alteration in arousal and reactivity that lasts for more than 1 month after the initial traumatic event.[9] The prevalence of lifetime PTSD in the general US population is estimated to be between 6.1% and 8.3%.[10,11] PTSD has been postulated to be associated with modification of stress response in the body as well as causing a pro-inflammatory state.[12] Several studies have identified PTSD as a risk factor for cardiometabolic diseases as well as a predictor of poor outcomes in comorbid conditions such as acute myocardial infarction, asthma, and cancer.[13-17] PTSD has also been shown to be associated with other psychiatric comorbidities (depression, anxiety), substance abuse, and noncompliance with medications and follow-up.[13,18-20]

With the association of PTSD with comorbidities, substance abuse, and poor compliance, patients with PTSD may not be viewed favorably when being considered for transplant candidacy. In addition, the majority of transplant programs consider a history of psychosocial conditions such as PTSD a relative or absolute contraindication for transplantation.[21,22] However, the data are sparse on the relationship of pretransplant PTSD with posttransplant outcomes or with access to transplantation. Previous studies have shown that posttransplant PTSD was associated with worse physical- and mental health-related quality of life,[23] whereas the association between presence of PTSD and medication adherence is conflicting.[24,25] Consequently, the association between a history of PTSD pretransplantation and graft and patient outcomes posttransplantation is still uncertain.

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

2 | MATERIALS AND METHODS

2.1 | Data source and cohort definition

We analyzed longitudinal data of kidney transplant recipients from the Transition of Care in Chronic Kidney Disease (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, 2015.[26,27] A total of 102 477 US veterans were identified from the United States Renal Data System (USRDS) as a source population. Only individuals who received preemptive kidney transplantation or transitioned to receive dialysis therapy and then subsequently received kidney transplantation were included in the source population. The algorithm for

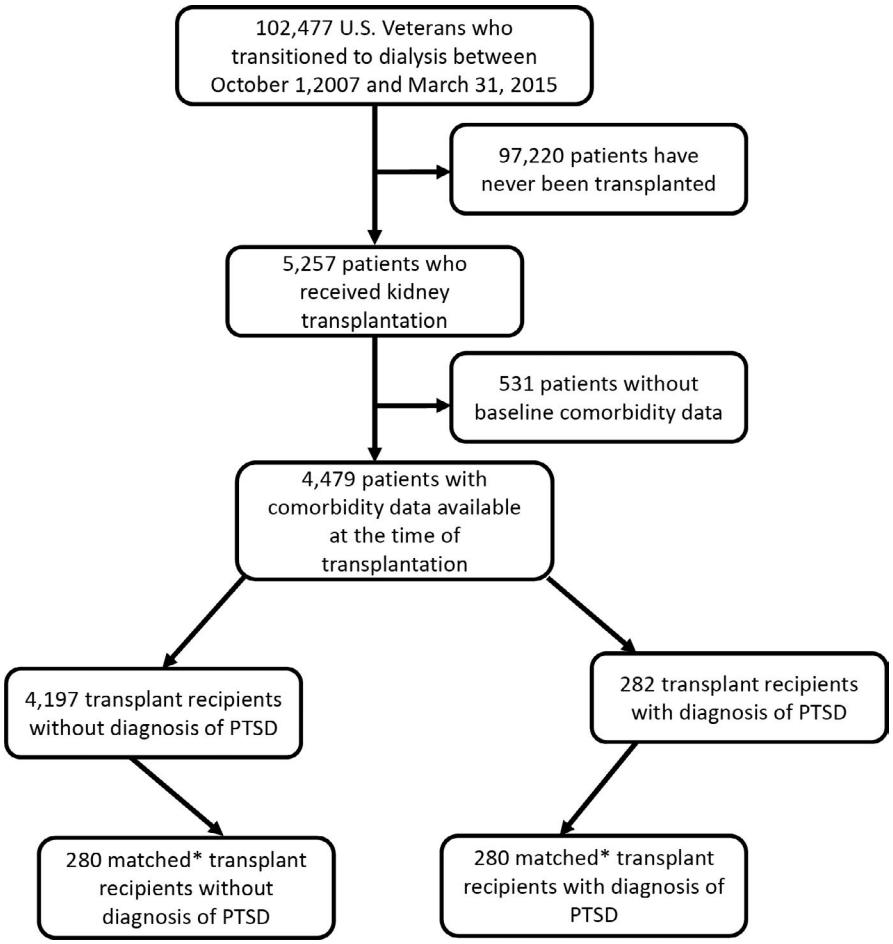

FIGURE 1 Flow chart of the patients' selection

the cohort definition is shown in Figure 1. We excluded patients who were never transplanted (n = 97 220) and those without any available information on comorbid conditions including a history of PTSD (n = 531), which resulted in a study population of 4479 patients. From these 4479 patients, a combined exact- and propensity score-matched cohort was created including 560 kidney transplant recipients.

2.2 | Exposure variable

Information on history of PTSD before transplantation was extracted from the Veterans Affairs (VA) Inpatient and Outpatient Medical Statistical Analysis System Datasets and from VA/Centers for Medicare & Medicaid Services (VA/CMS) data using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes (Medicare Provider Analysis and Review, Outpatient, Carrier and Inpatient files). We used the validated algorithm described by Gravely et al[28] to define history of PTSD, using outpatient or inpatient medical records prior to kidney transplantation. PTSD was identified if there were at least 2 instances of a PTSD ICD-9-CM diagnostic code (309.81) or at least one PTSD ICD-9-CM diagnostic code and clinical stop code for any mental health/PTSD visit in the 2 years before the patient's renal transplantation date.[28-30]

2.3 | Covariates

Data from the USRDS Patient and Medical Evidence Form 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 Statistical Analysis System Datasets, using ICD-9-CM diagnostic and Current Procedural Terminology codes, as well as from VA/CMS data (Medicare Provider Analysis and Review Outpatient, Carrier and Inpatient files). Medication data were collected from both CMS Data (Medicare Part D) and VA pharmacy dispensation records. Patients who received at least one dispensation of medication within the 24-month pretransplant period were recorded as having been treated with these medications. Laboratory data were obtained from VA research databases as described previously,[7,31,32] and their baseline values were defined as the average of each covariate during the 24-month pretransplant period.

2.4 | 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 = 348 for tacrolimus and n = 119 for mycophenolic acid), using both CMS Data (Medicare Part D) and VA pharmacy dispensation records. Proportion of days covered (PDC) and medication persistence were calculated. The detailed description of PDC has been published previously.[7,27,33-35] Figures S1–S2 shows the graphical description of the calculations for different adherence methods.

Briefly, PDC was defined as the proportion of days when the drug was available in the measurement period, capped at 100%.[34,35] 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 of whether the supply lasted until after the date of the first-year transplantation anniversary. Only outpatient prescriptions were taken into account. 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 days; otherwise, it was coded as 0 (absent, or nonpersistent).[35]

2.5 | Outcome assessment

The primary outcomes of interest were death, graft loss, 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.

2.6 | Statistical analyses

Baseline patient characteristics were summarized according to the presence or absence of history of PTSD 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 PTSD were assessed, using standardized differences before and after a combination of exact and propensity score matching.

We created a matched cohort of patients with and without PTSD by combining exact matching on key variables with propensity score matching on remaining variables, in order to ensure that the 2 groups were balanced for all key covariates.[36] Exact matching was performed on the following variables: gender, race, type of donor (living vs deceased), and diabetes. The propensity score calculations were based on a priori selected additional 10 variables (age at transplant, Charlson Comorbidity Index [CCI], use of native vitamin D, service connection, smoking status, depression, use of aspirin, use of alpha blockers, use of calcium channel blockers and use of potassium sparing diuretics) based on the predictors of PTSD, using multivariate logistic regression models (Table S1) and a literature review. When exact matching on the preceding 4 variables resulted in a subgroup with few patients, only a limited number of the 10 additional covariates entertained for the respective propensity score model was used. When such a model could not be estimated due to too few events in the subgroup, we matched on age at transplant and CCI directly (see Table 1 and Table S2 for details).

The following outcomes were defined a priori:

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.[26,27] For this analysis, we used Kaplan-Meier method and 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 1, 2015).[26,27] For this analysis, we used competing risks regression (by Fine and Gray [37]), 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.[26,27] For this analysis, we used competing risks regression (by Fine and Gray [37]), 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. Finally for *immunosuppressive medication adherence*, we calculated proportion of days covered (PDC) and medication persistence for tacrolimus and mycophenolic acid. The mean ± standard deviation (SD) of PDC for immunosuppressive drugs were compared, using *t* test, whereas chi-square tests were used to compare medication nonpersistence for different immunosuppressive drugs.

We conducted several sensitivity analyses to evaluate the robustness of our main findings. Association was examined in the entire population using unadjusted and multivariable-adjusted competing risks regression and Cox proportional hazard models as prescribed earlier. In our multivariable-adjusted model, we adjusted for the following variables: age at transplant, gender, race/ethnicity, service connection, marital status, income, smoking status, type of transplant donor (deceased vs living), type of dialysis modality, CCI, presence of comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, peptic ulcer disease, malignancy, liver disease, diabetes, depression), and medication use (phosphorus 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, thrombolytic, aspirin, digitalis, and erythropoietin-stimulating agents).

Associations were also examined in subgroups of patients stratified by sex, race, donor type, presence/absence of diabetes, and preemptive transplantation. Potential interactions were formally tested by including relevant interaction terms.

Finally, we performed a sensitivity analysis where we adjusted for variables (comorbid depression, usage of active vitamin D,

TABLE 1 Baseline characteristics of the study population

	Before matching			After matching		
	No history of PTSD (n = 4197)	History of PTSD (n = 282)	Std. Diff.	No history of PTSD (n = 280)	History of PTSD (n = 280)	Std. Diff.
Demographics						
Age (y), mean (SD)[a]	61 (11)	61 (9)	0.005	61 (9)	61 (9)	−0.028
Gender (male), n (%)	3797 (91)	275 (98)	0.300	273 (98)	273 (98)	0
Race, n (%)			0.226			0
White	2795 (67)	167 (59)		167 (60)	167 (60)	
African American	1155 (27)	106 (38)		105 (37)	105 (37)	
Other	247 (6)	9 (3)		8 (3)	8 (3)	
Comorbidities						
Myocardial infarction, n (%)	638 (15)	46 (16)	0.022	52 (19)	46 (16)	−0.056
Congestive heart failure, n (%)	1181 (28)	97 (34)	0.122	101 (36)	96 (34)	−0.037
Peripheral vascular disease, n (%)	1560 (37)	109 (39)	0.014	131 (47)	108 (39)	−0.167
Cerebrovascular disease, n (%)	903 (22)	81 (29)	0.156	77 (28)	80 (29)	0.024
Dementia, n (%)	1027 (25)	77 (27)	0.053	74 (26)	76 (27)	0.016
Chronic pulmonary disease, n (%)	1147 (27)	100 (36)	0.163	98 (35)	98 (35)	0
Connective tissue disease, n (%)	659 (16)	45 (16)	−0.002	52 (19)	44 (16)	−0.076
Peptic ulcer disease, n (%)	410 (10)	38 (14)	0.109	34 (12)	37 (13)	0.032
Paraplegia and hemiplegia, n (%)	292 (7)	24 (9)	0.052	32 (11)	23 (8)	−0.108
Diabetes, n (%)	2353 (56)	191 (68)	0.218	189 (68)	189 (68)	0
Liver disease, n (%)	1488 (36)	123 (44)	0.152	134 (48)	122 (44)	−0.086
Malignancy, n (%)	1104 (26)	97 (34)	0.291	86 (31)	95 (34)	0.069
HIV, n (%)	59 (1)	9 (3)	0.117	10 (4)	8 (3)	−0.041
Anemia, n (%)	2705 (65)	213 (76)	0.214	204 (73)	211 (75)	0.057
Atrial fibrillation, n (%)	1196 (29)	36 (13)	−0.410	54 (19)	36 (13)	−0.176
Depression, n (%)[a]	1222 (29)	155 (55)	0.528	87 (31)	153 (55)	0.490
Hyperlipidemia, n (%)	3572 (85)	267 (95)	0.182	254 (91)	265 (95)	0.090
Hypertension, n (%)	2424 (58)	191 (68)	0.271	177 (63)	189 (68)	0.151
Ischemic heart disease, n (%)	1327 (32)	106 (38)	0.111	111 (40)	106 (38)	−0.037
Preemptive transplantation, n (%)	812 (19)	50 (18)	−0.042	55 (20)	48 (17)	−0.065
Living donor transplantation, n (%)	1325 (32)	86 (31)	0.043	85 (30)	85 (30)	0
Dialysis modality: hemodialysis, n (%)	2644 (63)	196 (69)	0.179	176 (63)	196 (70)	0.160
Duration of dialysis (d), median (IQR)	1756 (1142-2301)	1725 (1140-2269)	0.004	1857 (1226-2407)	1735 (1143-2272)	−0.086

(Continues)

TABLE 1 (Continued)

	Before matching			After matching		
	No history of PTSD (n = 4197)	History of PTSD (n = 282)	Std. Diff.	No history of PTSD (n = 280)	History of PTSD (n = 280)	Std. Diff.
Medications						
ESAs, n (%)	377 (9)	61 (22)	0.357	45 (16)	60 (21)	0.138
Native vitamin D, n (%)[a]	432 (10)	94 (33)	0.581	75 (27)	93 (33)	0.141
Active vitamin D, n (%)	771 (18)	94 (33)	0.347	61 (22)	93 (33)	0.258
Sevelamer, n (%)	1073 (26)	103 (37)	0.239	85 (30)	103 (37)	0.136
Lanthanum, n (%)	295 (7)	29 (10)	0.116	29 (10)	29 (10)	0
Calcium acetate, n (%)	985 (24)	110 (39)	0.340	87 (31)	110 (39)	0.173
Anticoagulants, n (%)	393 (9)	66 (23)	0.386	49 (18)	66 (24)	0.151
Thrombolytics, n (%)	37 (1)	8 (3)	0.145	3 (1)	8 (3)	0.129
Aspirin, n (%) [a]	513 (12)	111 (39)	0.653	68 (24)	109 (39)	0.319
Digitalis, n (%)	32 (1)	3 (1)	0.032	6 (2)	3 (1)	−0.085
β-blockers, n (%)	1794 (43)	203 (72)	0.619	160 (57)	201 (72)	0.310
Alpha blockers, n (%)	632 (15)	96 (34)	0.452	62 (22)	95 (34)	0.265
Calcium channel blockers, n (%)	1661 (40)	193 (68)	0.605	134 (48)	192 (69)	0.430
Antianginals, n (%)	346 (8)	42 (15)	0.209	34 (12)	42 (15)	0.084
Statins, n (%)	1618 (39)	174 (62)	0.476	145 (52)	172 (61)	0.196
Vasodilators, n (%)	738 (18)	80 (28)	0.259	68 (24)	80 (29)	0.097
Thiazides diuretics, n (%)	256 (6)	36 (13)	0.230	20 (7)	34 (12)	0.170
Loop diuretics, n (%)	1244 (30)	143 (51)	0.440	116 (41)	141 (50)	0.180
Potassium-sparing diuretics, n (%)	154 (4)	17 (6)	0.110	22 (8)	16 (6)	−0.085
RAASi, n (%)	1438 (34)	142 (50)	0.330	124 (44)	140 (50)	0.115
Insulin, n (%)	942 (22)	123 (44)	0.462	100 (36)	121 (43)	0.154
Marital status, n (%)			0.080			0.095
Married	2629 (63)	201 (71)		188 (67)	199 (71)	
Single	313 (7)	18 (6)		16 (6)	18 (6)	
Divorced	657 (16)	54 (19)		60 (21)	54 (19)	
Widowed	116 (3)	7 (2)		6 (2)	7 (3)	
Missing	482 (11)	2 (1)		10 (4)	2 (1)	
Smoking, n (%)[a]			0.911			0.398
Never	883 (21)	82 (29)		81 (29)	82 (29)	
Current	673 (16)	91 (32)		66 (24)	90 (32)	
Past	686 (16)	81 (29)		63 (22)	80 (29)	
Missing	1955 (47)	28 (10)		70 (25)	28 (10)	
Income (USD), median (IQR)	19 224 (0-38 266)	32 052 (13 949-35 838)	−0.147	25 866 (8904-38 266)	32 052 (13 920-36 000)	−0.096
Service connection, %[a]	1846 (44)	269 (95)	1.324	216 (77)	267 (95)	0.542

(Continues)

TABLE 1 (Continued)

	Before matching			After matching		
	No history of PTSD (n = 4197)	History of PTSD (n = 282)	Std. Diff.	No history of PTSD (n = 280)	History of PTSD (n = 280)	Std. Diff.
Charlson Comorbidity Index, median (IQR)[a]	3 (1-7)	5 (2-8)	0.220	4 (2-9)	5 (2-8)	−0.056
Serum albumin (g/dL), mean(SD)	3.7 (0.5)	3.7 (0.5)	−0.123	3.6 (0.6)	3.7 (0.5)	0.124
Serum AST, (g/dL), median (IQR)	25.4 (38.2)	26.7 (21.2)	0.042	26.5 (21.3)	26.5 (21.2)	−0.001
Serum ALT, (g/dL), median (IQR)	25.2 (39.9)	26.3 (18.8)	0.036	24.5 (13.8)	26.2 (18.8)	0.104
Blood hemoglobin, (g/dL), mean (SD)	11.5 (1.4)	11.4 (1.4)	−0.104	11.4 (1.3)	11.4 (1.4)	0.032
Serum phosphorus, (g/dL), mean (SD)	4.9 (1.2)	4.9 (1)	−0.054	5.1 (1.3)	4.9 (1)	−0.218
Serum PTH, (g/dL), mean (SD)	305.4 (235)	332.4 (351.6)	0.090	336.2 (263.1)	334.1 (352.5)	−0.007
Systolic BP (mm Hg), mean (SD)	137.8 (16.5)	137.6 (14.6)	−0.012	137.9 (16.3)	137.5 (14.6)	−0.020
Diastolic BP (mm Hg), mean (SD)	75.6 (10.3)	75.9 (8.5)	0.032	75.5 (9.1)	75.9 (8.5)	0.050
BMI (kg/m^2), mean (SD)	28.6 (4.6)	28.9 (4.7)	0.063	28.7 (5.2)	28.9 (4.8)	0.035

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

[a]Variables used in the propensity score matching.

TABLE 2 Association between history PTSD and posttransplantation outcomes using Cox proportional regression and competing risks regression models in the propensity-matched cohort (n = 560)

	Hazard ratios (HRs)	95% confidence interval of HRs	*P* value
History of PTSD vs *no* history of PTSD (ref.)			
All cause death	1.05	0.69-1.58	.821
	Subhazard ratios (SHRs)	95% confidence interval of SHRs	*P* value
History of PTSD vs *no* history of PTSD (ref.)			
Death with functioning graft	0.97	0.61-1.54	.910
Graft loss	1.09	0.53-2.26	.815
	History of PTSD	No history of PTSD	*P* value[a]
Immunosuppressive adherence: proportion of days covered for			
Tacrolimus (%) (mean ± SD)	98 ± 4	99 ± 3	.733
Mycophenolic acid (%) (mean ± SD)	99 ± 4	98 ± 7	.369
Immunosuppressive persistence: 30-d gap			
Tacrolimus	98%	99%	.409
Mycophenolic acid	96%	98%	.630

HR, hazard ratio; SHR, subhazard ratio.

[a]*P* values for adherence are result of *t* test and chi-square test.

aspirin, beta-blockers, alpha-blockers, calcium channel blockers, history of smoking, service connection, and serum phosphorus level), showing a standardized difference >|0.2| in the matched cohort.

Reported *P* values were 2-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and STATA/MP Version 15 (STATA Corporation, College Station, TX). The study was approved by the institutional review boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

3 | RESULTS

3.1 | Baseline characteristics

The mean ± SD age of the cohort at baseline was 61 ± 11 years, 91% were male, and 66% and 28% of patients were white and African American, respectively. Eighteen percent of the transplantations were preemptive, 63% of the recipients were married, and 57% of the patients were diabetic. In the entire cohort, we identified 282 and 4197 patients with and without a history of PTSD, respectively. Baseline characteristics of patients categorized by history of PTSD status are shown in Table 1. In the original cohort (n = 4479), patients with history of PTSD were more likely to be male and white, a current smoker, have a higher prevalence of several comorbidities and were more likely to receive antihypertensive medications. These differences largely disappeared after matching (Table 1).

3.2 | Death with functioning graft

During a median follow-up period of 2 years, a total of 72 deaths (13%) occurred (crude incidence rate, 47 per 1000 patient-years; 95% confidence interval [CI] 37-59). The crude mortality rate was similar in patients with a history of PTSD (33 [12%] deaths, 45 per 1000 patient-years, 95% CI 32-63) vs patients without history of PTSD (39 [14%] deaths, 49 per 1000 patient-years, 95% CI: 36-68), as shown in Figure 2A. Compared to patients without a history of PTSD, patients with a history of PTSD had a similar risk of death with functioning graft in competing risks regression in the matched cohort overall (subhazard ratio [SHR] 0.97, 95% CI 0.61-1.54) (Table 2), in different subgroups (Figure 3A) and in the entire cohort after adjustment for confounders (SHR 1.08, 95% CI 0.73-1.59; Tables S3-S4) or after adjustment for unbalanced confounders (Table S5).

3.3 | All-cause death

Compared to patients without a history of PTSD, patients with a history of PTSD had similar all-cause mortality risk in the matched cohort overall (hazard ratio [HR] 1.05, 95% CI 0.69-1.58; Table 2), in different subgroups (Figure 3B) and in the entire cohort after adjustment for confounders (HR 1.17, 95% CI 0.83-1.65; Tables S3-S4) or after adjustment for unbalanced confounders (Table S5).

3.4 | Graft loss

A total of 29 graft losses (5%) occurred (crude incidence rate 19 per 1000 patient-years; 95% CI 13-27). The crude graft loss rate was similar in patients with a history of PTSD (15 [5%] graft loss, 20 per 1000 patient-years, 95% CI 12-34) vs patients without a history of PTSD (14 [5%] graft loss, 18 per 1000 patient-years, 95% CI 11-34), as shown in Figure 2B. Compared to patients without a history of PTSD, patients with a history of PTSD had similar graft loss risk in competing risks regression in the matched cohort overall (SHR 1.09, 95% CI 0.53-2.26; Table 2), in different subgroups (Figure 3C), and in the entire cohort after adjustment for confounders (SHR 1.02, 95% CI 0.56-1.85; Tables S3-S4), or after adjustment for unbalanced confounders (Table S5).

3.5 | Medication nonadherence

Of the 560 patients in the matched cohort, 348 patients received tacrolimus prescriptions. The average PDC for tacrolimus in the first year after transplantation was 98 ± 3%. There was no difference in PDC between patients with and without a history of PTSD (PDC:

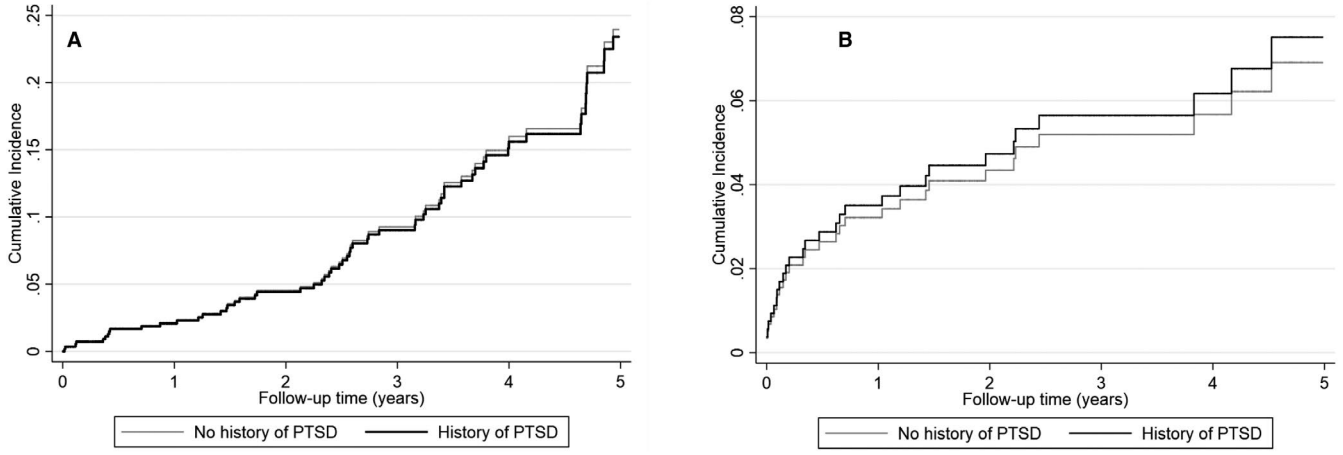

FIGURE 2 Cumulative incidence of death with functioning graft (A) and graft loss (B) using competing risks regression models in the propensity-matched cohort

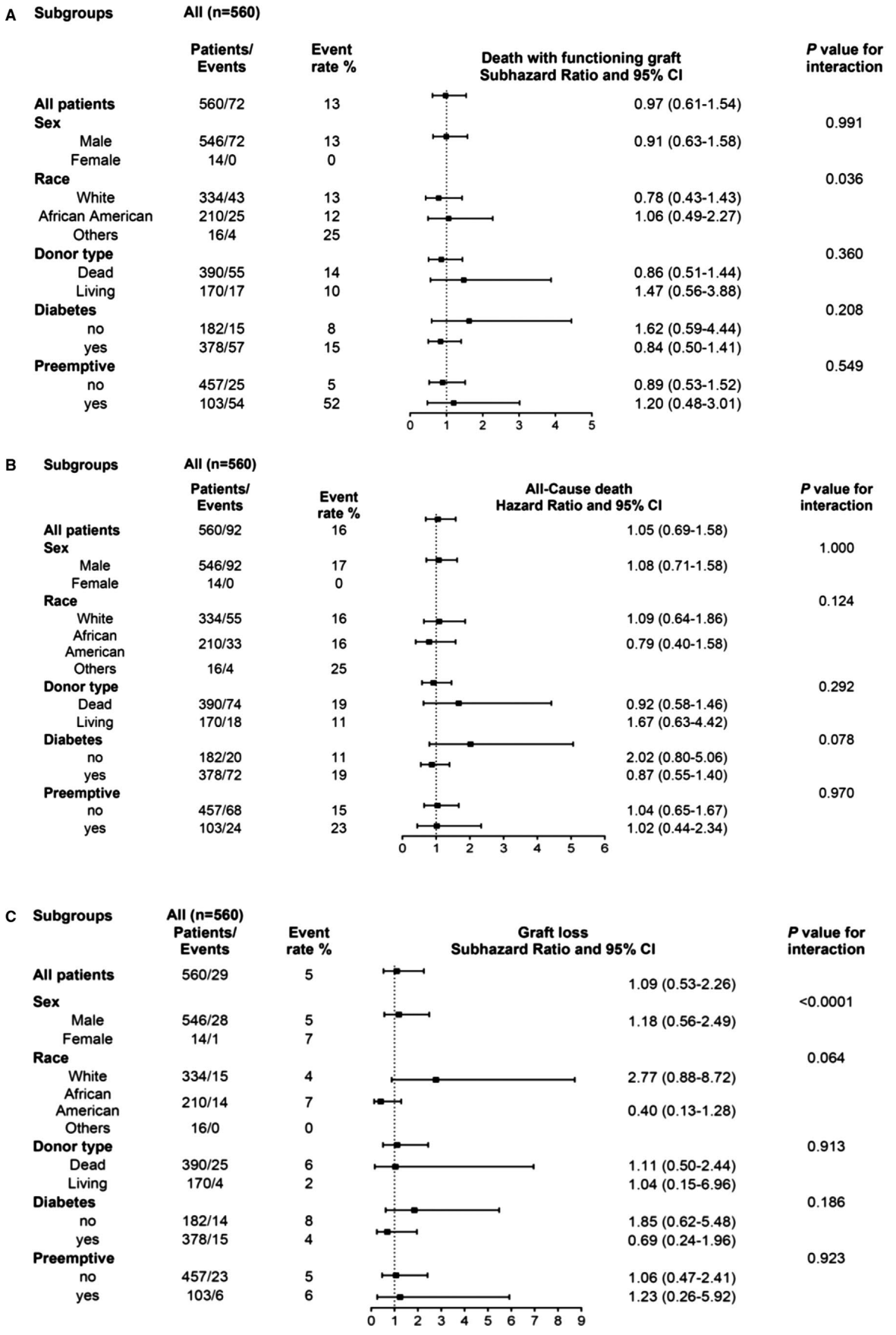

FIGURE 3 Association between history of PTSD and death with functioning graft (A), all-cause death (B), and graft loss (C) in the propensity-matched cohort in different subgroups

98 ± 4% vs 99 ± 3%, P = .733). In addition, the 30-day persistence with drug therapy was also similar in patients with and without a history of PTSD (98% vs 99%, P = .409).

Of the 560 patients in the propensity-matched cohort, 119 received mycophenolic acid prescriptions. The mean PDC for mycophenolic acid in the first year after transplantation was 98 ± 5%. There was no difference in PDC in patients with and a without history of PTSD (PDC: 99 ± 4% vs 98 ± 7%, P = .369). In addition, the 30-day persistence with drug therapy was also similar in patients with and without a history of PTSD (96% vs 98%, P = .630).

4 | DISCUSSION

In this large national cohort of incident kidney transplant US veterans, we found that recipients with a history of PTSD have similar survival and graft loss risk compared to recipients without a history of PTSD. In addition, we showed that these recipients with a history of PTSD have similar posttransplant immunosuppressive medication adherence compared to their counterparts without this diagnosis.

To our knowledge, our study is the first to assess the association between pretransplant PTSD and outcomes after kidney transplantation. There have been few studies that have assessed the relationship between PTSD and transplant outcomes, most of which assessed posttransplant PTSD and examined nonkidney solid organ transplant recipients, which may explain why their findings were different from ours.[23,24,38-41] Almost all of these studies were observational studies and examined a limited number of subjects. These studies have been consistently associated with poor outcomes such as worse mortality and physical and mental health.[23,38-40] More recent studies performed in US veterans showed no worse posttransplant outcomes in solid organ transplant patients who had pretransplant serious mental health disorders and in kidney transplant recipients with pretransplant psychosis or mania.[7,25] These results are consistent with our present findings in PTSD patients, which also show that patients with pretransplant PTSD had comparable degrees of medication adherence compared to patients without pretransplant PTSD. Previous studies have shown medication noncompliance to be a major risk factor for graft rejection and poor outcomes posttransplant.[38,42] Multiple studies in the past have also shown PTSD to be associated with poor medication adherence.[18,24,43,44] A potential explanation for the observed medication adherence in our study is that the veterans who underwent transplantation may, as a consequence of the transplant evaluation process, have less severe or well-managed PTSD symptoms compared to those not considered for transplantation.

There are several strengths of our study. We used a validated method to select patients with PTSD from administrative datasets.[28,45] In addition, we had sufficient power to examine different outcomes such as death and graft loss after transplantation. We were also able to take into consideration several important confounders such as demographic, medications, comorbidities, and laboratory results. Finally, our study is the first that has examined medication adherence as an outcome associated with PTSD.

Our study has certain limitations. More than 90% of our patient population was male and all our patients were US veterans; so, the study might have limited external validity when applied to women or patient populations outside the United States. We have used administrative database and ICD codes for evaluation of diagnoses and outcomes instead of direct clinical evaluation, which might have led to over- or underdiagnosis of PTSD. Our use of a definition based on a validated algorithm[28,45] is an attempt to eliminate this potential bias. Because this is a retrospective cohort study in patients who had already been selected for renal transplantation, our findings may not apply to patients with severe uncontrolled PTSD who were eliminated from transplant candidacy. In addition, patients may hide their PTSD symptoms from their healthcare providers due to concern that this may exclude them from transplantation. Notwithstanding the validity of this general concern related to administrative data, the priorities of the VA make identification and management of PTSD more likely in the VA than in other healthcare systems. Another disadvantage of using an administrative dataset for our study is that we did not have any details about symptoms, about the clinical care of these patients, and whether there was any special care or guidance received by these patients that might have skewed our results one way or the other. Our study cannot address whether outcomes are dependent on severity of symptoms and/or management of PTSD before and after transplantation, as this information is not deduced from our administrative data. Similarly, because the criteria for selection of individual veterans for transplantation is unknown, the extent to which PTSD factored into the selection process is also unknown. In addition, being an observational study, it is impossible to eliminate bias from unmeasured confounders.

Finally, our population consisted of transplant patients who were obviously selected for transplant waitlisting. It is very likely that patients with PTSD who were deemed high risk were excluded from waitlisting, and hence our study cannot answer the question whether a history of PTSD should be a relative contraindication of listing patients for kidney transplant.

5 | CONCLUSION

In conclusion, this large national cohort of US transplant recipients with a history of PTSD shows similar medication adherence and survival and graft loss risk compared to recipients without PTSD. This demonstrates that after evaluation and management, select patients with PTSD can safely undergo a transplantation, and hence PTSD should not be an absolute contraindication to kidney transplantation. Further studies are needed to define how we can safely select even more transplant candidates from the dialysis patient population with a history of PTSD.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from US Department of Veterans Affairs. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of US Department of Veterans Affairs.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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