doi: 10.30934/kusbed.456136 **e-ISSN:** 2149-8571

Kocaeli Üniversitesi Sağlık Bilimleri Dergisi

Özgün Araştırma / Original Article

http://dergipark.gov.tr/kusbed

EVALUATING EMERGENCY DEPARTMENT ADMISSIONS AMONG RENAL TRANSPLANT RECIPIENTS: ONE CENTER EXPERIENCE

ACİLE BAŞVURAN BÖBREK NAKİLLİ HASTALARIN DEĞERLENDİRİLMESİ: TEK MERKEZ DENEYİMİ

Mahmoud El Sawan[1], Serkan Feyyaz Yalın[2*]

[1]Yeni Yüzyıl Üniversitesi, Gaziosmanpaşa Hastanesi, İstanbul, Türkiye
[2]İstanbul Üniversitesi Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, İstanbul, Türkiye

ORCID iD: Mahmoud El Sawan: 0000-0001-5093-2680; Serkan Feyyaz Yalın: 0000-0002-8146-6966

***Sorumlu Yazar / Corresponding Author:** Serkan Feyyaz Yalın, **e-mail / e-posta:** serkanfyalin@yahoo.com

Geliş Tarihi / Received: 03.09.2018 **Kabul Tarihi / Accepted:** 04.11.2018 **Yayım Tarihi / Published:** 01.01.2019

Abstract

Objective: Renal Replacement therapy for end stage renal disease (ESRD) patients includes transplantation and dialysis. Kidney transplantation is the treatment of choice for ESRD. However, transplant patients are susceptible to infection and cardiovascular disease due to immunosuppressive regimens and existing multiple comorbidities. In this retrospective study, we aimed to investigate the demographic characteristics, clinical manifestations, laboratory findings and outcomes of transplant patients who were admitted to the emergency department.
Methods: Transplant patients who were subsequently admitted to the emergency department were retrospectively evaluated. The patients' demographic, clinical and laboratory findings, symptoms, diagnoses, duration of hospitalization and outcomes were obtained from medical records. Transplant patients with previous hospital protocol numbers of each patient were enrolled into study as control group.
Results: 208 patients were enrolled into study. More than half of the patients in each group were young women with live kidney donors. The mean (±SD) age of the patients was 39.4±13.2. Chronic glomerulonephritis was the leading etiology of kidney failure among both groups in those where the etiology was identified. The most common symptoms were fever and dysuria. Urinary tract infection was the most frequently diagnosed complication. Mean (±SD) duration of hospitalization was 11.7±9.2 day. Kidney function worsened in 35 patients (16%) and hemodialysis was initiated in 15 of them. Five patients (2.2%) died (sepsis in three, encephalitis in 2).
Conclusion: Physicians should have a high index of suspicion for infection during evaluation of organ transplant recipients in the emergency department.

Keywords: *Chronic kidney disease, renal transplantation, immunosuppression*

Öz

Amaç: Son dönem böbrek yetmezlikli hastalarda böbrek nakli ve diyaliz tedavi seçenekleridir. Böbrek nakli, bu hastalar için en iyi tedavi seçeneğidir. Fakat immunsüpresif rejimler ve ek hastalıklar nedeniyle böbrek nakilli hastalar enfeksiyon ve kardiyovasküler hastalıklara duyarlı hale gelirler. Bu retrospektif çalışmada, acile başvuran böbrek nakilli hastaların demografik yapıları, klinik bulguları, laboratuar bulguları ve hasta sonuçları incelenmiştir.
Yöntem: Acile başvurmuş olup, hastanemizde böbrek nakli yapılan hastaların demografik yapıları, klinik bulguları, laboratuar bulguları, tanıları, hastanede kalış süreleri ve hasta sonuçları tıbbi kayıtlardan incelenmiştir. Bu hastalardan bir önceki hastane protokol numarasına sahip böbrek nakil hastaları ise kontrol grubu olarak alınmıştır.
Bulgular: Çalışmaya 218 hasta dahil edildi. Hastalar genel olarak canlı böbrek vericisi olan genç kadın bireylerdi. Hastaların ortalama yaşları 39,4±13,2 idi. Nedeni bilinmeyen böbrek yetmezliğini dışladıktan sonra kronik glomerulonefrit her iki grupta da en sık böbrek yetmezliği nedeniydi. En sık saptanan semptomlar ateş ve idrar yaparken yanma idi. İdrar yolu enfeksiyonu en sık konulan tanıydı. Hastaların ortalama yatış süresi 11,7±9,2 gündü. Takipler sırasında 35 hastanın (%16) böbrek fonksiyonu bozuldu ve 15 hastaya hemodiyaliz tedavisi başlandı. Hastaların 5'i (%2,2) (üçü sepsis, ikisi ensefalit nedeniyle) ise kaybedildi.
Sonuç: Acil serviste çalışan klinisyenler organ nakilli hasta başvuralarında enfeksiyonlar açısından çok dikkatli olmalıdır.

Anahtar Kelimeler: *Kronik böbrek hastalığı, böbrek nakli, immünsüpresyon*

Atıf Gösterimi/How to Cite: El Sawan M, Yalın SF. Evaluating Emergency Department Admissions Among Renal Transplant Recipients: One Center Experience. *Kocaeli Üniversitesi Sağlık Bilimleri Dergisi*, 2019;5(1):20-24. doi: 10.30934/kusbed.456136

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Introduction

Chronic kidney disease, which is the progressive loss of nephrons over a period of months or years, may progress to end stage renal disease (ESRD). Renal Replacement therapy for ESRD patients includes transplantation, hemodialysis and peritoneal dialysis. In general, renal transplantation reduces the mortality and morbidity risk for most patients when compared with maintenance dialysis. Moreover, renal transplantation provides better long term outcomes than other modalities.[1] Therefore, kidney transplantation is the treatment of choice for ESRD.[2]

Transplant patients are susceptible to infection, cardiovascular disease and malignancy due to immunosuppressive therapy and pre-existing multiple comorbidities such as diabetes mellitus, coronary artery disease and vesicoureteral reflux. Thus, patients require close follow up after transplantation.

Infections are one of the leading causes of death following renal transplantation with cardiovascular diseases.[3,4] Transplant patients are prone to both common (upper respiratory infections, urinary tract infections) and opportunistic infections [cytomegalovirus (CMV), polyomavirus (BK virus), *Pneumocystis jirovecii* (PJP), Epstein-Barr virus (EBV), Hepatitis B and C viruses, herpes viruses, *Aspergillus fumigatus* and *Mycobacterium tuberculosis* (TB)]. The degree of immunosuppression of the recipient is the major reason for infection susceptibility after transplantation.

Infections mostly occur between the first and third months following transplant because the immunosuppression dose is at its maximum due to induction therapy in that period.[5] However, the risk of infection persists throughout life due to long term immunosuppressive medications.

Post-transplant infections can be divided into three periods[6,7]:

1- The early period (first month): Infectious complications of surgery and/or hospitalization (wound complications, catheter-related infections, urinary tract infections, nosocomial pneumonia) and pre-existing infection from either the donor or recipient (Hepatitis B and C viruses, TB, HIV, meningococcus, bacteremia at the time of donation). The effects of immunosuppresive drugs are not yet evident.

2- The intervening period (one to six months): The effect of immunosuppression is usually at a peak during this period. Therefore, patients are at greatest risk for opportunistic infections (PJP, BK virus, CMV, EBV, other herpes viruses,) and common infections.

3- More than six months: Community-acquired infections such as pneumonias and urinary tract infections are common in this period.

Urinary Tract Infections

Urinary tract infections (UTI) are the most common bacterial infections in the renal transplant recipient.[8-11] UTI may lead to acute T cell-mediated rejection, impaired allograft function, allograft loss and death via severe and/or recurrent sepsis.[9,11-14] The most common risk factors for UTI were: female sex, vesicoureteral reflux, advanced age, prolonged urethral catheterization, cadaveric kidney transplant, delayed graft function, history of polycystic kidney disease and recurrent UTI prior to transplant.[10,11,13]

The absence of a sphincter between the transplanted ureter and the native bladder may lead to transplant pyelonephritis.

Most centers use trimethoprim-sulfamethoxazole for at least six months to one year post-transplant in order to minimise the risk of UTI.[15]

In this retrospective study, we aimed to investigate the demographic characteristics, clinical manifestations, laboratory findings and outcomes of transplant patients who were admitted to emergency department.

Methods

Adult patients (>18 years) who underwent kidney transplantation in our hospital between January 2005–December 2017 and who were admitted to the emergency department were retrospectively evaluated by examining medical records. Data from medical records were collected using standardized forms by a physician who was blinded to the outcome of the patients. Patients who were followed up for less than 48 hours or underwent transplantation in another center were excluded from the study. In addition, patients who were admitted to the emergency department due to trauma, were excluded.

Transplant patients with previous hospital protocol numbers of each patient were enrolled into study as control group. This control group consisted of transplant patients who did not have any emergency department admissions. The patients' demographic, clinical and laboratory findings, symptoms, diagnosis and methods of diagnosis during admission, duration of hospitalization and outcomes were obtained from hospital medical records.

Demographic, clinical and laboratory findings of the control group were also extracted from medical records.

Demographic and clinical findings data items collected from the patients and control group were as follows:

- Age
- Gender
- Etiology of kidney failure
- Live or deceased donor
- Duration of transplant surgery
- Presence of acute rejection episode
- Immunosuppressive regimens

(Steroid+Mycophenolate mofetil (MMF)+calcineurin inhibitors (CNI)/Steroid+MMF+mammalian target of rapamycin (mTOR)/Steroid+azathioprine (AZA)+CNI/Steroid+CNI+mTOR).

Physical and laboratory findings collected from the patients and control group were as follows: Pulse rate, blood pressure, axillary body temperature (fever was defined as axillary temparature more than 38.0°C), presence of edema, costovertebral angle or abdominal tenderness; presence of cough, sputum, headache; presence of proteinuria (by dipstick during urinalysis), hematuria (excretion of more than two red blood cells per high-power field in a centrifuged urine specimen), pyuria (>5 leukocyte per high-power field in urine specimen), presence of diarrhea (the passage of loose or watery stools, typically at least three times in a 24-hour period), concentrations of urea, creatinine, sodium, potassium, calcium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), albumin, hemoglobin (Hb), hematocrit (Hct), leukocyte count and thrombocyte count and e-GFR according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

Diagnostic methods were as follows: blood, urine and stool culture, radiological examinations, tissue biopsy.

In addition, kidney function in both the patients and control groups was recorded.

This study was approved by local ethic committee (12/03/2015; 83088843-604.01.02-76220)

Statistical Analysis

Data were expressed as mean±SD. Data of the patients and the controls were compared using Student's *t* test or Mann-Whitney U test. For non-parametric tests, data were expressed as median (minimum-maximum). Categorical variables between two groups were compared using chi-square test and Fisher test. All computations were made using the SPSS for Windows v.17.0 software (SPSS Inc., Chicago, IL, USA). *p* values of <0.05 were considered significant.

Results

Patients admitted to the emergency department and recruited into the study numbered 218 (Female n=116; 53.2%) In addition 218 controls were selected (Female n=100; 45.9%). There was no difference between the subjects and controls in terms of age, gender distribution, type of transplanted organ or duration since transplant. Demographic findings of the patients and control group are shown in Table 1.

Table 1. Demographic features of two groups (n=436)

Features	Patients	Controls	*p*
Mean age (year)	39.4±13.2	37.3±13.1	0.181
Gender (male/female)	102/116	100/118	0.236
Type of transplantation (live/deceased)	171/47	176/42	0.507
Mean duration after transplantation (month)	80.2±70	83.1±63	0.386

The most common etiology of kidney failure was chronic glomerulonephritis in those patients in whom the etiology was known. The etiologies of renal failure are shown in Table 2.

Table 2. Etiologies of renal failure (patients/controls (n):218/218)

Etiologies	Patients n (%)	Controls n (%)	*p*
Chronic glomerulonephritis	46 (21.1)	48 (22)	0.690
Vesicoureteral reflux	35 (16)	46 (21.1)	0.172
Amiloidosis	16 (7.3)	16 (7.3)	0.438
Hypertensive nephropathy	14 (6.4)	3 (1.3)	**0.037**
Polycystic kidney disease	9 (4.1)	7 (3.2)	1.000
Pyelonephritis	9 (4.1)	0 (0)	0.510
Diabetic nephropathy	5 (2.5)	5 (2.5)	0.700
Vasculitis	4 (1.8)	8 (3.7)	0.740
IgA nephropathy	4 (1.8)	0 (0)	0.236
Unknown	76 (34.9)	85 (38.9)	0.121

Hypertension was the most frequent comorbid complaint in transplant patients who were admitted to the emergency service and the control group. The prevelance of chronic obstructive pulmonary disease, hepatitis C and coronary artery disease in patients admitted to emergency were significantly higher than in the control group (Table 3).

Table 3. Comorbid diseases (patients/controls (n):218/218)

Comorbid Diseases	Patients n (%)	Controls n (%)	*P*
Diabetes Mellitus	16 (7.3)	18 (8.25)	0.530
Hypertension	76 (34.8)	71 (32.5)	0.351
FMF*	19 (8.7)	14 (6.4)	0.420
COPD**	11 (5)	0 (0)	**0.006**
Hepatitis C	19 (8.7)	0 (0)	**<0,001**
Coronary artery disease	14 (6.4)	0 (0)	**0.002**
Vasculitis	1 (0.45)	1 (0.45)	1
SLE***	1 (0.45)	0 (0)	1

*FMF: Familial mediterranean fever, COPD:**chronic obstructive pulmonary disease, ***SLE: systemic lupus erythematosus

Triple immunosuppression with DC + MMF + CNI was the most used maintenance therapy in both groups. In terms of choice of immunosuppressive regimens between two groups, there was no significant difference (Table 4).

Table 4. Immunosuppressive regimens of two groups (n=436)

Immunosuppressive Regimens	Patients n (%)	Controls n (%)	*P*
DC* + MMF** + CNI***	189 (86.6)	180 (82.5)	0.376
DC + MMF + mTOR****	17 (7.8)	23 (10.6)	0.455
DC+ AZA***** +CNI	8 (3.8)	10 (4.6)	1.000
DC + CNI + mTOR	4 (1.8)	5 (2.3)	1.000

*DC: Deltacortil, **MMF: Mycophenolate mofetil, ***CNI: Calcineurin inhibitors, ****mTOR: Mammalian target of rapamycin, *****AZA: Azathioprine

When compared with the control group, patients had significantly lower blood pressure, higher pulse and higher axillary body temperature and serum urea, creatinine, CRP and leukocyte values were also significantly higher. Physical and laboratory findings of the two groups are shown in Table 5.

Table 5. Physical and laboratory findings of subjects and controls (n=436)

Physical Findings	Patients	Controls	*P*
Systolic blood pressure (mmHg)	121.8±26.2	127.3±21.4	**0.002**
Diastolic blood pressure (mmHg)	75.1±14.1	78.2±11.1	**0.025**
MAP* (mmHg)	90.3±18.1	94.9±14.1	**0.005**
Axillary fever (℃)	37.1±2.3	36.2±1.6	**<0.001**
Pulse (per min)	91±14.5	80.1±8.2	**<0.001**
Laboratory Findings (in serum samp.)			
Urea (mg/dl) Med. (Min-Max)	60 (45-200)	45 (40-95)	**<0.001**
Creatinine(mg/dl) Med. (Min-Max)	1.8 (1.5-5.3)	0.9 (0.6-2.1)	**<0.001**
GFR**(ml/min/1.73m^2) Med. (Min-Max)	35 (11-65)	65 (45-115)	**<0.001**
Sodium (mEq/L)	135.2±4.9	140.1±3.1	**<0.001**
Potassium (mEq/L)	4.5±0.9	4.5±0.5	0.574
Calcium (mg/dL)	9.6±1.2	9.5±0.2	0.625
Serum albumin (gr/dL)	3.5±1.6	4.1±0.8	**<0.001**
AST (IU/L) Med. (Min-Max)	25 (15-100)	20 (18-85)	0.420
ALT (IU/L) Med. (Min-Max)	24 (12-110)	25 (15-95)	0.168
CRP (mg/L) Med. (Min-Max)	57 (25-350)	3 (1-45)	**<0.001**
Hb (gr/dL)	10.5±2.0	13.0±1.7	**<0.001**
Hct (%)	32.5±5.5	41.3±17.3	**<0.001**
Leukocyte (/mm^3)	13350±4643	9740±4990	**<0.001**
Thrombocyte (/mm^3)	237700±87400	260800±68100	0.091

*MAP: Mean arterial pressure; **GFR: Glomerular filtration rate according to CKD-EPI

The most frequent symptoms of patients during emergency admission were: fever and dysuria in 51 patients (23.3%); fever, abdominal pain, diarrhea in 44 patients (20.1%); fever, cough, sputum in 42 patients (19.2%); fatigue, dyspnea, swelling in legs in 15 patients (6.8%); abdominal pain in 15 patients (6.8%), nausea and/or vomiting in 11 patients (5%); fever and headache in 11 patients (5%), chest pain in 4 patients (2.2%) and perianal tenderness in 4 patients (1.8%). UTI was diagnosed with the greatest frequency among these patients (67/218 (30.6%)) (see Table 6).

Fifty of the UTI patients were female (74.6%). 22 patients (15 female, 7 male) had vesicoureteral reflux in their medical history. All UTI patients had pyuria and 44 (65.7%) of them hematuria. 45 (67.2%) of the patients had positive urine culture and the most frequently identified pathogens were escherichia coli and klebsiella pnemonia (35%, 25%, respectively).

41 (76.1%) patients diagnosed with UTI had a living donor kidney transplantation. Prevelance of UTI among deceased donor transplantation was higher than patients with living donor (34% vs 29.8%) but not statistically significantly so (p=0.341).

Table 6. Diagnosis of patients admitted to the emergency department

Diagnoses (n=218)	n (%)
Infectious diseases (n=175, 80.2%)	
Urinary tract infection	67 (30.6)
Pneumonia	46 (21.1)
Acute gastroenteritis	34 (15.5)
Perianal abscess	8 (3.8)
Acute cholecystitis	5 (2.3)
Cellulitis	5 (2.3)
Zona	4 (1.6)
Encephalitis	3 (1.3)
Sepsis	2 (1.3)
Appendicitis	1 (0.4)
Other diagnoses (n=43, 19.8%)	
Acute rejection	18 (8.3)
Acute kidney injury	16 (7.5)
Hypertensive encephalopathy	3 (1.4)
Gastrointestinal bleeding	2 (0.9)
Deep vein thrombosis	2 (0.9)
FMF* attack	1 (0.4)
Hyperkalemia	1 (0.4)

*Familial Mediterranean Fever

Regarding diagnostic methods, clinical findings were the most informative in 100 patients (45.9%), radiological examinations in 60 patients (27.6%), culture results in 47 patients (21.5%) and kidney biopsy in 11 patients (5%). Mean duration of hospitalization was 11.7±9.2 day.

Kidney functions of 35 patients (16%) worsened and hemodialysis was initiated in 15 of them during the follow up. Five patients (2.2%) died during follow up. The cause of death was sepsis in three and encephalitis in two.

Discussion

The number of patients who undergo kidney transplantation increases every year. Survival of ESRD patients is prolonged after transplantation. Therefore, the number of transplant patients who are admitted to emergency departments also increases every year.[16]

In our study, most patients who were admitted to the emergency department were young females. The study conducted by Schold *et al.* showed similar demographic findings in USA.[17]

Transplant patients are susceptible to infection due to immunosuppressive drugs. Therefore, most transplant patients present with symptoms of infection.[18,19] Consistent with previous studies, 175 (80.2%) of the patients were diagnosed with infectious diseases in our study. UTI (30.6%) was the most frequently seen infectious complaint among patients in our study. In this group, there was a female preponderance, consistent with previous data.[13,20,21] In addition, presence of a history of vesicoureteral reflux seemed to be a risk factor for UTI. In the studies conducted by Trzeciak *et al.* and Kartal et al, UTI was also the most common infectious presentation (43%, and 16.5% respectively).[16,22]

In terms of the prevelance of pneumonia, our rate (21.1%) was similar to the study of Trzeciak et al where 18 of 77 (23.3%) patients had pneumonia.[16] These patients mainly presented with fever, cough and sputum. Since there was no specific data about pneumonia in the study conducted by Kartal *et al*., this pneumonia prevelance seems to be the first data for renal transplant patients from Turkey.[22] Regarding the prevelance of acute gastroenteritis, our rate was similar to the studies conducted by both Trzeciak et al and Kartal et al (12.8% and 18.6%, respectively).[16,22]

Eight patients (3.8%) were diagnosed with perianal abscess. These patients were discharged without any problem after drainage and appropriate antibiotic treatment. Interestingly, this transplant complication seemed to be unusual regarding previous data. Therefore, this is the first report of this type of infectious complication among kidney transplant patients.

Though renal transplant recipients are given antimicrobial and antiviral prophylaxis after transplantation, opportunistic infections may still occur. In our study, three patients were diagnosed with encephalitis and two of them died. Unfortunately the causative pathogens could not to be identified in these two patients. However, in the study performed by Kartal et al, one patient was diagnosed with CMV encephalitis.[22]

Diabetes mellitus is a risk factor for infection and sepsis in transplant patients.[23,24] In our study, we found that 16 (7.3%) of patients had diabetes mellitus. This finding was consistent with the that of Kartal et al who reported a prevelance of diabetes mellitus of 8%.[22]

Since most of the patients presented with clinical manifestations of infection, patients had lower blood pressure, higher temperature and pulse rate compared to the control group. In addition, systemic infections may lead to abnormal laboratory findings, reflecting an acute phase response and severity of the infection. Consequently, patients had higher serum urea, creatinine, CRP concentrations and leukocyte counts accompanied by, lower albumin and sodium concentrations compared to the control group. Apart from infection, 18 patients (8.3%) presented with acute rejection in the emergency department. This result was again consistent with the study of Kartal *et al.*. who reported 8.6% of patients with rejection.[22]

The most important limitation of our study was the retrospective nature. It may not be reliable to ascertain causality in retrospective studies.

In conclusion, transplant patients are immunocompromised individuals and consequently at high risk for severe infectious complications due to anti-rejection immunosuppressive drug therapy and pre-existing comorbidities. Physicians should have a high index of suspicion for both common and opportunistic infections during evaluation of organ transplant recipients.

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