ORIGINAL ARTICLE

Safety of renal transplantation in patients with bipolar or psychotic disorders: a retrospective study

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SUMMARY

Solid organ transplantation societies recommend a relative contraindication of transplantation for people with bipolar or psychotic disorders. Very few data are available on the outcome of kidney transplantation and the increased risk of kidney disease in those patients. We conducted a retrospective multicenter cohort study (1979-2014) including kidney allograft recipients with either bipolar (BD) or psychotic disorders prior to transplant. Objectives were kidney allograft and patient outcomes compared to a matched control group without psychiatric disorders and the evolution of psychiatric disorder at 60 months after transplantation. Forty-seven patients including 25 women were identified, 34 with BD and 13 with psychotic disorder. Patients' overall cumulative death rates at 60 months were not significantly different in both groups [12.2%; 95% confidence interval: (4.5-24.1) in the group with psychiatric disorder versus 5.2%; (1.7-11.7) in control group P = 0.11 as for cumulative allograft loss rates [11.7%] (3.5-25.2) vs. 9.4% (4.4-16.8) in control group (P = 0.91)]. Twenty-three patients (16 with BD and seven with psychotic disorder) experienced at least one psychiatric relapse [incidence rate: 1.8/100 persons- months; 95% CI; (1.2–2.7)] totaling 13 hospitalizations within 60 months of follow-up. Four patients stopped immunosuppressive therapy leading to allograft loss in three. Our study suggests that patients with BD or psychotic disorders have to be considered for renal transplantation with close psychiatric follow-up after transplant.

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Key words

bipolar disorder, psychosis, psychiatric outcome, transplant outcome, kidney transplantation

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Introduction

The prevalence of both schizophrenia and bipolar disorder (BD) in the general population is around 1-4% [1,2]. Seemingly having schizophrenia or BD increases the risk of kidney disease and patients present higher rates of cardiovascular disease, hypercholesterolemia, diabetes, and hypertension [3]. Furthermore, people with BD are at particularly high risk of renal failure due to the use of lithium for treatment [4]. However, patients with psychiatric disorders are clearly underrepresented in the transplant population. They are often excluded for fear of transplant physicians of their hypothetical incapacity to adhere to complex immunosuppressant regimes, and of a possible exacerbation of their psychiatric disease secondary to these drugs [5]. Posttransplant drug compliance ratios in psychiatric patients are generally low because of the drugs severe side effects, and patients' low awareness of the illness [6]. Nonetheless, such noncompliance is common in the general transplant population and is usually associated with graft loss reaching 40% in some types of renal transplants [7]. However, no study has looked at the risks associated with the presence of psychiatric disorders prior to transplant [3].

The concern that people with psychiatric disorders may be at greater risk of graft loss due to an inability to comply with their treatment regime does not appear to be substantiated by any evidence. Considering the increased risk of immunosuppressant-induced postoperative psychosis, two recent reviews concluded that there is no convincing evidence that a history of psychiatric illness predicts a susceptibility to steroid-induced psychiatric symptoms [8,9]. However, the solid organs transplantation societies are keen to maintain a relative contraindication of transplantation people with psychiatric disorders [10–13].

Few data that deal with allograft outcomes in patients with psychiatric disorders are available, and they generally address the development of psychiatric syndrome after transplantation rather than assess the outcomes of patients with pre-existing disease [14–21]. Those case reports and small studies have shown the feasibility of transplantation in patients with psychiatric disorders with an excellent patient and allograft survival rate [14– 20]. Well-known risk factors of allograft loss are homelessness, antisocial behavior, associated depression, medical noncompliance, history of psychotic episode more than 1 year before transplantation, and isolation [3,22,23]. No published study has directly assessed the rates of postoperative psychiatric complication in Given the insufficient evidence of psychiatric disorders negative impact on kidney allograft outcomes, we conducted a retrospective multicenter study on renal transplant recipients with who had already had bipolar or psychotic disorder before transplant. We compared the patient and allograft survival with that of the general transplant population, and we studied the outcome of psychiatric disease after transplant.

Materials and methods

Patients

Our study is a multicenter, retrospective cohort study conducted in five French kidney transplant departments. The inclusion criterion was the presence of psychiatric disorder including any schizophrenia spectrum and other psychotic disorders or BD at the time of kidney transplant but with no past history of infantile psychosis. All patients were followed by local transplantation teams and local psychiatrists. The diagnosis of psychiatric disease was based on a local psychiatrist evaluation. All patients were stable at the time of transplantation with an optimal exposure to medications.

All patients' characteristics before and after kidney transplant regarding their kidney and psychiatric diseases were recorded. Delayed graft function (DGF) was defined as the need for dialysis within the first 7 days after transplant. To analyze allograft and patient survival, the psychiatric patients were compared with a control allograft kidney recipients group (in a ratio of one patient with psychiatric disorder for two patients in the control group). Patients in the control group were randomly selected from the French national registry (CRISTAL) and were matched with the psychiatric patients for age, sex, time of transplant, and center of transplant. The outcome of kidney transplantation was examined in terms of patient death and allograft loss rates, acute rejection, acute cardiovascular events (cardiac death, myocardial infarction, acute congestive heart failure, and acute cerebral ischemic stroke), post-transplantation infectious episodes, and cause of death.

Firstly, the psychotic disorder was assessed considering the number of pre- and post-transplant treatments, need for new drugs or new approaches such as electroconvulsive therapy, psychiatric relapse (PR), hospitalization, discontinuation of immunosuppressive treatment, and suicidal attempt. Secondly, patients were divided into two groups according to type of psychiatric condition, BD, or psychotic disorder.

The study was presented at the *CPP Sud Est* 4 (People's Protection Committee) that gave no restriction to our study.

Statistical analysis

Continuous variables were presented using means (standard deviation, SD) or medians (IQR) according to variable distribution and were compared using Student's *t*-test or Wilcoxon–Mann–Whitney test when appropriate. Categorical variables were expressed in percentages and compared using Pearson chi-square test or Fisher's exact test, when appropriate.

Time-to-event approaches were used to assess different outcomes, for example, psychiatric relapse, acute rejection, graft loss, and death. Date of origin was date of transplantation, and end date was date of event or date of last follow-up visit or 60 months after transplantation whichever occurred first.

We applied Kaplan–Meier curves and the log-rank test to estimate the patient incidence of psychiatric relapse in patients with baseline psychiatric disorder and compare incidence of psychiatric relapse in patients with BD versus psychotic disease.

We used cumulative incidence function and Fine and Gray's test to estimate and compare death rate (competing events: allograft loss), allograft loss rate (competing event: death), and acute rejection (competing event: death) over a period of 60 months, between the group with psychiatric disorder versus without, and between the group with BD versus psychotic disease, respectively.

All comparisons were two-sided, and a value of P < 0.05 was considered significant. Data were analyzed using the STATA STATISTICAL software (StataCorp 2005, Release 13.0, College Station, TX, USA).

Results

A total of 47 kidney recipients (25 women and 22 men) with pre-existing psychiatric disorder engrafted between 1979 and 2014 were identified. Of whom, two patients were transplanted in the 80's, three in the 90's, 26 in the 2000's, and 16 between 2010 and 2014. Demographic, psychiatric disease type, and transplant data are depicted in Tables 1 and 2. On the whole, 8750 patients

were transplanted during this time frame in our five centers.

Characteristics at transplantation

The psychiatric disorder was BD in 34 (72%) patients and psychotic disorder in 13 (28%) patients. Among the latter, ten had schizophrenia, two had chronic paranoid schizophrenia, and one had paranoid psychosis. The age of onset of psychiatric disorder was 35 (± 11) years. Before renal transplantation, 22 (56%) patients (of the total, N = 39 with all data available) experienced at least one PR with hospitalization. Age of the 1st dialysis was 49 (± 14) years. Initial nephropathy was as follows: lithium-induced nephropathy (N = 16), unknown (N = 9),hereditary nephropathy (N = 6),IgA nephropathy (N = 4), reflux nephropathy (N = 2), diabetic glomerulosclerosis (N = 2), focal segmental glomerulosclerosis (N = 2),nephroangiosclerosis (N = 1),membranoproliferative glomerulopathy (N = 1), HIV (N = 1), Goodpasture disease (N = 1), sarcoidosis (N = 1), and monoclonal-induced deposition disease (N = 1).

Age at the time of kidney transplant was 53 (\pm 13) years, and all but four (8%) received the allograft from a deceased donor. Preemptive renal transplantation was performed in two (4%) patients. Induction therapy included antiR-IL2 [N = 21 (51%)] and thymoglobulin [N = 20 (49%)]. All were treated with high-dose steroids at the time of induction. Maintenance immuno-suppression included steroids, calcineurin inhibitors (CNI), and antiproliferative drugs in 34 (74%) patients. Steroids were stopped in 11 (24%) patients shortly after transplant.

Patients' death rates and graft lost rates

To analyze patient and allograft survival, our group of 47 patients was compared with 94 kidney allograft recipients who were matched for age, sex, and time of transplant. Both groups were similar in terms of cold ischemia time (P = 0.64) and donor age (P = 0.06) (Table 1). After taken into account graft loss as competing event, patients' overall cumulative death rates were not different in both groups within 60 months [12.2%; 95% confidence interval (4.5–24.1) in the group with psychiatric disorder versus 5.2%; (1.7–11.7) in control group; P = 0.11] (Fig. 1). Similarly, after adjustment for death as competing event, cumulative allograft loss rates were not significantly different between the group with psychiatric disorder [11.7%; (3.5–25.2)] and the

Variables	Psychiatric patients	Control group	Bipolar disorder group	Psychotic group	P-value*
Patients, N (%)	47 (100)	94 (100)	34 (72)	13 (28)	
Female, N (%)	25 (53)	50 (53)	23 (68)	2 (15)	0.002
Dialysis before transplant, N (%)	45 (96)		32 (94)	13 (100)	1.00
Hemodialysis, N (%)	42 (93)		29 (91)	13 (100)	1.00
Age, years, mean (士SD)	49 (土14)		53 (土13)	39 (土12)	0.002
Time to transplant, months, median (IQR)	36 (18–61)		33 (18–43)	58 (27–82)	0.05
Psychiatric disease					
Age of onset of psychiatric disease, years, mean $(\pm \text{SD})$	35 (土11)		34 (土10)	35 (土14)	0.86
Psychiatric relapse (hospitalization), N/N data available (%)	22/39 (56)		13/27 (48)	9/12 (75)	0.17
Psychotropic drugs, N/N data available (%)	30/41 (73)		24/31 (77)	6/10 (60)	0.41
Number, median (IQR)	1 (0–2)		1 (1–2)	1 (0–2)	0.81
Kidney transplant					
Age, years, mean (±SD)	53 (土13)	53 (\pm 12) <i>P</i> = 0.93	56 (土11)	44 (土12)	0.002
Donor age, years, mean (±SD)	52 (土17)	$57 (\pm 14) P = 0.06$	53 (土17)	48 (土17)	0.34
Deceased donor, N (%)	43 (91)		32 (94)	11 (85)	0:30
Cold ischemia time, min, median (IQR)	1170 (916–1620)	1188 (905 - 1353) P = 0.64	1100 (780–1400)	1320 (1114–1943)	0.06
HLA matches, median (IQR)	3 (1–3)		3 (1–4)	2 (1–3)	0.70
Immunosuppressive regimen					
Induction, N (%)	41/45 (91)		30/33 (91)	11/12 (92)	1.00
Antithymocyte globulin, N (%)	20 (49)		13 (43)	7 (64)	0.31
Interleukin receptor-2 blockers, N (%)	21 (51)		17 (57)	4 (36)	
Maintenance					
Standard† regimen, N (%)	34/46 (74)		27/33 (82)	8/13 (61)	0.25
Without steroids, N (%)	11/46 (24)		6/33 (18)	5/13 (39)	
IQR, interquartile; SD, standard deviation.					
*Comparison of bipolar disorder group and psychotic group	using <i>n</i> Pearson chi-sc	auare test or the Fisher's exa	act test, when appropriat	te for categorical varia	bles, Stu-
dent's t-test or the Wilcoxon–Mann–Whitney.	0		······································		

Table 1. Patients characteristics at baseline.

 † Standard regimen consists in the association of steroids, a CNI and an antimetabolite drug.

Variables	Psychiatric cohort	Bipolar disorder group	Psychotic group	P-value*
Patients, N (%) Transolant complications	47 (100)	34 (72)	13 (28)	
Delayed graft function, N (%)	12/45 (27)	5/33 (15)	7/12 (58)	0.007
Acute rejection, N (%)	16/47 (34)	12/34 (35)	4/13 (31)	1.00
Bacterial or opportunistic infections, N (%)	32/47 (68)	23/34 (68)	9/13 (69)	1.00
Cardiovascular events, N (%)	11/47 (23)	8/34 (24)	3/13 (23)	1.00
nanspiant outconne N alloaraft loss: Cumulative alloaraft loss	4: 11.7 (3.5–25.2)	3: 11.1 (2.6–6.2)	1: 10.2 (0.6–36.3)	0.71
rate (95% Cl)†				
Disruption of immunosuppressive therapy	4/46 (9)	2/33 (6)	2/13 (15)	0.13
followed by allograft loss, N (%)	3 (75)	2 (100)	1 (50)	1.00
N death; Cumulative death rate(95% Cl)†	5; 12.2 (4.5–24.1)	4,14.0 (4.4–29.0)	1; 8.3 (0.5–31.1)	0.66
Psychiatric disease outcome				
N patients with psychiatric relapse; Psychiatric	23; 1.8/100; (1.2–2.7)	16; 1.8 (1.1–2.9)	7; 1.8 (0.1–3.7)	0.96
relapse incidence rate (95% CI), persons-months PM)†				
With steroid in maintenance therapy, N (%)	18 (53)	14 (52)	4 (50)	
Without steroid in maintenance therapy, N (%)	9 (82)	5 (83)	4 (80)	
Hospitalization, N (%)	13 (56)	8 (50)	5 (71)	I
Psychotropic drugs, N/N data available (%)	41/46 (89)	29/33 (88)	12/13 (92)	1.00
Number, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.33
Increase, N/N data available (%)	17/30 (57)	11/24 (46)	6/6 (100)	0.02
95% Cl, 95% confidence interval; IQR, interquartile range.				
*Comparison of bipolar disorder group and psychotic group u	Ising Pearson chi-square test or the	The Fisher's exact test, when app	propriate for categorical variable	es, Student's
t-test of the Wilcoxon-Ivianin-VVniuneV for continuous variable	s and Fine and urav lest וטו מווטכ	זנפון וסצא פווט מפמנה פווט וטט-ופוו	TK Lest Tor Dsychiatric relapse.	

Renal transplantation in psychiatric patients

†Cumulative allograft loss rate and death rate were calculated by Cumulative Incidence Function with death and allograft loss as competing events, respectively, within

60 months of post-transplant follow-up; psychiatric relapse was estimated using Kaplan-Meier method.

Transplant International 2018; 31: 377–385 © 2017 Steunstichting ESOT controls [9.4 (4.4–16.8)], (P = 0.91) (Fig. 2). In our psychiatric patients, the causes of the five deaths were sepsis (N = 2) and undetermined (N = 3).

Post-transplant complications

Twelve (26%) patients experienced DGF; 32 (68%) had at least one episode of bacterial or opportunistic infection; 11 (23%) had an acute cardiovascular event, and 15 (34%) had an acute rejection episode (T-cellmediated rejections N = 8, acute antibody-mediated rejections N = 2, mixed acute rejection N = 1). Acute rejection episodes occurred before PR in three patients (1, 11, and 13 months before PR, respectively), after PR in four (1, 8, 9, and 48 months after PR, respectively), and concomitantly in one patient. Thus, three patients presented acute rejection within 2 months around their PR. Of the four patients who discontinued immunosuppressive therapy, three lost their allograft.

Drug regimen and complications are comparable to those used in a French retrospective study dealing with kidney transplantation outcome in patients with AA amyloidosis [24].

Psychiatric outcome

In terms of post-transplant psychiatric disorder (Table 2), 41 patients (89%) required psychotropic treatment compared to with 34 (73%) for pretransplant disorders with a significant increase of psychotropic drugs use [2 (1–3) for the post-transplant versus 1 (0–2) for the pretransplant; P < 0.0001]. Psychiatric medications were not stopped throughout the postsurgical



Figure 1 Cumulative incidence function of death rate (competing event: allograft loss) within 60 months of post-transplant follow-up between group of patients with psychiatric disorder (n = 47) and the group without (n = 94). *Fine and Gray test.



Figure 2 Cumulative incidence function of allograft loss rate (competing event: death) within 60 months of post-transplant follow-up between group of patients with psychiatric disorder (n = 47) and the group without (n = 94). *Fine and Gray test.

period. However, we cannot exclude formally that modifications in medications dosage were not made during the perioperative or the early postsurgery period. Twenty-three patients presented at least one episode of PR over the 60 months follow-up (incidence rate: 1.8/ 100 persons-months; 95% CI; 1.2–2.7), mostly short after transplant (N = 8 within the first 3 months and N = 12 within the first year). PR required hospitalization in psychiatric unit for 13 (56.5%) patients, of whom six required several hospitalizations.

Comparison between bipolar and psychotic patients

In addition, we compared patients who had BD (N = 34) with patients who had psychosis (N = 13). There were significantly more women in the BD group than in the psychosis group [N = 23 (68%) vs. N = 2(15%); P = 0.002]. Age of onset of psychiatric disorder was similar in both groups (Table 1). Prior to renal transplantation, admission to hospital for PR, the number of treated patients, and the number of psychotropic drugs were similar in both groups. Psychotic patients were significantly younger at the time of dialysis (P = 0.002), and at the time of transplant (P = 0.002)(Table 1). However, the interval between dialysis and kidney transplant was significantly longer in psychotic patients [58 (27-82) vs. 33 (IQR 18-43) in BD; P = 0.05] (Table 1). DGF was significantly more common in psychotic patients [N = 7 (58%) vs. N = 5(15%); P = 0.007]. Cumulative acute rejection incidence, with death as competing events, was 36.2% (21.8-50.8; 15 events) within 60 months with no significant difference between groups (P = 0.22). Two recipients in the BD group and two in the psychotic group discontinued immunosuppressive therapy leading to allograft loss in three of them. After transplant, psychotropic treatment was prescribed in 29 (88%) BD recipients and in 12 (92%) psychotic recipients (P = 1.00). The number of psychotropic drugs increased in 11 (46%) BD patients and in 6 (100%; as data are available for only six of 13) psychotic patients (P = 0.02). Electroconvulsive therapy was introduced in two BD patients. The incidence of PR was not different between groups (P = 0.96), but it required admission to psychiatric ward in eight BD and five psychotic patients. Three patients in both groups required several hospitalizations. In BD patients, PR included major depressive syndrome (N = 7), manic episodes (N = 7), major depressive syndrome followed by a manic episode (N = 2), and psychosis (N = 1), whereas in psychotic patients, relapses were only psychosis. No suicide attempt was observed in the whole psychiatric patients group over the entire 60 months.

Discussion

We reported the results of what we believe is the first retrospective multicenter study analyzing both the outcome of kidney allograft recipients who had pre-existing psychiatric disorder including either schizophrenia spectrum and other psychotic disorders or BD, and the outcome of their psychiatric disease.

However, and due to the retrospective design of the study, some data are missing. Furthermore, our study is underpowered, presents important confounders, and lacks of full adjusted models. Thus, results should be taken with precautions.

Both graft loss and death incidence rates were not significantly different to a matched transplant population who had no psychiatric disorder, regardless of the psychiatric disorder type but a possible reason why there was no significant difference might be the lack of power.

To our knowledge, this is also the first study comparing psychiatric kidney recipients to a matched control kidney recipients from the general population even if our study lack data on controls immunization, immunosuppressor regimen and kidney disease. Furthermore, our results are similar to those seen in the U.S. population with five-year allograft survival reaching 71% and five-year patient survival of up to 83% (UNOS database).

Beyond all our limitations, we can extrapolate our results and conclude that post-transplant allograft and patient survival in highly selected patients with psychotic disorders or BD are similar to those found in the general kidney transplant population.

The main cause of graft loss was discontinuation of immunosuppressive drugs. Patient's compliance with treatment is a major concern in transplantation [25]. Noncompliance rates vary from 15% to 50% of patients depending on numerous factors such as definition of compliance, patient's age, characteristics, and country [7,26–28]. Unfortunately, we could neither use any compliance questionnaire in our general transplant cohort, nor could routinely evaluate patient's compliance which is clearly subjective and depends on patients' self-reporting. Besides, no objective evaluation is currently available. The risk of noncompliance should not be considered an obstacle to transplantation in psychiatric patients. However, as almost every treatment discontinuation ended in graft lost, these patients should be carefully monitored.

For the first time, as far as we know, we analyzed psychiatric outcomes after transplantation. Half of our patients (49%) developed post-transplant PR, and there was a significant increase in the number of psychotropic drugs those patients took, although their psychiatric condition was stable prior to transplant and at a psychiatric follow-up visit shortly after transplant. Additionally, more than half of those patients required hospitalization (representing 27.6% of our cohort), of whom 46% needed several hospitalizations. These results have to be considered with caution because the exact rate of hospitalizations in the general population of psychiatric patients is not well defined. In a Finnish retrospective study conducted between 2002 and 2007 which examined the outcome of schizophrenic patients, 1496 patients (57.8%) were rehospitalized because of a relapse of schizophrenia symptoms during a mean follow-up period of 2.0 years (5221 person-years) [29]. In bipolar patient, the psychiatric hospitalization rate varies from 10% to 67.9% [30] and is even higher at 79% 2 years after a first episode of psychotic major depression [31]. Very little is known about the impact of surgery in those patients. In a retrospective study of 144 patients with bipolar disorder undergoing bariatric surgery between 2006 and 2009, 13 patients (9%) required psychiatric hospitalization compared with 153 who did not undergo surgery (10.6%) [32].

Even if we observed cases of PR around acute rejection episodes, our study was not designed and empowered to analyze the implication of steroids or antirejection therapy, using pulse of methyl prednisolone at induction time, and the occurrence of PR. Two recent reviews concluded that a history of psychiatric illness does not predict a susceptibility to steroid-induced psychiatric symptoms [8,9]. In the general population, after organ transplantation, the risk of psychosis increases because of the high doses of immunosuppressive drugs used to prevent graft rejection [33]. Nevertheless, the increase in immunosuppressive therapy during an acute rejection, mimicking the postoperative situation, or the lower patient's adherence compliance with treatment during PR might explain the concomitant occurrence of acute rejection and PR. To seek more evidence on the susceptibility of having steroid-induced psychosis in patients with a history of psychiatric illness, we need to analyze the prevalence of psychosis after acute rejection treatment in the general kidney recipient population. The absence of matched nontransplanted patients is also a limitation of our study. The prevalence of PR in our cohort should be compared with its prevalence in psychiatric patients treated with dialysis.

Apart from the high prevalence of PR after transplant, we did not find any significant effect on both allograft and patient survival. PR after transplant should not be considered as having a negative impact on patient and allograft outcome and should not be considered as a valid reason to exclude such candidates from the programs at many heart, liver, and renal transplantation centers as has previously been the case for solid organ recipients [12,13,34,35].

Finally, we separately analyzed BD and psychotic disorder patients and several differences were observed. Psychotic patients were significantly younger at the time of transplant with a longer interval between dialysis and transplantation. A previous report has already underlined the influence of a history of psychotic disorder on transplant waiting time [36]. The psychotropic treatment was intensified for all psychotic patients and only for half of the BD patients. Multiple hospitalizations because of PR were more frequent in psychotic patients. Post-transplant management should include a closer and more frequent psychiatric follow-up visits in psychotic patients than in BD patients to evaluate their condition, and potentially prevent and diminish the prevalence of PR. Despite the poorer psychiatric prognosis in psychotic patients compared to with BD patients, both patient and allograft survival rates were similar in both groups.

Several conclusions can be drawn from our study. First, this first primary analysis of both graft loss and death rates in highly selected kidney recipients with BD or psychotic disorders demonstrate similar results to those observed in a matched control group. This strongly suggests that such recipients should not be excluded from transplant program because of their psychiatric condition. Next, we observed that the outcome of psychiatric disease seems significantly affected by the transplant procedure. Thus, we suggest (i) to include a pretransplant psychiatric evaluation, (ii) a close monitoring of psychotropic medications, in particular during the peri and early postoperative period. Clearly defining the best therapeutic option in patients having BD or psychotic disorders with ESRD is of importance. Further New randomized prospective studies aiming to compare patients' survival and psychiatric outcome in patients maintained on dialysis or transplanted are therefore necessary.

Authorship

TK: designed the study, collected data, wrote manuscript, performed statistical analysis. FP, NK, PM, HF, FM and CL: collected data, reviewed article. FC-P and EB: performed statistical analysis, reviewed article. VA and PL: designed the study, reviewed article. MM and PG: designed the study, wrote manuscript, performed statistical analysis.

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Conflict of interest

The authors declare no conflict of interests.

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