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Predictive Factors Associated with Delayed Graft Function Following Renal Transplantation: A Retrospective Cohort Study

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ABSTRACT

Kidney transplantation has become a routine procedure for end-stage renal disease.
Although improvement in short term graft patency has been achieved, delayed graft function (DGF) is one of the important complications following kidney transplantation. DGF results from ischemia-reperfusion injury and involves a multitude of contributing elements including donor characteristics and etiology of the end-stage renal disease. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are easily applicable methods for evaluation of systemic inflammation. We hypothesized that these parameters could refine the detection of the patients with DGF in post- renal transplantation and guide management. To test our hypothesis, we investigated whether the NLR, PLR, and creatinine reduction ratio CRR could serve as prognostic indicators for identifying patient cohorts at an elevated risk of negative treatment outcomes following renal transplantation. We also assessed demographic and clinical factors as an independent predictor to detect negative early graft function outcomes in patients after renal transplantation. This single center retrospective cohort trial comprising 55 patients who received a kidney graft from deceased or living donors was performed in Northern Cyprus Ministry of Health's Dr. Burhan Nalbantoglu State Hospital, over a 6year period. The demographic and clinical variables included age, gender, body mass index, the etiology of end-stage renal disease, kidney graft from living or deceased donors, NLR, PLR and CRR. DGF was defined as GFR<60 on the 21th day following renal transplantation. Of the patients included in this study, 26 (47.3%) and 29 (52.7%) received deceased and living donor kidney transplantation, respectively. On the 21st day following transplantation, 27 patients (49%) had an eGFR<60, whereas 28 patients (51%) had an GFR≥60. None of the patients had undergone dialysis within the first week after transplantation. There were no significant differences in demographic and clinical characteristics between the patients with eGFR 60 and eGFR 60. In logistic regression analysis, none of the predictors including etiology of the end-stage renal disease, source of donor, or demographic baseline characteristic were associated with DGF. We suggest that the NLR and PLR parameters are not associated with the presence of DGF after renal transplantation.

Keywords: Renal transplantation, Delayed graft function, Renal failure, Glomerular filtration rate, End-stage renal disease

INTRODUCTION

End-stage kidney disease constitutes an expanding global public health crisis, exerting a significant influence on the life expectancy and overall well-being of affected individuals.[1] In developed nations, kidney transplantation has evolved into a standard medical practice due to its superior medical and economic efficacy, standing as the most efficient treatment modality for

patients with end-stage renal disease.[2] Nevertheless, a significant proportion of these patients face prolonged periods on dialysis due to the persistent expansion of kidney transplant waitlists and the limited availability of deceased donor organs.[3] In response to the problem of renal transplantation shortage, a concerted focus has been directed toward optimizing treatment outcomes and implementing various initiatives aimed at streamlining the renal transplantation process.

Acute rejection is one of the main complications of renal transplantation, which leads to long-term graft dysfunction. In cases of early kidney graft dysfunction, potential etiologies encompass delayed graft function (DGF), infections, nephrotoxicity, or surgical complications. DGF results from ischemia-reperfusion injury (IRI) and involves a multitude of contributing elements including donor characteristics, and the age of the donor.[4,5] A pivotal determinant in the development of DGF is the IRI process, which triggers the generation of free radicals and other noxious metabolites, culminating in inflammatory damage to the graft tissue. The severity of this IRI is not solely influenced by donor-related factors but is significantly impacted by the recipient's systemic inflammatory response.[6]

Kidney graft biopsy constitutes a standard diagnostic modality for the differential diagnosis process of DGF. [6] However, for patients experiencing satisfactory early graft function, the detection of ongoing subclinical rejection can be only diagnosed upon early protocol biopsy. The universal adoption of a protocol biopsy program remains variable across transplant centers, resulting in a wide range of timing strategies, spanning from the initial post-transplant hospitalization up to 12 months post-transplantation. Therefore, there is an urgent need for biomarkers to better stratify patients for the prediction of graft function after kidney transplantation.[7] The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte (PLR) are easily and inexpensively measured from a complete blood count (CBC), and have indicated severity in trials of diabetes, cardiovascular and renal disease, malignancy and COVID-19. [8-11] Moreover, NLR and PLR levels are applicable options for evaluating systemic inflammation. [12,13] However, it is not known whether these parameters will refine the detection of the patients with delayed graft function in post- renal transplantation and guide management.

The discovery and validation of prognostic and predictive biomarkers in end-stage renal disease is crucial for the management of post-renal transplantation period. We aimed to evaluate demographic and clinical factors as an independent predictor to detect negative early graft function outcomes in patients after renal transplantation. Secondary outcome was to assess whether the NLR, PLR, and creatinine reduction ratio (CRR) could serve as prognostic indicators for identifying patient cohorts at an elevated risk of negative treatment outcomes following renal transplantation.

MATERIALS & METHODS

Study design and participants

We conducted a single center retrospective cohort trial utilizing prospectively obtained data from a renal transplantation center in Northern Cyprus Ministry of Health's Dr. Burhan Nalbantoglu State Hospital, over a 6 year period. A total 55 patients who received a kidney graft from deceased or living donors were included. Institutional review board approval (Northern Cyprus Ministry of Health's Dr Burhan Nalbantoglu State Hospital Ethic Committee-Reference: 09/23) was obtained for this retrospective study.

We conducted a thorough selection of variables encompassing a spectrum of demographic and clinical factors. Variables were selected by an extensive review of prior studies examining their impact on renal transplantation outcomes and by collaborative discussions among the authors of the present study. The demographic and clinical variables considered in this

investigation encompassed the following aspects: age, gender, body mass index (BMI), the etiology of end-stage renal disease, kidney graft from living or deceased donor, NLR and PLR values which were calculated from full blood count with differential and CRR. Our data collection process involved a retrospective examination of patients' electronic medical records and the image archive system to compile and assess these variables.

Outcomes

Preoperative assessments were conducted to determine the levels of lymphocytes and neutrophils from CBC, along with their respective ratios. CBC parameters were obtained shortly before transplantation. Using the CBC, the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were calculated. Additionally, serum creatinine levels were monitored at specific time points, namely, on the 0th, 1st, 2nd, and 21st day following renal transplantation surgery.

Renal function was assessed by using glomerular filtration (GFR). The GFR was calculated according to the Modification of Diet in Renal Disease; GFR=186 x creatinine-1.154 x age-0.203 x 1.212x 0.742 (if female).[14] The CCR parameter was calculated as; CRR(%) = [(creatinine level at 24 hours– creatinine level at 24 hours)x100%]/creatinine level at 24 hours. In this trial, we identified two groups of patients based on their renal function on the 21st day post-transplantation. Group 1 consisted of patients with an GFR less than 60, while Group 2 comprised patients with an GFR equal to or greater than 60.

Statistical Analysis

The IBM Co.'s SPSS version 23.0 statistical software program (Armonk, NY) was used for the analysis. Demographic and clinical characteristics of the patients were presented using descriptive statistics. Continuous outcomes were summarized through means and standard deviations, while categorical outcomes were expressed as frequencies (%). Chi-square tests with Fisher's exact tests were used to compare categorical variables. To assess the potential predictors of delayed graft function, univariate logistic regression analyses were conducted. The predictive factors such as age, gender, body mass index (BMI), the etiology of end-stage renal disease, NLR, PLR and CRR values were included in the univariate analysis. Due to the limited size of our sample and to prevent overfitting, regression analysis in multivariate models included 3 independent variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and a significance level of $P < 0.05$ was considered statistically significant.

RESULT

A total of 55 patients were included in this study. All subjects received a standardized immunosuppressive regimen and steroids. Among them, 22 (40%) were female, and 33 (60%) were male. The patients had an average age of 52.6 years with a standard deviation of 12.6. The mean BMI was 28.1 with a standard deviation of 6.93. Of the patients included in this study, 26 (47.3%) and 29 (52.7%) received deceased and living donor kidney transplantation, respectively. The clinical characteristics of study subgroups are given in Table 1.

In this cohort study, none of the patients had undergone dialysis during the first week after transplantation. On the 21st day following transplantation, 27 patients (49%) had an GFR<60, whereas 28 patients (51%) had an GFR≥60. The causes end-stage renal disease was as follows: hypertensive nephropathy (30.9%), diabetic nephropathy (25.45) polycystic kidney disease (9.1%), IgA Nephropathy (9.1%), hereditary (5.45%), and other (14.55%). No significant difference was found between the groups regarding the etiology of the end-stage renal disease (p=0.245).

A comparison of the demographics and clinical characteristics between the groups was provided in Table 2.

Table 1. Baseline characteristics and clinical variables of patients

Patient data	(n=55)
Age (years)	52.6±12.6
Sex (n%)	
• Female	22 (40%)
• Male	33 (60%)
Donor type (n%)	26 (47.3%)
• Cadaver	29 (52.7%)
• Living	
BMI (kg/m^2)	28.1±6.93
Primary etiology (n%)	
• Hypertension	17 (30.9%)
• Diabetes mellitus	14 (25.45%)
• Polycystic Nephropathy	5 (9.1%)
• VUR	3 (5.45%)
• IgA Nephropathy	5 (9.1%)
• Hereditary	3 (5.45%)
• Other	8 (14.55%)
Laboratory characteristic	
Hemoglobin (g/L)	10.7±1.77
Hematocrit	33.7±6.13
White blood cell count (10^9/L)	10.4±4.17
NLR	2.82±1.09
PLR	113±62.1
CCR	35.7±24.3
Urea	56.5±20.8
Creatinin	7.55±2.63
GFR	73.4±86.7

Values are expressed as the mean ± standard deviation or number of patients (%). BMI: body mass index, GN: Glomerulonephritis, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, VUR: Vesicoureteral reflux.

Vesicoureteral reflux. The patients exhibited similarities in terms of age, gender, and baseline laboratory assessments, which included urea and creatinine levels, white blood cell count, hemoglobin and hematocrit levels. There was no significant difference between the groups regarding the NLR, PLR and CRR levels (Table 3). Moreover, no significant difference was present between the groups in the source of the donor (p=0.135).

Table 2: Univariate logistic regression of the demographic and baseline clinical characteristics associated with occurrence of delayed graft function.

	GFR<60 (n=27)	GFR≥60 (n=28)	p
Age (years)	54.9±10.6	50.4±14.2	0.187
Gender (n%)			0.135
• Female	11 (37%)	13 (57.2%)	
• Male	16 (63%)	17 (42.8%)	
Donor type (n%)			0.135
• Cadaver	10 (37%)	16 (57.2%)	
• Living	17 (63%)	12 (42.8%)	
BMI (kg/m^2)	27.53±6.01	28.65±7.78	0.553
Primary etiology (n%)			0.245
Hypertension	7 (29.9%)	10 (35.7%)	
Diabetes mellitus	8 (29.6%)	6 (21.4%)	
Polycystic Nephropathy	4 (14.8%)	1 (3.5%)	
VUR	1 (3.7%)	2 (7.1%)	
IgA Nephropathy	3 (11.1%)	2 (7.1%)	
Hereditary	2 (7.4%)	1 (3.5%)	
Other	2 (7.4%)	6 (21.4%)	

Data are expressed numbers (%), and mean, standard deviation. BMI: body mass index, GFR: glomerular filtration rate, VUR:

Table 3: Univariate logistic regression of the laboratory characteristic associated with occurrence of delayed graft function

	GFR<60 (n=27)	GFR≥60 (n=28)	p
White blood cell count (10^9/L)	10.6±4.04	10.2±4.36	0.747
Hemoglobin (g/L)	10.82±1.92	10.68±1.65	0.767
Hematocrit	34±6.34	33.4±6.02	0.730
NLR	2.80±1.07	2.83±1.12	0.921
PLR	106.47±63	118.90±61.84	0.464
CCR	35.22±17.53	36.14±29.73	0.890
Urea (mg/dL)	55.97±16.61	56.95±24.48	0.863
Creatinine (mg/dL)	7.63±2.75	7.48±2.56	0.835

Data are expressed numbers (%), and mean, standard deviation. CCR: Creatinine reduction ratio, GFR: glomerular filtration rate, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio.

Logistic Regression Analysis

Univariate binary logistic regression analysis was performed to analyze each factor affecting DFG. Logistic regression analysis showed that there was no significant association with the presence of DGF after renal-transplantation and NLR [OR: 1.023, 95 % CI: (0.628-1.67), P = 0.919], PLR [OR: 1.003, 95 % CI: (0.955-1.01), P = 0.456] and CRR [OR: 1.002, 95 % CI: (0.980-1.02), P = 0.888] levels. Serum urea [OR: 1.021, 95 % CI: (0.977-1.03), P = 0.860] and creatinine levels [OR: 0.978, 95 % CI: (0.799-1.20), P = 0.832] were not statistically significantly associated with the presence of DFG (Table 4).

Table 4: Laboratory predictors of delayed graft function.

	Odds Ratio	95% CI	p
White blood cell count	0.979	0.861-1.11	0.742
Hemoglobin	0.954	0.705-1.29	0.762
Hematocrit	0.984	0.903-1.07	0.725
NLR	1.023	0.628-1.67	0.919
PLR	1.003	0.995-1.01	0.456
CCR	1.002	0.980-1.02	0.888
Urea	1.021	0.977-1.03	0.860
Creatinine	0.978	0.799-1.20	0.832

CI: confidence intervals, CCR: Creatinine reduction ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio.

There was no significant association between having living or deceased donor transplantation or the presence of DGF [OR: 0.441, 95% CI: 0.125 (0.15-1.30), P = 0.138] (Table 5).

Table 5: Demographic and baseline clinical predictors of delayed graft function.

	Odds Ratio	95% CI	p
Age	0.971	0.929-1.01	0.186
Sex			0.912
Female	1 (Ref)		
Male	1.06	0.361-3.13	
Donor type • Cadaver • Living	 1 (Ref) 0.441	 0.15-1.30	0.138
BMI	1.025	0.946-1.11	0.548
Primary etiology			
Hypertension	1 (Ref)		
Diabetes mellitus	1.90	0.45-7.98	0.378
Polycystic Nephropathy	5.71	0.52-62.66	0.154
VUR	0.71	0.05-9.50	0.799
IgA Nephropathy	2.14	0.28-16.37	0.463
Hereditary	2.85	0.21-37.99	0.426
Other	0.47	0.07-3.09	0.437

CI: confidence interval, BMI: body mass index, VUR: Vesicoureteral reflux.

DISCUSSION

Kidney transplantation is often the answer for patients with end-stage renal failure. End-stage kidney disease is a devastating syndrome with a variable clinical course and with a growing global public health epidemic. Although renal transplantation frequently serves as the optimal solution for individuals experiencing end-stage renal failure, DGF is a common complication following kidney transplantation. Despite the frequent utilization of renal transplantation in clinical practice and the abundance of studies documenting outcomes, there is a paucity of data in the literature investigating clinical and demographic factors predicting DGF following renal transplantation. In the present study, we evaluated the predictive factors for identifying patients at risk of DGF in the early period after kidney transplantation. Moreover, we explored whether an ideal biomarker could be identified in the serum via a simple and widely available test and whether it could accurately predict the diagnosis of DGF.

The findings of our current study indicate that demographic and clinical factors, such as age, gender, BMI, the etiology of end-stage renal disease, and whether the donor was living or deceased did not exhibit statistically significant differences between patients with DGF and those without DGF. Moreover, our results have indicated that the NLR and PLR were not correlated with the prediction of renal function for identifying patient cohorts at a higher risk of DGF following renal transplantation. Given that none of our patients underwent dialysis within the initial week post-transplantation and considering the study's limited sample size, it may not be appropriate to generalize the results of the study. Moreover, DGF was defined as GFR<60 on the 21th day following renal transplantation, which could impede the finding of the study.

Acute tubular damage and inflammation are linked to post-ischemic acute renal allograft failure and DGF. DGF is a consequence of IRI and encompasses various contributing factors, including donor characteristics and donor age.[15,16] While there's uncertainty regarding whether DFG accelerates graft fibrosis and leads to premature transplant loss, an examination of paired donor kidneys indicates that DGF represents a risk factor for graft loss.[4,5] A crucial factor in the presence of DGF is the IRI mechanism, which initiates the production of harmful substances such as free radicals, leading to inflammatory harm to the transplanted organ. It's worth noting that the extent of this IRI is not solely determined by donor-related variables; the recipient's systemic inflammatory response also plays a substantial role in its severity. [15,16]

DGF represents a distinct form of acute kidney injury in the context of renal transplantation. Unlike acute kidney injury in native kidneys, which is typically defined as a rapid increase in serum creatinine within 48 hours of an inciting etiology, timing in diagnosing DGF in transplant cases is less straightforward.[17-19] The challenge lies in the numerous definitions of DGF that vary among transplant centers, regions, and countries, with more than 10 distinct definitions documented in the literature.[20-22] In the past decade, DGF has

often been defined as the necessity for dialysis within seven days following the transplant.[23] However, this criterion has its limitations, as dialysis might be required in the initial week after transplantation without confirmed kidney damage. In this present study, none of our patients required dialysis during the first week following the transplant. Recently, in several studies, GFR lower 30 mL/min/1.73 m^2 on the 21st day after transplantation is defined as a threshold for DGF diagnosis.[24] With these defined cut-off points, the DGF group was relatively smaller in our study. Therefore, in this current study, we have defined DGF as GFR <60 on the 21st day after transplantation to facilitate a more comprehensive analysis. The challenges continue in understanding the mechanisms of acute kidney injury in transplants and exploring potential strategies for the definition and management of DGF.

The NLR and PLR can be readily and cost-effectively assessed through a CBC. They have been shown to reflect the severity in various research studies related to conditions such as diabetes, cardiovascular diseases, renal issues, chronic obstructive pulmonary disease, cancer, and COVID. [8-11] Moreover, NLR and PLR can serve as a predictive indicator for both the onset and severity of lung fibrosis in individuals with systemic sclerosis, dermatomyositis, and polymyositis. [25-27] Previous studies have also specifically considered NLR as a biomarker in end-stage renal disease. [28-29] Of these studies; the first found NLR raised NLR was elevated in the group of renal transplant recipients in comparison to healthy controls. This elevation could be explained by the ongoing inflammatory processes in patients with end-stage renal disease undergoing renal transplantation.[28] The second study of 398 renal transplant recipients found that preoperative NLR was associated with the risk of developing DGF, which seems to be more prominent in subjects receiving grafts from living donors. In their study, DGF was defined as the requirement for dialysis during the first week after surgery and 26% of the renal recipients developed DGF.[29] An additional study indicated that individuals with end-stage renal disease exhibited elevated inflammation markers as determined by their NLR levels in comparison to a control group comprising healthy subjects.[30] Although these data could help predict which patients have the risk for developing DGF, it is unlikely to alter the clinical decision of whether a patient should undergo transplantation when a suitable deceased donor becomes available. On the other hand, the identification of an elevated preoperative NLR in a transplant recipient scheduled to receive a living donor graft could potentially lead to a decision to postpone the surgery until the NLR returns to normal levels. Although this decision may consequently reduce the DGF development, it also results in delay for transplantation surgery. Our results differed from the studies investigating the association between NLR and PLR and the developing DGF. None of the predictive factors including demographic and clinical characteristics and laboratory parameters were associated with the presence of DGF.

Our study has several limitations. First, it is important to recognize that our study has limitations due to the relatively small number of patients involved. The single-center and retrospective design of the study hinders the generalizability of the results. To validate the results of this study, a more extensive prospective study involving multiple centers is required. Second, although DGF was defined as post transplantation GFR of less than 60 mL/min/1.73 m^3 21 days after the procedure, there are many different definitions of DGF in the literature. [20-22] Third, retrospective study may be associated with poor and missing data. Notably, we encountered a deficiency in fundamental demographic information, including ethnicity, smoking habits, and co-morbidities, which were not uniformly accessible across all the cohorts. Additionally, relying on a single

measurement of NLR or PLR may not fully capture the relationship over an extended period. Future research should aim to monitor serial changes in NLR, as this could provide valuable insights into the role of NLR in the follow-up of DGF. Further studies are needed to compensate for these limitations.

CONCLUSION

In summary, DGF continues to present a significant clinical challenge for transplant physicians. Apart from initiatives aimed at refining the understanding of DGF in the context of IRI and conducting research to gain a clearer insight into its underlying biological mechanisms, an increasing array of treatment approaches and interventions are under exploration. Herein, we investigated predictive factors for identifying patients at risk of DGF in the early period after kidney transplantation. In univariate regression analysis, none of the predictors including etiology of the end-stage renal disease, source of donor, or demographic baseline characteristic were associated with DGF. Our data have shown that recipient preoperative NLR, PLR and CCR were not associated with postoperative graft function. We recommend the execution of meticulously planned studies to assess the predictive potential factors in patients diagnosed DGF. Furthermore, there is a need for well-structured research to delve into the significance of NLR and PLR levels in individuals experiencing DGF, including its impact on immune responses and inflammatory markers.

Declaration by Authors

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