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Prevalence of renal pathological disorders in kidney transplant recipients: an observational study in the north of Iran

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ABSTRACT

Introduction: There are possible adverse effects and pathological disorders that can occur after kidney transplantation. The prevalence of these outcomes in kidney transplant patients is different worldwide.

Objectives: In this study, we decided to take a general look at the prevalence of pathological disorders in kidney transplant patients undergoing biopsy.

Patients and Methods: This cross-sectional study was conducted on 206 kidney transplant recipients who underwent biopsy of transplanted kidney at Razi medical education center in Rasht city between 2008 and 2019. Information was collected from medical records and interviewing patients. The data were analyzed using SPSS software version 26. They were summarized as the mean (SD) or as median (IQR). The frequency distribution (percentage) was conducted to describe the qualitative variables.

Results: Out of 206 patients, 143 (69.4%) were male and the mean age at transplantation was 46.7 ± 13.6 years. About 42.72% were non-relative donors, 47.57% were brain dead donors and 9.71% were family donors. The most common pathological disorder was nephrotoxic caused by calcineurin inhibitors (CNIs) (41.75%) and the most common type of graft rejection was antibody-dependent graft rejection (46.12%). In terms of transplant outcome, 35.92% of the patients suffered transplant rejection and 23.3% of them died. The results of this study did not show a significant relationship between the administration of immunosuppressive drugs and the pathological disorders.

Conclusion: The present study showed that the most common pathological disorder in kidney transplant patients was CNIs nephrotoxicity, and the most common type of transplant rejection was antibody-dependent transplant rejection.

Implication for health policy/practice/research/medical education:
In a cross-sectional study conducted on 206 kidney transplant patients undergoing biopsy, we found out that the most common pathological disorder in kidney transplant patients was calcineurin inhibitors (CNI) nephrotoxicity (41.75%), and the most common type of transplant rejection was antibody-dependent transplant rejection (46.12%). However, no significant relationship was found between the administration of immunosuppressive drugs and the pathological disorders.

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Introduction

Nowadays, chronic kidney disease (CKD) has been introduced as one of the most common chronic diseases and a global burden on the healthcare system (1). According to the definition of Kidney Disease Improving Global Outcomes (KDIGO), the presence of glomerular filtration rate (GFR) of less than 60 mL/min and albumin of more than 30 mg per a gram of creatinine along with abnormalities of kidney structure and function for more than three months indicates CKD (2,3). The global

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prevalence of this disease is estimated to be about 13.4% (4). End-stage renal disease (ESRD) is the last stage of CKD which is defined as a GFR of less than 15 mL/min (2,3). This disease is progressive and irreversible, in which the body has an inability to maintain the balance of fluids and electrolytes, leading to uremia and azotemia. These patients are unable to survive without alternative treatment. The worldwide prevalence of ESRD has reached over one million people. Diabetes mellitus, hypertension, vascular diseases, glomerular diseases (primary or secondary), cystic kidney disease, tubulointerstitial disease, obstruction or dysfunction of the urinary tract, recurrent kidney stones, congenital defects of the kidney or bladder, untreated acute renal failure, certain drugs including nonsteroidal anti-inflammatory drugs, calcineurin inhibitors (CNIs) and antiretroviral drugs are some of the causes of ESRD (5). Kidney transplant is the best alternative treatment in end stage kidney disease. This treatment method increases the quality of life along with life expectancy and reduces costs and risk of death compared to the dialysis method (6-9). The results of kidney transplantation are influenced by several factors, including age, gender, race of the donor, tissue compatibility, previous primary disease, the condition of the patient before transplantation, the skill level of the surgeon, the nature and extent of immunosuppressive treatment, and factors related to the donor such as cold ischemia (10, 11). Although kidney transplantation is the most cost-effective strategy for survival of patients with kidney failure, it is not without potential side effects. Vascular and urological complications, dysfunction of the transplanted kidney, and transplant rejection are some of the possible complications. Among these, transplant rejection is a big problem that always threatens kidney recipients (12,13). Therefore, to minimize these vital problems, the kidney recipient and donor should be thoroughly examined from an immunological point of view before the kidney transplant operation (14-16).

Post-transplant patients are under complex immunosuppressive regimens. Therefore, they are more vulnerable to infection, malignancy and cardiovascular diseases and need continuous follow-up. In addition, such patients have several problems in terms of underlying kidney disease or transplant outcomes. In general, patients after kidney transplantation are carefully monitored for allograft function, minimizing the risk of infection, malignancy, bone disease, cardiovascular disease, and diabetes (9,17,18). Monitoring allograft function usually includes serum creatinine and proteinuria. In most cases, when there is a sign of allograft dysfunction such as increased serum creatinine, decreased urinary output, or worsening proteinuria, a biopsy is taken from the transplanted kidney. However, in some centers, patients are subjected to periodical biopsies (protocol biopsy) according to the protocol, regardless of the presence of dysfunction (9,18). The causes of damage to the transplanted kidney are divided into different types, namely pre-renal, renal and post-renal, and the histopathological appearance of transplant rejection is divided into two general categories, transplant rejection caused by T cells and antibody-mediated transplant rejection. These classifications require taking a sample and performing pathology studies on them. The findings of pathology studies are divided into six general categories based on the Banff classification. These divisions include normal tissue, antibody-mediated rejection (ABMR), borderline changes, T cell-mediated rejection (TCMR), interstitial fibrosis and tubular atrophy, and other non-transplant rejection changes (19).

Objectives

The prevalence of causes of kidney transplant failure in patients is different worldwide. Furthermore, no study has been done on the prevalence of the mentioned pathology in Iran. Considering these facts, in this study, we decided to take a general look at the prevalence of pathological disorders in kidney transplant patients who underwent surgery at the kidney transplant center of Razi hospital in Rasht. The results of this study can be fundamental for more extensive multicenter studies with larger sample sizes and a basis for investigating the causes of the high prevalence of known pathologies.

Patients and Methods

Study design

This cross-sectional study was conducted on all kidney transplant recipients who underwent biopsy of transplanted kidney at Razi medical education center in Rasht city between 2008 and 2019. Patients who did not cooperate in giving a complete history were excluded. About 206 patients were categorized into groups including tubular atrophy, transplant glomerulopathy, acute antibody-mediated transplant rejection, chronic antibody-mediated transplant rejection, antibody-dependent transplant rejection, acute cellular transplant rejection, chronic cellular transplant rejection, CNI nephrotoxicity, polyomavirus-associated nephropathy (PVAN). Demographic information of patients including age, gender, place of residence, smoking, alcohol consumption, underlying disease, place of transplantation, type of donation, gender of the donor, time interval of the patient's death from the transplant (years), time interval of the first biopsy from the transplant (years), patient's medication regimen after the transplant, outcome Patient (death or survival), transplant outcome (rejection and non-rejection) were collected using the information in the medical record and interviewing the patients.

Statistical analysis

All data were analyzed using SPSS software version 26 (IBM SPSS Statistics for Windows, version 26, IBM Corp., Armonk, NY, USA). Continuous variables were

summarized as the mean ± standard deviation (SD) if normally distributed or otherwise as median and interquartile change (Q1-Q3). Frequency (percentage) is used to describe qualitative variables.

Results

The demographic and background characteristics of the 206 kidney transplant recipient patients and their donors who have undergone biopsy are shown in Table 1. There were 143 (69.4%) male patients, and the mean age at transplantation was 46.7 ± 13.6 years. The majority of donors were men (83%). One hundred and eight (52.4%) patients received the transplant from living, and 186 (90.3%) people were unrelated donors. Moreover, only three of the patients smoked and less than 1% consumed alcohol. The outcome of 48 (23.3%) patients was death and 74 transplanted kidneys were rejected. The median time for the first biopsy from the transplant was 2 (1-6) years. The data showed that, the most common underlying and transplant-related diseases in kidney transplant recipients who have undergone biopsy were hypertension (51.0%), diabetes (19.4%), and NODAT (new onset diabetes mellitus after transplantation) (17.5%), respectively.

Regarding the drugs used in kidney transplant recipients, corticosteroids (92.2%), mycophenolate mofetil (66.5%), CNIs (64.1%) and mammalian target of rapamycin (mTOR) (23.8%) were used respectively (Table 2).

Results showed that in the 206 patients, 29.1% suffered from 5-10% tubular atrophy, 18% from 10-15% tubular atrophy, 10.7% from 35-30% tubular atrophy and about 12.1% from more than 45% tubular atrophy. 33% of the samples had transplant-related glomerulopathy. Out of all the antibody-related transplant rejections (46.1%), about 23.8% of them were acute while 22.3% were chronic. Furthermore, 39.8% of the samples showed C4d nephrotoxicity and 41.8% showed drug-induced nephrotoxicity by CNIs. 20.9% of the cellular graft rejections were acute and 7.3% were chronic. PVAN occurred in 7.8% of the samples (Table 3).

Table 1. Demographic and clinical characteristics of patients (n = 206)

Recipient factors	No. (%)
Age (years)[a]	46.7±13.6
Gender (male)	143 (69.4)
Smoking (yes)	3 (1.5)
Alcohol (yes)	2 (1.0)
Donor factors	
Gender (male)	171 (83.0)
Transplantation factors	
Donor (living)	108 (52.4)
Donor (unrelated)	186 (90.3)
First biopsy from the transplant[b]	2 (1-6)
Patient (death)	48 (23.3)
Transplant outcome (rejected)	74 (35.9)
Underlying and transplant-related diseases	
Hypertension (yes)	105 (51.0)
Diabetes (yes)	40 (19.4)
NODAT (yes)	36(17.5)
Kidney stone (yes)	17 (8.3)
Polycystic kidney (yes)	4 (1.9)

NODAT, New onset diabetes mellitus after transplantation.
[a] Mean ± SD; [b] Median (IQR).

Discussion

Kidney transplantation is one of the advanced treatments in end stage renal disease worldwide. Various causes such as nephropathy, diabetes and glomerulonephritis can lead to ESRD. Dialysis is a temporary treatment for the patient, but for long-term treatment, kidney transplantation has been used as a favorable approach in the last few decades.

In this study, the biopsy results of 206 patients undergoing kidney transplantation in Rasht from 2008 to 2019 were used. Pathological disorders of transplanted kidney were investigated by using kidney biopsy.

Studies have been conducted on the relationship between the age of kidney transplant recipients and

Table 2. Drugs used in kidney transplant recipients (n = 206)

Drugs	No. (%)
Corticosteroids (yes)	190 (92.2)
Mycophenolate mofetil (yes)	137 (66.5)
CNIs (yes)	132 (64.1)
mTOR (yes)	49 (23.8)

mTOR; mammalian target of rapamycin; CNIs, calcineurin inhibitors.

Table 3. Pathological disorders of kidney biopsy in patients (n = 206)

Pathological disorders	No. (%)
Tubular atrophy	
5%-10%	60 (29.1)
10%-15%	37 (18.0)
15%-20%	13 (6.3)
20%-25%	9 (4.4)
25%-30%	18 (8.7)
30%-35%	22 (10.7)
35%-40%	7 (3.4)
40%-45%	15 (7.3)
>45%	25 (12.1)
Transplant-related glomerulopathy (yes)	68 (33.0)
Antibody-related transplant rejections (yes)	95 (46.1)
C4d nephrotoxicity (Positive ABMR)	82 (39.8)
CNIs nephrotoxicity (yes)	86 (41.8)
Acute cellular graft rejections (yes)	43 (20.9)
Chronic cellular graft rejections (yes)	15 (7.3)
PVAN (yes)	16 (7.8)

AMBR, antibody-mediated rejection; PVAN, polyomavirus-associated nephropathy.

donors. Matching the age of kidney transplant recipients and donors is important in terms of clinical and transplant outcomes. The effect of recipient age on kidney transplant outcomes is still under discussion. In our study, the average age of transplant recipients was 46.7±13.6 years and most of the samples were men. 54.37% of transplanted kidneys were from living donors whereas 45.63% of them were from brain dead donors. Additionally, the results of the present study showed that there was no significant relationship between the age groups of transplant recipients and any of the transplant rejection types. In Bashir et al.'s study, the average age of the transplant recipients was about 10 years lower than our study. Furthermore, most of the transplant recipients were male, and all the transplanted kidneys were received from living donors, which was different from the present study (20). In Kuma's study, the average age was about 42 years, and female recipients were more than males (21). In the study by Alkindi et al, the average age of the recipients was about 44 years, most of the transplant recipients were men, and more than 70% of the transplanted kidneys were received from non-living donors (22). In some other studies, the average age of transplant recipients was lower than the average age of our study (23,24). Moreover, Castro Filho et al study showed a significant relationship between recipient's age and acute transplant rejection, which was not consistent with our study (25). Whereas, Özkul et al did not find a significant relationship between age groups of older and younger than 65 years and the rate of graft survival. This result was consistent with the results of our study, with the difference that in the study we conducted, the age of recipients was classified and compared in younger age groups (26).

In the present study, the most frequently used drugs in the transplant recipients included corticosteroids, mycophenolate, CNIs, and mTOR respectively. The study by Ali et al is similar to our results in terms of drug regimen. Around 98% of patients were treated with corticosteroids, and after that, the most frequently used drugs were mycophenolate and CNIs. However, none of the patients were treated with mTOR (24).

In terms of transplant outcome, our study showed that about 36% of cases suffered transplant rejection, and the survival rate of these patients was reported to be about 70%. In a study conducted by Angel-Korman et al, results reported that the one, three, and five-year graft survival rate were 94%, 89%, and 81%, respectively (27). In another study, conducted by Özkul et al, 94.7% of graft survival rate was reported in patients younger than 60 years old and those older than 60 years had graft survival rate of 92.5% (26).

The most frequent pathological disorders in our study were CNI nephrotoxicity, C4d nephrotoxicity, transplant glomerulopathy, 5-10% tubular atrophy and PVAN. In the study by Piñeiro et al, the most common type of graft rejection was acute graft rejection which was not consistent with our study (28). However, results of a study conducted by Parajuli et al showed that the highest frequency of pathological disorders in the biopsy of transplant recipients were interstitial fibrosis and tubular atrophy, acute graft rejection, and glomerulopathy caused by transplantation. Furthermore, most graft rejections occurred within two years after transplantation (29). Özkul et al showed, acute antibody-mediated transplant rejection, chronic antibody-mediated transplant rejection, and CNI nephrotoxicity were the most common causes of transplant rejection, respectively (26). The findings from both of these studied were consistent with ours. The results of the study by Shimizu, who analyzed the clinical and pathological borderline changes after kidney transplantation, showed a total graft rejection rate of 30%, antibody-mediated graft rejection of 20%, cell-mediated graft rejection of 5%, and chronic antibody-mediated graft rejection of 5%. The results of this study are not completely comparable with the present study considering that borderline changes were examined in Shimizu's study. However, in some types of graft rejection, such as chronic cellular graft rejection and acute antibody-mediated graft rejection, the results were close to our study (30). The most common pathological disorder in patients studied by Castro Filho et al, was acute tubular necrosis, and most of the transplant rejections were of the acute cellular type. This study was close to our study in terms of acute cellular transplant rejection, with the difference that the population of this study were patients with delayed graft function (25).

In general, the incidence of transplant glomerulopathy is increasing and occurs in approximately 20 cases up to 5 years after transplantation. Transplant-related glomerulonephritis is rarely diagnosed clinically in the first year of transplantation. Graft-related glomerulonephritis is related to graft survival. Therefore, early diagnosis of transplant glomerulopathy and tubular atrophy through biopsy and its treatment can help transplant survival (29).

There was a difference in the frequency of different types of pathologies as well as types of graft rejection in different studies. This can be due to biopsy samples being taken at different time frames. Moreover, the characteristics of each patient in terms of race, underlying diseases and usage of different types of drugs along with genetic and environmental factors can play a role in this finding.

The results of the present study showed that the most common pathological disorder in kidney transplant patients undergoing kidney biopsy was CNI nephrotoxicity, and the most common type of transplant rejection was antibody-mediated transplant rejection. Choosing appropriate and low-risk drug regimens, as well as precise dosage adjustment of immune-suppressing drugs, is very important in reducing pathological disorders. Therefore, the need to perform periodic biopsies based on standard protocols can help reduce the incidence of pathological disorders and transplant rejection.

Limitations of the study

Due to the retrospective nature of the study and the deficiencies in the medical records of the patients, it was not possible to collect more comprehensive information. Another limitation was the small sample size of our study. Moreover, it was not possible to investigate different types of polyomavirus due to technical limitations. Since information of transplant organ donors is usually unavailable, examining and comparing the genetic characteristics and other related characteristics of donors and recipients with various pathological disorders were impossible.

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Authors' contribution

Conceptualization: ER, RGH and AM.
Methodology: ER, RGH and EKL.
Validation: ER and RGH.
Formal analysis: EKL and TY.
Investigation: ER, RGH and MKH.
Resources: ER and RGH.
Data curation: RGH and TY.
Writing–original draft preparation: ER, RGH and TY.
Writing–review and editing: ER, RGH, AM, TY and MKH.
Visualization: EKL.
Supervision: ER.
Project administration: ER.

Conflicts of interest

Authors have no conflicts of interest to declare.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study was approved by the Guilan University of Medical Sciences Ethics Committee (# IR.GUMS.REC.1400.246). Informed consent was obtained from patients. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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