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Original article

Mental Disorders and their Relationship with Survival and Graft Rejection in Deceased Donor Kidney Transplant Recipients

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Abstract

Introduction: A significant association has been documented between the severity of depression and renal graft loss in post-transplant patients. ***Objective:*** To determine the relationship between mental disorders during the pre-transplant period and outcomes of graft rejection, graft loss, and mortality. ***Method:*** A retrospective cohort study was conducted on deceased donor kidney transplant recipients to assess whether mental disorders modify the risk of experiencing adverse outcomes during the post-transplant period. ***Results:*** Psychiatric comorbidity is associated with a longer duration of the pre-transplant evaluation protocol and time on the waiting list. Renal transplant candidates with psychiatric histories are more likely to experience renal graft loss compared to those without such histories. Recipients diagnosed with anxiety disorders during the pre-transplant protocol experience an increased risk of graft rejection during the post-transplantation period. ***Conclusion:*** Identifying and treating psychiatric disorders in renal transplant recipients could help reduce the likelihood of adverse outcomes during the post-transplant period. The study's main limitation is the lack of standardized instruments to identify psychiatric diagnoses during the pre-transplant evaluation protocol.

Keywords: ***Kidney transplant, psychosocial factors, depression, anxiety, graft rejection.***

Introduction

Renal transplantation (RT) is the treatment of choice for patients with end-stage renal disease (ESRD). It has been suggested that mental disorders are risk factors for morbidity and mortality in the post-transplant period. However, data in the literature is contradictory [1,2,7,8,14].

A significant association has been documented between the severity of depression and mortality, with a hazard risk (HR) of 1.03 (confidence interval (CI): 1.01-1.04) for each point increase in the depression severity score. In a univariate analysis, the depression severity score was related to mortality, with a RR of 1.02 (CI: 1.00-1.04) and an HR of 1.03 (CI: 1.01-1.05) for graft loss [12]. Additionally, in a multivariate analysis, an association between graft loss and depression with a HR of 1.03 (CI: 1.01-1.05) for each point of depression severity has been observed [12].

Zelle et al., in a cohort study, reported an increased risk of cardiovascular and all cause mortality in patients with depression, with an HR of 1.77 (CI: 1.01-3.10), p = 0.047. In the multivariate analysis, an association of depression with graft failure was seen when the model included (age, dialysis duration in months), but when it was adjusted for proteinuria and creatinine clearance, the relationship disappeared [16]. Likewise, in a study by Gumabay, the history of mental health was not associated with biopsy-proven acute rejection (HR 1.11, CI: 0.75-1.64), death-censored graft failure (HR 0.69, CI: 0.32-1.50) or total graft failure (HR 0.96, CI: 0.60-1.53) [4].

Given this background, we aimed to determine whether psychiatric history or diagnosed mental disorders during the period before transplantation could be a risk factor for outcomes such as survival, graft loss, and the first graft rejection event (confirmed by biopsy).

Materials and Methods

We designed a retrospective study at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). We reviewed the medical records of all recipients of a deceased donor kidney graft from January 2012 to December 2017. Patients over 18 years old, with any etiology of ESRD and a minimum one-year follow-up in

the post-transplantation period were included. Patients who had previously received a kidney transplant from a living donor or a second kidney transplant from a deceased donor were excluded. The study was approved by the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) ethics committee.

Variables included were sociodemographic factors (sex, age, education, marital status), clinical factors related to ESRD: etiology of renal failure, duration of the disease, type of renal replacement therapy, duration of renal replacement therapy, complications associated with renal replacement therapy, comorbidities, time in the pre-transplant protocol, time on waiting list, cold ischemia time, Kidney Donor Profile Index (DKPI) score, Panel Reactive Antibodies (PRA), and development of Donor-Specific Antibodies. Mental health variables such as history of mental disorders diagnosed during the pre-transplantation period were included. The study also recorded transplant-related variables, such as the number of hospitalizations, post-transplant infections, delayed graft function or graft failure, graft rejection, and patient and graft survival.

Frequencies and percentages were utilized for the statistical analysis of categorical variables. Continuous variables with a normal distribution were described using means and standard deviation (SD), while non-normally distributed variables were described using medians and interquartile ranges (IQR). Chi-square tests were employed to compare categorical variables between groups. The Mann-Whitney U test was used for variables with non-normal distribution. Actuarial analysis was performed as needed. Proportional hazard risk models explored univariate and multivariate correlations between exposure and outcome. A $p < 0.05$ was considered statistical significant. Statistical analysis employed SPSS version 25.

Results and Discussion

In all, 167 patients meet the inclusion criteria. Male (54.5%), with a mean age of 39 years (19-57). The mean follow-up time during the study was 5.6 years (IQR 4.1-7.1), and the mean post-transplant follow-up was 3.1 years (IQR 1.7-4.5).

Causes of ESRD included Cryptogenic (41.3%), Type 2 Diabetes (20%), Systemic Lupus Erythematosus (9.6%), Polycystic Kidney Disease (9%), Preeclampsia (5%), and other etiologies (14.4%). The mean duration in the transplant protocol was 13.4 months (IQR 8.8-20.5), and the mean wait time for transplantation was 11.5 months (IQR 6-19.5). 52% of patients had a psychiatric history, and 44% received a psychiatric diagnosis before transplantation. The "Personal history of noncompliance with medical treatment or regimen" diagnosis was found in 10% (n=17) of patients. Table 1 describes the psychiatric history and diagnoses of the sample. (place Table 1)

Patients with psychiatric histories had longer durations in the transplant protocol (14.8 vs. 11.9 months, p=0.04) and a higher prevalence of graft loss (11.5% vs. 2.5%, p=0.008)

No significant difference was found in comparing cumulative probabilities of the first graft rejection event for patients with and without psychiatric history. However, for graft loss, a statistically significant difference was observed at two years (17% vs. 4%), four years (29% vs. 4%), and six years (29% vs. 4%) between the two groups (p=.005). (place Figure 1)

Patients with psychiatric diagnoses during the transplant protocol took longer to complete the protocol for transplantation (14.3 vs. 11.6 months, p=.019), had a higher incidence of dialysis-related complications (71% vs. 56%, p=.041), and experienced delayed time for transplantation (13.6 vs. 9.5 months, p=.028).

No significant differences in mortality (n=5) were found during follow-up when comparing patients with psychiatric history or psychiatric diagnoses to those without these characteristics.

To determine risks associated with mental disorders, proportional hazard models were designed, incorporating previously described predictors and significant psychiatric variables related to outcomes. In univariate analysis, patients with active smoking during the transplant protocol had a higher probability of death during post-transplant follow-up, with an RR=14.90, 95% CI=1.15-192, p=0.03. (place Table 2)

The mean survival time for the active smoking group during the protocol was 4.3 ± 0.95 years (CI=2.4-6.1) vs. 6.5 ± 0.11 years (CI=6.3-6.7) for the non-smoking group. The difference between both survival functions was statistically significant with a $\chi^2(1, N=167)=6.32$, p=.012.

Patients with psychiatric history at the initial protocol assessment had a higher probability of graft loss than their counterparts, with an RR=5.77, 95% CI=1.23-27.05, p=0.02. (place Table 3)

In multivariate analysis, patients diagnosed with anxiety had a higher probability of experiencing a graft rejection event confirmed by biopsy, with an RR=4.49, 95% CI=0.97-20.8, p=0.05. The risk was adjusted for immune sensitization level (human leukocyte antigens antibodies), Kidney Donor Profile Index percentage, cold ischemia time, delayed graft function, de novo development of Donor-Specific Antibodies, smoking history, active smoking during the protocol, depression, and signs of non-adherence to medical treatment during the pre-transplantation period. (place Table 4)

The average time to experience the first rejection event for patients with any anxiety disorder during the protocol was 3.5 ± 1.17 years (CI=1.2-5.8) vs. 4.7 ± 0.23 years (CI=4.2-5.1) for patients without an anxiety disorder. No significant difference was found in the Log Rank test when comparing survival curves.

Table 1: Psychiatric history and diagnoses during the pre-transplantation period (N=167)

	Total (%)
History of Psychiatric Disorders	87(52.1)
Depressive Disorders	43(25.6)
Substance Use Disorders	35(21)
Harmful pattern of use of nicotine	27(16.1)
Nicotine dependence	5(3)
Harmful pattern of use of alcohol	5(3)
Alcohol dependence	4(2.4)
Harmful pattern of use of cannabis	2(1.2)
Adjustment disorders	12(7.1)
Personal history of noncompliance with medical treatment or regimen	10(6)
Delirium	6(3.6)
Anxiety or fear-related disorders	4(2.4)

Psychiatric diagnosis during pre-transplantation period	73(44)
Depressive Disorders	42(25)
Personal history of noncompliance with medical treatment or regimen	17(10)
Personality traits or coping style affecting disorders	9(5.4)
Problems related to primary support group, including family circumstances	7(4.2)
Anxiety or fear-related disorders	5(3)
Active smoking during the renal transplant protocol	5(3)
Harmful pattern of use of nicotine	4(2.4)
Nicotine dependence	1(0.6)
Adjustment disorders	4(2.4)

Table 2: Univariate analysis for risk of death

Predictors	**RR**	**CI 95%**	**P value**
Sex (man)	0.51	0.084-3.195	0.47
Age (≥70 years vs.<70 years)	4.40	0.45-42.78	0.20
Diabetes vs. Absence	2.73	0.53-13.86	0.22
Time in waiting list (months)	1.006	0.93-1.07	0.85
Active smoking during the renal transplant protocol vs. Absence	14.90	1.15-192	0.03*
* P ≤ 0.05			

Table 3: Univariate analysis for risk of graft loss

Predictors	HR	CI 95%	P value
Delayed graft function vs. Absence	0.72	0.15-3.38	0.68
At least one rejection event vs no event	0.84	0.26-2.71	0.78
Smoking history vs. Absence	0.83	0.17-3.93	0.82
Active smoking during protocol vs. Absence	4.01	0.53-29.90	0.17
Depressive Disorder during protocol vs. Absence	1.50	0.48-4.67	0.47
History of Psychiatric Disorders vs. Absence	5.77	1.23-27.05	0.02*
* P ≤ 0.05			

Table 4. Multivariate analysis for Graft Rejection

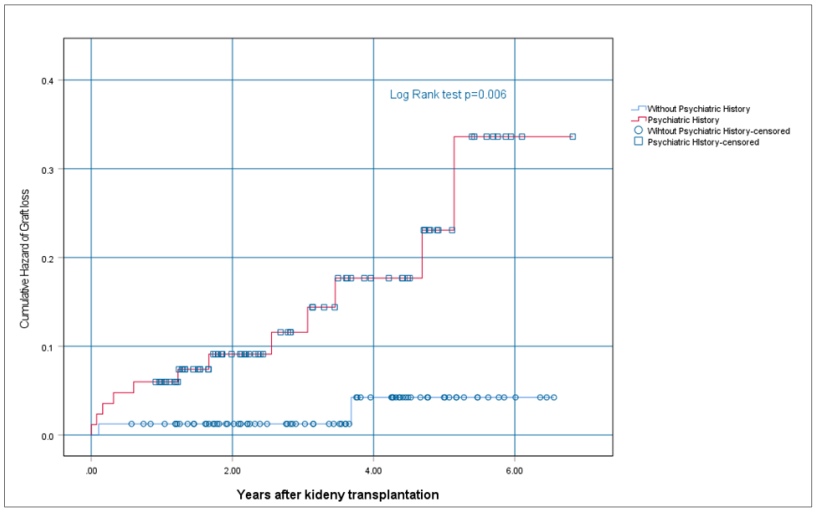
Model 1[a]	*B*	OR (IC 95%)	P value
Degree of immunological sensitization (≥30% vs <30%)	1.21	3.37 (1.2-8-9)	0.01**
KDPI (%)	-.020	0.98 (0.96-0.99)	0.01**
De novo development of Donor Specific Antibodies vs. Absence	0.76	2.13 (0.98-4.6)	0.05*
Model 2[b]	*B*	OR (IC 95%)	P value
Anxiety disorders during protocol vs. Absence	1.45	4.28 (0.95-19.3)	0.05*

KDPI=*Kidney Donor Profile Index*

[a]Adjusted for cold ischemia time (hours) and delayed renal injector function.

[b] Adjusted for variables from model 2 + history of tobacco use, active tobacco use during the protocol, depression and history of noncompliance with medical treatment

* P ≤ 0.05, **P ≤0.01



Number of patients in risk				
Without Psychiatric History.	**80**	**79**	**78**	**78**
With Psychiatric History	**86**	**79**	**76**	**74**

Figure 1: Cumulative Hazard for Graft loss during post-transplantation period in patients with and without Psychiatric History

Discussion

Patients in the deceased donor Renal Transplant protocol had a higher prevalence of psychiatric history than reported for the general population at any time in the National Psychiatric Epidemiology Survey in Mexico [9]. Similarly, this prevalence was higher than reported in other renal transplant cohorts and the one recorded in a previous study of renal transplant recipients [4].

The prevalence of depression and anxiety in TR recipients is higher during the first year after transplantation when compared to the general population [1]. However, the prevalence of depression and anxiety is similar in TR candidates and patients who have been transplanted (21% vs. 13.4% for depression and 21.6% vs. 25% for anxiety) [10].

Comparing the psychiatric history of patients, a higher prevalence of depressive disorders (25.6% vs. 4.8%) and substance use disorders (21% vs. 9.2%) was found compared to the general population in México. The prevalence of anxiety history in the general population is higher than in this cohort (14.3% vs. 7.1%) [3]. The prevalence of depression during the pre-transplant period is similar to that reported by other renal transplant cohorts (22%-31%) [12,16]. The prevalence of anxiety disorders was lower than reported in patients waiting for renal transplants in other studies (3% vs. 27%) [11].

Psychiatric comorbidity, both history and psychiatric diagnoses during the transplant protocol, were associated with a longer duration of the transplant protocol. Similarly, having a psychiatric diagnosis during the transplant protocol was associated with a longer waiting time for transplantation. This is relevant because mortality from cardiovascular causes increases during the time on the waiting list compared to those who receive a renal transplant [5].

We found that candidates for renal transplantation with a psychiatric history have a higher probability of experiencing renal graft loss during the post-transplant follow-up, unlike what was found in other studies where the probability was less than one for graft loss in patients with any psychiatric history. However, information on psychiatric histories and disorders was not corroborated by a mental health professional in that study [4].

In the multivariate analysis, the diagnosis of an anxiety disorder increased the probability of the first rejection event of the graft confirmed by biopsy. In a meta-analysis conducted by Dew and colleagues, no studies were found that described anxiety as a predictor of renal graft rejection [1]. The results of studies attempting to identify the relationship between anxiety disorders and poor adherence to treatment are contradictory [13]. However, a hypothesis that would explain the increased probability of graft rejection is that anxiety disorders interfere with adherence to immunosuppressive treatment during post-transplant follow-up [15].

Conclusions

We found that psychiatric comorbidity is associated with a longer duration of the transplant protocol and waiting time. Active smoking during the renal transplant protocol increases the probability of death after transplantation. It is not possible to conclude that psychiatric history is related to a higher probability of renal graft loss during follow-up, as previous evidence contradicts the findings of this study. More studies are needed to confirm that anxiety disorders increase the likelihood of graft rejection.

Identifying psychiatric disorders in recipients could help reduce the probability of negative outcomes after transplantation. Limitations of this study include the bias of recording psychiatric diagnoses, as standardized instruments for diagnostic screening were not used during the transplant protocol. The result of a neuropsychological evaluation of candidates was also unavailable, and other biochemical variables were not considered for multivariate analysis.

Ethics considerations

The protocol was approved by the Research Committee and the Research Ethics Committee at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Registration No. CIIBH: SME-2612-18-19-1).

List of abbreviations

INCMNSZ: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
RT: Renal Transplantation
ESRD: End-stage renal disease

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

MGA and JGS advised on the methodological design of the study, LMB supervised the statistical analysis, and HCR advised and supervised the writing of the manuscript. All authors read and approved the final manuscript.

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Supplementary Materials

Non

References

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