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CLINICAL STUDY

Evaluation of the relationship between neutrophil lymphocyte ratio and the most common bacterial urinary tract infections after transplantation

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ABSTRACT

OBJECTIVE: We aimed to evaluate the relationship between neutrophil lymphocyte ratio and the most common bacterial urinary tract infections after transplantation. We also assessed the frequency of bacterial infections, e.g. *Escherichia coli, Klebsiella,* and *Enterococcus* in the urinary tract, and determined the important factors affecting neutrophil/lymphocyte ratio (N/L).

METHODS: We compared the percentage of neutrophils (NE%), percentage of lymphocytes (Lym%), and N/L, along with blood urea nitrogen (BUN), creatinine, and white blood cells (WBC) in all patients before and after renal transplantation.

RESULTS: The Lym% and WBC significantly increased after surgery while N/L%, BUN, and creatinine levels were significantly decreased. Postoperative infections were evaluated by measuring WBC, NE%, Lym%, N/L%, serum urea and creatinine levels, and no significant differences were seen compared to the preoperative values. Univariate analysis also did not show any significant differences between pre- and post-operative parameters. However, a significant difference in N/L% ratio was seen between the *E. coli* infected and uninfected recipients.

CONCLUSIONS: Any significant difference in NE%, Lym%, and N/L%, BUN, creatinine, and WBC parameters among infected and non-infected renal transplant patients were not found. The steps should be taken to prevent pre-transplantation infection and patients should be continuously monitored for infections post-transplantation *(Tab. 6, Fig. 1, Ref. 24)*. Text in PDF *www.elis.sk.*

KEY WORDS: renal transplantation, urinary tract infection, neutrophil lymphocyte ratio.

Introduction

The incidence of chronic kidney disease is on the rise and many people die every year due to chronic kidney failure. The most effective treatment for chronic renal failure is undoubtedly organ transplantation, with over 17,600 kidney transplants performed in the United States in 2013 alone (1). After renal transplantation, 75 % of the patients contracted a viral and bacterial infection within the first year. Bacterial infections of the urinary tract are a common complication of renal transplantation and are classified as infections due to technical and anatomical abnormalities, urinary tract infections (UTI), pyelonephritis, the infections of the mucocutaneous surface, and mycobacterial infections (2, 3). Since gram-negative bacteria are causative agents of the most of these infections, trimethoprim, sulfamethoxazole, fluoroquinolone, and other antibiotics that are effective against gram-negative bacteria are often used for those complications.

UTIs are common in the first three months after renal transplantation and are often the result of infected donor kidneys. The most dangerous and life-threatening complications that can arise due to transplantation-related UTIs are massive infective vesicoureteral reflux, polycystic disease, infected stones, and papillary necrosis (4). Therefore, the donors should be evaluated for UTIs before the transplantation.

Renal transplantation surgery removes the need for dialysis and improves the quality of life. Recent developments in immunosuppressive and anti-microbial therapies and surgery techniques have made renal transplantation the most preferred and successful treatment in the patients with renal failure (5). Renal transplantation can be performed using living as well as cadaveric organ donors. The survival rate of the transplant recipients from a living donor is about 97 % within the first year and drops to 84 % within five years. However, the survival rate in the recipients from cadaveric donors is 93 % within the first year and drops to 75 % within five years. The most dangerous complication post renal transplantation is UTI which develops at the frequency of 30 % within the first six months (6, 7).

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Neutrophil-to-lymphocyte ratio (N/L) which was first described in 1967 as an indicator of ozone exposure, may be used as a marker of inflammation (8). NLR was shown as a beneficial inflammatory marker to assess outcome in surgery with cancer and cardiovascular diseases (9, 10). It may also be used to assess the outcome of kidney allograft function in renal transplant recipients (11). High NLR was inversely associated with good prognosis for patient and graft survival (11).

We aimed to evaluate the relationship between neutrophil lymphocyte ratio and the most common bacterial urinary tract infections after transplantation. We also assessed the frequency of bacterial infections, e.g. *Escherichia coli*, *Klebsiella*, and *Enterococcus* in the urinary tract, and determined the important factors affecting N/L.

Materials and methods

Patient selection

The present study was approved by Sanko University Medical Faculty Ethics Committee (2018/02/20). We included 213 patients (141 males, 73 females, and aged 5–65 years at the time of surgery), who had applied for renal transplantation to Private Sani Konukoglu Hospital (Sanko University, School of Medicine, Gaziantep, Turkey) for this study.

The patients were asked whether they want to participate in the study; after acceptance of patients, written informed consents were obtained from all participants. Patient details like demographic features, clinical/laboratory findings, comorbidities, intraoperative details and postoperative follow-up records were obtained from the file archives and hospital database. Only patients whose clinical records showed infection symptoms such as fever, malaise, uremia, dizziness and white ball height were selected and the patients were classified according to the presence or absence of UTIs.

Patient monitoring

The serum samples were analyzed for biochemical parameters, drug levels, and other hematological indices. In addition, the etiology of chronic renal failure, comorbidities, and immunosuppressive therapy were also examined. The recipients were followed up for 77.42 ± 0.7 months after transplantation to determine post-op infection or organ rejection.

Biochemical parameters

Neutrophil percentile (NE%), lymphocyte percentile (Lym%), neutrophil/lymphocyte% ratio (N/L%), serum blood urea nitrogen (BUN) and creatinine and white blood cells (WBC) were evaluated in all patients before and after surgery. Preoperative Neutrophil and lymphocyte percentile were obtained from samples collected in the ethylenediaminetetraacetic acid tubes. Measurements of Neutrophil and lymphocyte were performed with a calibrated automatic hematology analyzer (Cell-dyn ruby,Abbott,Chicago,USA)

Statistical analysis

Normal distribution was checked by Shapiro–Wilk test. Mann–Whitney U-test was used to compare numerical variables between groups. Generalized linear regression analyses were performed to determine important factors affecting N/L%. Mean survival time was estimated by using Kaplan Meier method. All analyses were performed in SPSS for Windows version 24.0. A two-sided p value < 0.05 was considered statistically significant.

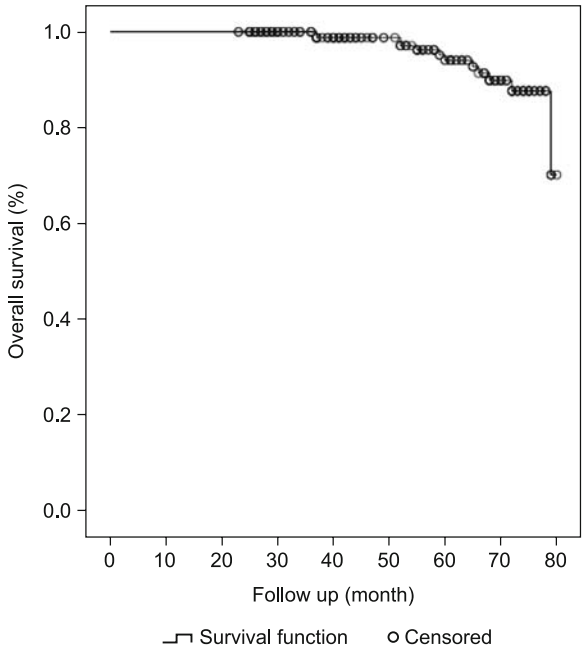

Fig. 1. Kaplan Meier curve for overall survival of patients.

Results

The overall survival rates of all recipients were 100 % in the first three years after transplantation and declined to 94.1 % in the next two years (total five years). Mean survival duration was 77.42 ± 0.7 months, during which 12 patients died (Fig. 1).

Biochemical analysis of serum indicated that Lym% and WBC levels significantly increased after surgery but the post-operative N/L%, BUN, and creatinine values were significantly decreased (Tab. 1). To determine whether in the patients who were infected postoperatively, WBC, NE%, Lym%, N/L%, urea, and creatinine

Tab. 1. Comparison of the biochemical parameters before and after surgery.

Variables	n	Before Surgery	n	After Surgery	p
NE%	213	64.71±16.25	213	64.1±12.45	0.983
Lym%	212	21.12±11.57	212	23.43±9.38	0.003*
N/L%	209	16.31±41.99	209	4.27±6.49	0.001*
BUN (mg/dL)	213	45.71±20.87	213	21.97±15.22	0.001*
Creatinine (mg/dL)	213	7.72±2.86	213	1.69±1.73	0.001*
WBC (x10^3)	213	8.28±3.08	213	9.23±7.77	0.005*

NE%: percentage of neutrophils; Lym%: percentage of lymphocyte; N/L%: neutrophil/lymphocyte ratio; BUN (unit): serum blood urea nitrogen (mg/dL); WBC (unit): white blood cells (cells/mm3); Creatinine (unit): serum creatinine (mg/dL)
* Significant < 0.05 level

Tab. 2. Comparison of numerical measurements in the infected and non-infected groups.

Variables	Group		p
	Infection (n=92)	No infection (n=121)	
WBC pre	8.41±3.3	8.19±2.91	0.638
WBC post	9.75±11.16	8.83±3.45	0.729
NE% pre	65±16.66	64.49±16	0.905
NE% post	64.28±10.85	63.96±13.57	0.955
LYM% pre	21.06±12.05	21.17±11.23	0.937
LYM% post	23.73±8.28	23.02±10.35	0.566
N/L% pre	19.6±50.74	13.55±33.31	0.965
N/L% post	3.99±6.51	4.49±6.49	0.783
Urea (BUN) pre	43.76±19.17	47.2±22.04	0.326
Urea (BUN) post	22.11±14.31	21.87±15.94	0.889
Creatinine pre	7.54±2.86	7.87±2.87	0.444
Creatinine post	1.91±2.13	1.52±1.35	0.338

NE%: percentage of neutrophils; Lym%: percentage of lymphocyte; N/L%: neutrophil/lymphocyte ratio; BUN (unit): serum blood urea nitrogen (mg/dL); WBC (unit): white blood cells (cells/mm3); Creatinine (unit): serum creatinine (mg/dL)
* Significant < 0.05 level

Tab. 3. General linear model to estimate post op N/L% ratio.

Variables	Beta	95% Confidence Interval		p
		Lower	Upper	
Woman & Man	–2.608	–4.232	–0.984	0.002*
NELYM pre	.025	–0.002	0.052	0.070
Age	.014	–0.061	0.089	0.716
Hospitalization	-.032	–0.163	0.100	0.638
Number ATG	.001	–0.002	0.005	0.446
Infection Yes/No	–2.267	–3.875	–0.659	0.006*
E. coli + vs –	–2.644	–4.557	–0.731	0.007*
Klebsiella + vs –	1.053	–1.746	3.852	0.461
Enterococci+ vs –	–0.783	–4.925	3.360	0.711

* Significant at 0.05 level

Tab. 4. Comparison of the measurements in the presence or absence of *E. coli* infections.

Variables	*E. coli*		p
	Presence (n=66)	Absence (n=147)	
WBC pre	8.72±3.58	8.09±2.82	0.379
WBC post	10.3±13.05	8.75±3.34	0.823
NE% pre	65.92±16.28	64.17±16.26	0.641
NE% post	63.75±11.62	64.26±12.83	0.752
LYM% pre	20.71±12.54	21.31±11.14	0.758
LYM%post	23.96±8.5	23.04±9.93	0.430
N/L% pre	22.31±57.05	13.4±32.48	0.680
N/L% post	3.49±3.06	4.63±7.52	0.541
Urea (BUN) pre	43.89±19.86	46.53±21.32	0.432
Urea (BUN) post	22.96±15.82	21.53±14.98	0.838
Creatinine pre	7.36±2.87	7.89±2.86	0.239
Creatinine post	1.97±2.25	1.56±1.44	0.319

NE%: percentage of neutrophils; Lym%: percentage of lymphocyte; N/L%: neutrophil/lymphocyte ratio; BUN (unit): serum blood urea nitrogen (mg/dL); WBC (unit): white blood cells (cells/mm3); Creatinine (unit): serum creatinine (mg/dL)
* Significant < 0.05 level

values were evaluated but no significant differences were seen relative to the preoperative values (Tab. 2).

Univariate analysis also did not indicate any significant difference between the parameters (Tab. 3). After adjusting for gender, age, hospitalization, number of ATG and pre-operative N/L%, a significant difference was seen between the pre- and postoperative N/L% (Beta = –2,267, p = 0.006). Furthermore, a significant difference in N/L% was found between the *E. coli* infected and uninfected patients (Tab. 3). Finally, WBC, NE%, Lym%, N/L%, urea, and creatinine values were not significantly different between the patients infected with *E. coli, Klebsiella* and *Enterococcus* and the non- infected patients (Tabs 4–6).

Tab. 5. Comparison of the measurements in the presence or absence of *Klebsiella* infectious.

Variables	Klebsiella		p
	Presence (n=18)	Absence (n=195)	
WBC pre	9.03±3.58	8.22±3.03	0.272
WBC post	8.7±3.49	9.28±8.06	0.524
NE% pre	66.98±14.71	64.5±16.4	0.542
NE% post	65.93±9.68	63.93±12.68	0.795
LYM% pre	23.17±10.92	20.93±11.63	0.382
LYM%post	23.59±8.94	23.3±9.57	0.957
N/L% pre	10.83±25.95	16.69±43.01	0.651
N/L% post	3.76±3.08	4.32±6.72	0.896
Ure (BUN) pre	47.67±18.41	45.53±21.12	0.478
Ure (BUN) post	21.56±13.06	22.01±15.44	1.000
Creatinine pre	8.22±2.96	7.68±2.86	0.502
Creatinine post	1.73±1.6	1.69±1.75	0.727

NE%: percentage of neutrophils; Lym%: percentage of lymphocyte; N/L%: neutrophil/lymphocyte ratio; BUN (unit): serum blood urea nitrogen (mg/dL); WBC (unit): white blood cells (cells/mm3); Creatinine (unit): serum creatinine (mg/dL)
* Significant < 0.05 level

Tab. 6. Comparison of the measurements according to the presence or absence of *Enterococcus* infectious.

Variables	*Enterococcus*		p
	Presence (n=18)	Absence (n=195)	
WBC pre	7.66±3.02	8.34±3.09	0.508
WBC post	9.35±2.73	9.22±8.08	0.417
NE% pre	63.09±15.43	64.86±16.35	0.643
NE% post	64.83±7.35	64.03±12.83	0.769
LYM% pre	21.65±12.33	21.07±11.52	0.891
LYM%post	24.66±6.65	23.2±9.72	0.742
N/L% pre	23.98±69.49	15.46±38.45	0.907
N/L% post	2.89±1.08	4.4±6.76	0.993
Urea (BUN) pre	41.83±20.92	46.07±20.88	0.300
Urea (BUN) post	21.74±15.28	22±15.26	0.952
Creatinine pre	6.88±2.62	7.8±2.88	0.134
Creatinine post	1.91±2.11	1.67±1.7	0.664

NE%: percentage of neutrophils; Lym%: percentage of lymphocyte; N/L%: neutrophil/lymphocyte ratio; BUN (unit): serum blood urea nitrogen (mg/dL); WBC (unit): white blood cells (cells/mm3); Creatinine (unit): serum creatinine (mg/dL)
* Significant < 0.05 level

Discussion

We found that the Lym% and WBC significantly increased after renal transplantation surgery while N/L%, serum BUN, and creatinine levels were significantly decreased. When we comparing the renal transplant recipients whether they had postoperative infection or not, we found no differences in terms of Lym%, WBC, N/L, serum creatinine and BUN levels. Also; we did not find any differences among different microorganism's groups in terms of Lym%, WBC, N/L, serum creatinine and BUN levels.

UTIs occur most frequently within the first six months post-transplantation (12–13). Valeria et al reported that 50 % of all

infections in the renal transplant recipients occurred within the first 44 days.(12) According to a retrospective study in 28,942 patients whose data were obtained from the Kidney Disease Data Bank in the United States, UTI was more common within the first six months (13). Takai et al reported the highest incidence of infections within the first year post-transplantation in a cohort of 363 kidney recipients (14). Most studies that investigated post-transplantation infections evaluated biochemical parameters like WBC, NE%, LYM%, N/L%, urea, and creatinine. We did not observe any differences in these parameters between the patients who were infected with *E. coli, Klebsiella,* and *Enterococcus* and the non- infected patients [Table 4 (*E. coli*), Table 5 (*Klebsiella)*, Table 6 (*Enterococcus*)]. We may speculate that biochemical screening for UTI in the transplant recipients should be verified by further clinical tests. However; we must keep in mind that the only clinical examination may also not be sufficient since asymptomatic bacteriuria is a common complication after renal transplantation (15).

Abbott et al found significant differences in UTIs between genders within the first six months, and the infection rates increased to 60 % in women and 47 % in men within three years' post-transplantation, indicating that gender is a risk factor for UTI (13). Takai et al also reported a higher infection rate in women (49 %) compared to men (14 %) (14). Another study followed-up 500 kidney recipients for 42 months and found that the rates of UTI were 68 % in women and 30 % in men (16). In the present study, the infection rate was not significantly different between genders. There were no significant differences among genders in terms of the biochemical indices of infection, except for N/L%.

N/L%, a surrogate marker of inflammation, has been recently adopted to predict postoperative outcomes (17, 18). It also predicts the severity of clinical course in patients with chronic disease and in patients who had surgery (19). In the present study, we found that N/L% did not show any significant differences between infected and noninfected patients.

UTI is generally caused by *Escherichia coli* (30–80 %) or other Gram-negative bacteria such as *Klebsiella* (≈10 %), *Proteus* (≈5 %) or *Pseudomonas aeruginosa* (≈10 %). Gram-positive enterococci (15–30 %) or *Staphylococcus aureus* (≈10%) is also found more often in UTI patients compared to the normal population (20–22). Our N/L ratio findings for *E. coli* infections is consistent with previous reports but that for *Klebsiella* and *Enterococcus* contradicts published reports ($p < 0.05$) (Tab. 3). The transplant recipients have a 90% rate of UTI, and the frequencies of *E. coli*, *Klebsiella*, *Enterococcus*, *Enterobacter*, *Pseudomonas aeruginosa*, *Citrobacter*, *A. baumannii*, *Staphylococcus* and *S. marcescens*are reportedly 59.1 %, 16.9 %, 6.5 %, 6.5 %, 4 %, 0.8 %, 0.8 %, 1.6 % and 0.8 %, respectively (23). In another study evaluating 500 patients, the frequencies of *E. coli, Enterococci, Staphylococci,* and *Klebsiella pneumoniae* were 29 %, 24 %, 12 %, and 10 %, respectively (24).

Chronic renal failure, chronic pyelonephritis and diabetes mellitus and delayed postoperative graft function are the major risk factors for UTIs in patients with renal transplantation (23). The rate of UTI is 28 % in the patients transplanted from cadaveric donors and 23 % in those who are transplanted from living donors (16). Earlier studies indicate that acute UTIs affect the survival rate of the recipients but since the infected patients in our cohort were only positive for *E. coli* (Tab. 3), the overall survival rates of the patients were similar during the acute period and dropped to 0.6 % at the end of 80 months (Fig. 1).

Conclusion

Although UTIs remain a significant cause of morbidity and mortality after renal transplantation, improved prophylactic, diagnostic, and treatment strategies might decrease the risk and negative effect of infection on transplantation outcomes. The steps should be taken to prevent pre-transplantation infection and patients should be continuously monitored for infections post-transplantation.

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