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Long-term complications in kidney transplantation -- 14 years of experience

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MAIN POINTS

- Cholelithiasis is one of the most frequent gastroenterological problems in society. Post-transplant cholelithiasis was encountered in 34% of the patients in our study.
- The post-transplant CMV rate was the highest in the first year, while that of BKV was significant in the first two years. Post-transplant opportunistic fungal infections, mucor, less frequently encountered in the literature, developed in 2 patients.
- NODAT incidence, particularly after renal transplantation, was determined to be between 7 and 30%. However, during long-term renal transplantation follow-up, the incidence of NODAT was 4–25%.

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ABSTRACT

Aim: The increase in the number of kidney transplants and prolonged survival following kidney transplantation has increased the risk of posttransplant complications. The present study aims to investigate complications in kidney transplant recipients (eg, cardiac, hepatobiliary, opportunistic infections, avascular necrosis, NODAT) in our institution.

Materials and Methods: A total of 300 patients who underwent renal transplantation in our institution have been evaluated in this retrospective analysis. The sociodemographic properties of age, sex, graft type, need for pre-transplant dialysis, and KFRT etiologies were obtained from hospital records. Avascular necrosis, malignancy, heart failure, or development of coronary arterial disorder, NODAT, opportunistic infections, and hepatobiliary complications have been evaluated.

Results: The NODAT incidence in renal transplant patients was 17.5% in the case of living donor renal transplants versus 28.6% in cadaveric renal transplants (p=0.07). Again, 34% of the patients had hepatobiliary disorders such as cholelithiasis in the follow-ups, which was significantly higher in patients who received cadaveric transplants (p=0.009). Cytomegalovirus infection was observed in 50 patients, and BK virus infection in 36 patients. The rate of CMV infection was significantly higher in the first year after kidney transplantation. BK virus infections were found to be considerably higher in the first two years (p<0.05).

Conclusion: This study evaluated the risk factors and incidence of complications in renal transplant recipients. Our results regarding the incidence and or cholelithiasis and risk factors related to this condition are novel. We also emphasized the importance of hepatobiliary complications in this patient group.

Keywords: Renal transplant, Cholelithiasis, Opportunistic infection, New-onset diabetes after transplantation

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INTRODUCTION

Renal transplantation is the gold standard treatment option for chronic renal failure. Kidney failure replacement therapy (KFRT) has found worldwide acceptance since 1954 [1, 2]. In time, the public awareness of the topic increased, and the donor acceptance criteria were extended [3]. Currently, immunosuppressive treatments have been considered [4]. These developments caused a gradual increase in the number of renal transplants [2, 5]. Chronic rejection represents the most significant factor contributing to long-term graft function loss [6, 7]. However, rejection rates vary from center to center. The best strategy to diagnose and treat complications such as rejections is to form a follow-up strategy [5].

Previous studies on complications of transplantation showed that avascular necrosis, malignancy, cardiac pathologies, diabetes (NODAT – new-onset diabetes after transplantation), and opportunistic infections were the most common ones following renal transplants [8 – 11]. Hepatobiliary complications are uncommon following renal transplantation. Notably, Turkey experienced one of the highest increases in an-

nual renal transplant numbers worldwide from 2003 to 2013, ranking among the top 10 countries [12]. The increase in the annual number of renal transplantations and the prolonged graft and patient survival following renal transplants resulted in a higher incidence of complications that are observed.

The present study aims to investigate the incidence and risk factors related to complications following renal transplantation, including cardiac, hepatobiliary, opportunistic infections, avascular necrosis, NODAT in our institution.

MATERIALS AND METHODS

Study design

A total of 300 patients who underwent renal transplantation in Nephrology Clinics of Turgut Özal Medical Medical Center were analyzed retrospectively for the present study. In total, 632 patients were admitted to Turgut Özal Medical Centre Nephrology outpatient clinic for evaluation. Non-probability selection was used for patient allocation to the study. Those who did not meet the inclusion criteria were excluded from the study. Patients ≥18 years of age who received renal transplants and who were followed for at least three months with functional grafts between January 2007 and January 2021 were included in the analysis. Pregnant patients, patients aged <18 years, and patients who were followed up for less than 3 months were excluded from the study. In addition, patients who had insufficient data were also excluded from our study.

A total of 300 patients were enrolled in this study. All procedures were conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), aligning with the Helsinki Declaration of 1975, as revised in 2008. The study received approval from the institutional review board for ethical and scientific conduct (Date: May 4, 2021; Approval No: 2021/2055).

Study parameters

Sociodemographic and clinical data, including age, sex, graft type, pre-transplant dialysis status, and kidney failure with renal replacement therapy (KFRT) etiologies, were obtained from hospital records. The study evaluated the incidence of avascular necrosis, malignancy, cardiac deficiency, coronary artery disorder, new-onset diabetes after transplant (NODAT), opportunistic infections, and hepatobiliary complications.

The primary outcome was the frequency of hepatobiliary complications. Secondary outcomes included rates of opportunistic infections, cardiac complications, diabetes, avascular necrosis, and malignancies.

Statistical analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (SPSS Inc., Chicago, IL, USA). Number (n) and percentage (%) were given for descriptive data. Mean, median, standard deviation, and min-max values were given for continuous variables. Statistical tests and assumptions for hypothesis testing are the Pearson Chi-Square Test and the Fisher Exact test for categorical data. The distribution between the functional graft and KFRT periods was evaluated using the Kolmogorov–Smirnov test. Any p-value less than 0.05 was considered as statistically significant.

RESULTS

All renal transplant patients included in this study were evaluated for complications. The NODAT incidence was 17.5% after living donor renal transplants, whereas it was 28.6% following cadaveric transplants (p=0.07) (Table 1). Thirty-four percent of the patients had biliary or liver disorders such as cholelithiasis.

The incidence of hepatobiliary complications was significantly higher in the transplants from cadavers type (p=0.009) (Table 1). The ages of patients who developed cholelithiasis were assessed. Remarkably, the association between the age at the time of transplantation and cholelithiasis development was observed. Younger patients developed cholelithiasis more frequently; however, this difference was not statistically significant (p=0.034) (Table 2).

The incidence of cardiovascular disease was reported to be high in the post-transplant surveys [10]. In our study, we determined the incidence of cardiovascular disease in our cohort to be 7.3%. The incidence of cardiovascular diseases in living and deceased donor transplants was 7.5% and 6.1% in the cadaveric transplants (p=0.50) (Table 1).

The incidence of avascular necrosis in our patient cohort was 7.2%, and there was no significant difference according to the graft type (p=0.54) (Table 1).

Our long-term follow-up showed that hematologic and solid organ malignancies developed in 4% of our patients who received living donor renal transplants. No significant difference was observed according to the graft type (p=0.65) (Table 1).

Cytomegalovirus (CMV) infection was the most common opportunistic infection, affecting 50 patients. BK virus was the second most common cause of opportunistic infection in 36 patients. We found that CMV infection was significantly more prevalent in the first year after renal transplantation, while BK virus infection was considerably more common in the first two years (p=0.001) (Table 3). In addition, two patients developed Mucor mycosis, an opportunistic fungal infection sometimes seen after transplantation.

Our surveys after renal transplants showed that urological disorders, such as ureteral obstruction or pyelonephritis, occurred in 38.2% of patients. Interestingly, there was no statistically significant difference in these urological problems based on the type of graft received (p=0.57) (Table 2).

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Table 1. Comparison of non-urological complications developing after transplantation in kidney transplant patients by graft type.

	Total N(%)	Alive Donor* N(%)	Cadaver N(%)	p
Diabetes				
Yes	51(19.5)	37(17.5)	14(28.6)	0.07***
No	210(80.5	175 (82.5)	35(71.4)	
Malignity				
Yes	11(4.2)	9(4.3)	2(4.1)	0.65**
No	249(95.8)	202 (95.7)	47(95.9)	
Cholelithiasis				
Yes	34(13.2)	22(10.5)	12(24.5)	0.009**
No	224(86.8)	187(89.5)	37(75.5)	
Avascular Necrosis				
Yes	18(7.2)	16(7.5)	2(4.1)	0.54**
No	243(92.8)	196(92.5)	47(95.9)	
Coronary Artery / Cardiac Disorder				
Yes	19(7.3)	16(7.5)	3(6.1)	0.50**
No	242(92.7)	196(92.5)	46(93.9)	

**Related and non-related **Fisher Exact Test ***Pearson Chi Square*

Table 2. The relation between cholelithiasis development and transplantation age in the patients receiving renal transplants.

	Patients With Developing Cholelithiasis N	%	p
Sex			
Female	14	14.9	0.598*
Male	21	12.6	
Age Group			
18-30	15	18.5	0.175*
31-44	8	9.9	
>45	8	10.7	
Graft			
Cadever	12	24.5	0.027*
Alive non relative	21	11.0	
Alive relative	1	5.6	
Survey Period			
0-1 year	1	3.7	0.005**
0-2 years	2	5.7	
0-3 years	6	25.0	
0-5years	4	8.7	
5-10years	16	26.2	
10-20years	6	11.8	
HbsAg			
Negative	28	11.4	0.003**
Positive	7	41.2	

**Fisher Exact Test **Pearson Chi Square*

DISCUSSION

Renal transplantation commenced globally in 1954 [1]. Following transplantation, acute rejection Renal transplantation commenced globally in 1954 [1]. Following transplantation, acute rejections posed a considerable challenge; however, advancements in immunosuppressive agents significantly elevated first-year patient survival rates [8]. Concomitant with improved survival, the adverse effects of these new immunosuppressants became more frequently observed, with patient mortality often attributable to malignancy, cardiac pathologies, and opportunistic infections [13]. Despite numerous publications in the existing literature addressing various post-transplant complications, there is a notable paucity of data concerning the development, incidence, or risk factors associated with cholelithiasis.s caused a considerable challenge; however, advancements in immunosuppressive agents significantly elevated first-year patient survival rates [8]. The prolonged survival of the patients resulted in observation of adverse effects of these new immunosuppressants, with patient mortality often attributable to de novo malignancies in the post-transplant period, cardiac pathologies, and opportunistic infections [13]. Despite numerous publications in the existing literature addressing various post-transplant complications, there is a notable paucity of data concerning the development, incidence, or risk factors associated with cholelithiasis.

Cholelithiasis represents a prevalent gastroenterological issue within the general population, with an estimated incidence between 10% and 15%. Prophylactic cholecystectomy is a consideration for patients with solid organ transplants, thalassemia, or diabetes [14]. Despite its frequency, research specifically addressing the development of post-transplant cholelithiasis is notably absent from published literature. Furthermore, studies on cholelithiasis, particularly prior to renal transplantation, are quite limited, with one report indicating an incidence of 18.69% [15]. Within our cohort, post-transplant cholelithiasis occurred in 34% of patients. Of

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Table 3. Comparison of several variables with regard to survey period in the renal transplant patients.

Survey Period	CMV				BK				Posttransplant urological complication status			
	Yes		No		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	N	%	N	%
0-1 year	14	56.0	11	44	5	20.0	20	80.0	12	44.4	15	55.6
0-2 years	11	31.4	24	68.6	11	31.4	24	68.6	14	40.0	21	60.0
0-3 years	7	29.2	17	70.8	3	12.5	21	87.5	8	33.3	16	66.7
0-5years	8	18.2	36	81.8	5	11.4	39	88.6	17	37.0	29	63.0
5-10years	4	6.6	57	93.4	7	11.5	54	88.5	23	37.7	38	62.3
10-20years	5	9.8	46	90.2	4	7.8	47	92.2	17	32.7	35	67.3
Irregular follow-up	1	5.9	16	94.1	1	14.0	16	86.0	11	50.0	11	50.0
Total N(%)**	**257 (100)**				**257 (100)**				**267 (100)**			
p	**0.001***				**0.08***				**0.84***			

**Pearson Chi-Square Test, CMV: Sitomegalo Virus, BK:Human Poliomma Virus.*

these, 40% were female, and 20% had co-morbid diabetes. Although not statistically significant, a trend towards higher transplantation age was observed in younger individuals. Further investigations are warranted to elucidate the mechanisms contributing to these hepatobiliary disorders, with potential factors including diabetes, gallbladder dysmotility, or ciclosporin.

NODAT represents a frequent and significant complication following renal transplantation, associated with increased morbidity and mortality [16]. The reported first-year incidence of NODAT post-transplant ranges from 7% to 30% [11], whereas long-term renal transplantation follow-up studies indicate an incidence between 4% and 25% [17]. In our investigation, which included follow-up periods of up to 20 years, the NODAT development rate was 17.5% in living donor recipients and 28.6% in deceased donor recipients, consistent with existing literature. Established risk factors for NODAT encompass male sex, advanced age, deceased donor renal transplant, a history of acute rejection, polycystic kidney disease, the use of certain immunosuppressive agents, hepatitis C, and cytomegalovirus (CMV) infection [18]. Similarly, in our study, NODAT was encountered more frequently among individuals with polycystic kidney disease or a history of acute rejection. Conversely, no significant difference in NODAT development was observed according to gender. After a kidney transplant, heart-related problems are the top cause of death [10]. Interestingly, if heart issues are controlled when a patient is on renal replacement treatment for kidney failure, their survival improves [19]. Studies have shown that about 15% of transplant patients develop coronary artery disease and heart failure, with new cases appearing at a rate of 7% over four years [19, 20]. Our study's findings are right in line with this, showing a 7.3% rate of these heart conditions. Another concern is avascular necrosis, a bone complication after transplant, largely caused by corticosteroids. Before today's advanced immunosuppressants, this problem affected as many as a third of patients. Now, thanks to current treatments, that number has dropped significantly to just 4–7% [9, 21].

Considering risk factors for avascular necrosis in both the general population and renal transplant recipients, alcohol consumption, steroid use, dyslipidemia, and secondary hyperparathyroidism are significant contributors. Specifically, corticosteroids used in post-transplant immunosuppressive treatment and those administered for acute rejection are known risk factors for necrosis development [9, 21]. In our hospital, we use anti-thymocyte globulin (ATG) for induction therapy, followed by a maintenance regimen of oral prednisone, mycophenolate mofetil, and tacrolimus. Our data shows that avascular necrosis developed in 7.2% of patients, with a higher incidence observed in recipients of living donor transplants. Although not statistically significant, 15.8% of patients in the necrosis group experienced rejection after transplantation.

Opportunistic infections are also crucial for patient survival after transplantation. Both CMV (Cytomegalovirus) and BK viruses can replicate in kidney tissue, potentially leading to acute allograft rejection [22]. While the incidence of post-transplant CMV infection ranges from 8% to 32%, BK virus rates are reported between 1% and 10% [23, 24]. In our study, post-transplant CMV infection was most frequent in the first year, whereas BK virus infection was particularly significant within the first two years. Mucor mycosis, an opportunistic fungal infection less commonly reported in literature, developed in two of our patients.

Our study evaluates complications and their risk factors in renal transplantation patients during long-term follow-up. We reviewed various complications that may arise post-transplant. Notably, data on hepatobiliary complications in the literature are very limited, making our study unique in its detailed analysis of cholelithiasis. Furthermore, we assessed NODAT and opportunistic infections, examining their associated risk factors. This study thus provides valuable regional data on these aspects.

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CONCLUSION

Comprehensive studies on long-term renal transplant complications in Turkey are scarce. Our study addresses this gap by detailing complication rates and comprehensively compiling their risk factors. It is particularly original in providing data on post-transplant cholelithiasis development and incidence, in addition to highlighting other hepatobiliary complications.

Abbreviations

ATG : Antithymoctye globulin

BKV : Human polyomavirus 1

CMV : Cytomegalovirus

KFRT : Kidney failure replacement therapy

NODAT : New onset diabetes after transplantation

RRT : Renal replacement treatment

SPSS : Statistical Package for the Social Sciences

Ethics Committee Approval: This study was conducted in accordance with the ethical standards of our local and national committees on human experimentation and the 2008 revision of the Helsinki Declaration of 1975. Ethics committee approval was secured from our institution prior to commencing the research (Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee, Date: May 4, 2021; Approval No: 2021/2055).

Informed Consent: Given the retrospective nature of the study, informed consent was not required from individual participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no competing interests.

Data Availability: This original research article does not include any personal or patient data.

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