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Original Article

The Predictive Value of Serum NGAL for the Diagnosis of Delayed Graft Function in Kidney Transplantation

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HIGHLIGHTS

- The superior serum NGAL to serum Cr is an early predictor of graft function and DGF.
- NGAL is a better biomarker for early accurate predictor of DGF than traditional biomarkers.
- Serum NGAL at early hours of post-transplantation is a valuable biomarker.

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ABSTRACT

Introduction
The role of serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting delayed graft function (DGF) after kidney transplantation is poorly defined. The objective of this study was to evaluate the serum NGAL expression in the early postoperative phase after kidney transplantation and compare it with serum creatinine (Cr).

Methods
We studied 29 patients who received kidney transplantation from deceased (n=24) and lived (n=5) donors from October 2017 to December 2018 at the Urology Research Center, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran. Serum NGAL, Serum Cr, and urine output were measured at 1 to 7 days after transplantation. The need for dialysis in one week after transplantation was evaluated.

Results
Among 29 recipients with serum biomarkers measurements, 8 (27.5%) developed DGF (need to hemodialysis within one week of transplantation). Resulted in areas under ROC curves (AUCs) for serum NGAL at early hours following transplantation was (0.839, 95% CI: 0.69-0.98, p-value=0.005) that could accurately predict DGF compared to urine output (0.747, 95% CI: 0.55-0.93, p-value=0.045) and serum Cr (0.607, 95% CI: 0.34-0.86, p-value=0.398) at 24 hours after transplantation. Multivariate analysis revealed that only serum NGAL was a significant independent predictor of DGF (OR: 0.996, 95% CI: 0.993-1.000, p-value=0.039).

Conclusions
Serum NGAL at early hours of post-transplantation was a valuable biomarker for an early accurate predictor of DGF in kidney transplantation compared with traditional biomarkers such as serum Cr and urine output.

Keywords: Kidney Transplantation; Delay Graft Function; Serum NGAL; Predictive Biomarkers

Introduction
According to the Global Observatory Donation and Transplantation (GODT) data, 90,306 kidney transplants were performed worldwide in 2017 (1). Kidney

transplantation is the highest potential treatment for long-term survival for patients with end-stage renal disease (ESRD) (2). However, in some cases, acute kidney injury (AKI) can lead to allograft and early renal dysfunction, increasing the risk of acute or chronic rejection and chronic allograft nephropathy and consequently graft loss (3,4). Delayed graft function (DGF) is one of the complications after kidney transplantation, which is defined as the necessity of dialysis during the first week after renal transplantation (5-8). The cause of DGF is related to donor and recipient parameters such as ischemia-reperfusion injury, immunological response, and immunosuppressive medications (9-11). The prevalence of DGF is significantly higher in the deceased donor (5-50%) than the live donor (4–10%) kidney transplant (12). Unfortunately, there is no effective treatment for DGF. However, early detection of DGF and intervention treatment may improve outcomes. Due to possible severe consequences of DGF, there is a necessity to identify early biomarkers that will rapidly and reliably detect acute and chronic allograft rejection and DGF.

Serum creatinine (Cr) levels are currently being measured to determine acute renal failure (ARF) (13). Unfortunately, Cr is an unreliable indicator during AKI because it is affected by many factors such as body weight, age, sex, and muscle metabolism (14, 15). Also, a detectable increase in Cr serum occurs at a stage where significant allograft damage has occurred (16). Thus, neutrophil gelatinase-associated lipocalin (NGAL) has been introduced as an early marker protein for kidney dysfunction in various clinical settings (17, 18).

The clinical value of NGAL in predicting AKI associated with cardiac surgery and regular AKI with radiologic contrast has been demonstrated in several studies (19, 20). Hall et al., (21) showed that NGAL levels following kidney transplantation could predict the DGF, whereas serum Cr could not Mishra et al., (22) demonstrated that NGAL expression was significantly increased in patients who developed DGF after transplantation, and they found a strong correlation between NGAL staining intensity and cold ischemia time as well as serum Cr. Most previous studies used urinary NGAL as a biomarker to predict DGF. Thus, there is not enough information on serum NGAL as a biomarker. Therefore, we conducted this study to evaluate the serum NGAL expression in the early postoperative phase after kidney transplantation and to examine the role of serum NGAL as a biomarker in predicting DGF and acute allograft rejection.

Methods

In this prospective cohort study, 32 adult patients who underwent first-time kidney transplantation at the Urology Research Center, Sina Hospital, Tehran, Iran, were enrolled from deceased and live donors from October 2017 to December 2018. But in three patients was not possible to recognize the DGF because of early acute rejection and

Table 1. Demographic and clinical characteristics of recipients and donors in DGF and non-DGF groups

Variables	Total (n=29)	Non-DGF (n=21)	DGF (n=8)	P-value
Recipient characteristics				
Age (year)	45.21±13.86	45.14±13.29	45.38±16.23	0.969∞
Sex (male)/ n (%)	21 (72.4)	15 (71.4)	6 (75)	0.615≠
BMI (kg/m^2)	24.79±4.66	23.87±3.67	27.21±6.25	0.084∞
Diabetes/ n (%)	7 (24.1)	4 (19.0)	3 (37.5)	0.357≠
Hypertension/ n (%)	13 (44.8)	9 (42.9)	4 (50)	0.526≠
Ischemic heart diseases/ n (%)	3 (10.3)	1 (4.8)	2 (25.0)	0.176≠
Smoking / n (%)	6 (20.7)	5 (23.8)	1 (12.5)	0.475≠
Duration of dialysis (months)	21.34±15.42	20.90±16.60	22.50±12.72	0.809∞
Serum NGAL pre-transplant	951.25±332.29	944.42±379.51	974.37±171.22	0.822∞
Serum Cr pre-transplant	7.15±2.50	6.42±2.01	9.15±2.94	0.059∞
Donor characteristics				
Type of donor (deceased)/ n (%)	24 (82.7)	17 (80.9)	7 (87.5)	0.575≠
Age (year)	37±11.5	37.56±11.5	35.57±12.43	0.708∞
Sex (male)/ n (%)	21 (72.4)	15 (71.4)	6 (75)	0.618≠
Findings				
Hospitalization (day)	20.79±10.58	18.19±7.05	27.63±15.23	0.029∞
Mortality	3 (10.3)	3 (14.3)	0	0.364≠

Data are expressed as number of total (%), mean ± standard division, DGF: delayed graft function, BMI: body mass index, NGAL: neutrophil gelatinase-associate lipocalin, Cr: creatinine, ≠ chi-square test or Fisher's exact test, ∞ Student t-test

Table 2. Biomarker outcomes in patients according to DGF and non-DGF groups following transplantation

Biomarkers	Total (n=29)	Non-DGF (n=21)	DGF (n=8)	P-value
Serum NGAL (ng/ml)				
Post-transplant	866.72±366.32	761.32±356.11	1143.40±231.59	0.009
Day 7	316.91±217.74	220.45±67.78	574.13±290.71	0.007
Serum Cr (mg/dl)				
Day 1	5.42±2.55	5.01±1.84	6.31±3.64	0.245
Day 2	5.08±2.42	4.61±2.29	6.26±2.49	0.105
Day 3	3.48±2.24	2.97±1.98	4.88±2.46	0.053
Day 4	3.11±2.28	2.42±1.72	4.75±2.73	0.012
Day 5	2.87±2.08	2.21±1.42	4.52±2.62	0.006
Day 6	2.87±2.21	2.04±1.03	5.01±3.02	0.001
Day 7	2.46±1.72	1.84±0.84	3.77±2.38	0.006
Urine output (ml)				
Day 1	3150.0±2495.2	3746.5±2610.7	1658.7±1398.7	0.043
Day 2	3748.2±2611.4	4100.0±2484.9	2868.7±2882.0	0.268
Day 3	3469.6±1955.8	3815.1±1929.8	2606.2±1858.4	0.143
Day 4	3211.1±1461.5	3365.7±1292.5	2843.7±1899.0	0.407
Day 5	3265.3±1463.3	3377.5±1379.5	29.85.1±1722.8	0.532
Day 6	3012.5±1226.6	3020.00±983.2	2993.7±1782.9	0.960
Day 7	2677.8±1088.5	2752.5±1002.1	2491.2±1337.2	0.576
Follow-up findings of serum Cr (mg/dl)				
Month 1	1.58±0.42	1.50±0.31	1.79±0.59	0.101
Month 3	1.58±0.44	1.59±0.49	1.54±0.29	0.799
Month 6	1.69±0.53	1.66±0.63	1.74±0.22	0.722

All data are expressed as mean ± standard division, NGAL: neutrophil gelatinase-associate lipocalin, Cr: creatinine

mortality then these patients were excluded from analysis. For patients under 18 years old, re-transplantation or combined transplantation with another organ and graft impairment caused by renal artery thrombosis or bleeding from the vascular graft anastomosis were excluded from the study. The development of DGF was evaluated in all patients, which is defined as a need for dialysis within the first week after transplantation (23). All participants received the same immunosuppressive regimen: thyroglobulin induction and prednisolone, mycophenolate mofetil, and tacrolimus. The Ethics Committee approved the Tehran University of Medical Sciences (Code: IR.TUMS.VCR.REC.1397.173), and the patients were enrolled after giving written informed consent.

Demographic and clinical characteristics of recipients and donors were collected from the patient's medical records. Age, sex, height, weight, cause of end-stage renal disease, duration of dialysis before transplantation, comorbid conditions such as diabetes, hypertension, and ischemic heart disease were collected. Besides, serum NGAL, serum Cr and urine output were measured preoperatively and postoperatively. All patients were followed within six months of transplantation, and all aspects of graft function, serum Cr, other complications, and mortality were recorded. Preoperative samples were taken before surgery. Postoperative serum NGAL were collected at first and seven days following the transplantation. Samples were immediately processed and stored at 70 °C. We utilized a commercial double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, Shanghai, China) for measuring plasma NGAL concentrations. Post-transplantation samples of urine output and serum Cr were measured at 1 to 14 days after transplantation and the day of the patient's discharge from the hospital. Moreover, serum creatinine was measured at 1, 3, and 6 months after transplantation to evaluate the glomerular filtration rate. Serum creatinine was measured by the Jaffe method (Roche Diagnostics).

Qualitative variables were reported as number or percentage and quantitative variables as mean±standard deviation (SD). The normality distribution of data was tested using the Kolmogorov-Smirnov test. Demographic and clinical characteristics of the patients with and without DGF were compared by two-sample student's t-test or Mann-Whitney test in quantitative variables and by chi-square test or Fisher exact tests in qualitative variables. The association between biomarkers and DGF was evaluated in a multivariate logistic analysis while adjusting the variables selected by univariate analysis and risk factors for DGF. Pearson's correlation coefficients evaluated the correlation between NGAL and other variables. A receiver-operating characteristic (ROC) curve was used to determine the cutoff point for serum

Table 3. Area under the receiver-operating curves for DGF prediction

Biomarkers	AUC (95% CI)	P-value	Cut-off	Sensitivity (%)	Specificity (%)
Serum NGAL (ng/ml)					
Post-transplant	0.839 (0.694-0.985)	0.005	884.64	100	76.5
Day 7	0.917 (0.731-1.000)	0.041	232.98	100	75.0
Serum Cr (mg/dl)					
Day 1	0.607 (0.346-0.868)	0.398			
Day 2	0.725 (0.491-0.959)	0.067	4.39	88.0	65.0
Day 3	0.714 (0.463-0.966)	0.099	3.18	83.0	62.0
Day 4	0.770 (0.562-0.977)	0.029	2.02	83.0	55.0
Day 5	0.794 (0.597-0.991)	0.017	1.79	83.0	54.0
Day 6	0.810 (0.584-1.000)	0.018	3.94	67.0	85.0
Day 7	0.768 (0.558-0.979)	0.033	3.05	67.0	77.0
Urine output (ml)					
Day 1	0.747 (0.555-0.939)	0.045	1075.0	80.0	50.0
Day 2	0.653 (0.410-0.896)	0.213			
Day 3	0.659 (0.432-0.887)	0.195			
Day 4	0.520 (0.262-0.777)	0.873			
Day 5	0.481 (0.226-0.736)	0.897			
Day 6	0.463 (0.189-0.736)	0.760			
Day 7	0.556 (0.300-0.813)	0.647			

AUC: area under the curve, CI: confidence interval, NGAL: neutrophil gelatinase-associate lipocalin

NGAL and creatinine level to predict DGF. The statistical analysis was conducted with SPSS version 21.0 (SPSS Inc., IMB Corporation, and Chicago, Illinois, USA). A p-value<0.05 (two-tailed) was defined as statistically significant for all analyses. Confidence intervals (CI) were calculated on a 95% level.

Results

Recipients and donors' characteristics

A total of 29 patients were enrolled in this study. The demographic and clinical characteristics of the recipients and donors and findings in patients DGF and non-DGF are shown in Table 1. The mean age of patients at transplantation time was 45.21±13.86 years (range:17–69 years), and the majority of the 21 (72.4%) were men. In 13 (44.8%) patients, the cause of end-stage renal disease (ESRD) was unknown. Diabetes (DM) and hypertension (HTN) was the cause in 7 (24.1%) and 6 (20.7%) patients, respectively. The source of the kidney was from deceased and live donors in 24 (82.8%) and 5 (17.2%) patients, respectively. The mean age of donors at transplantation time was 37±11.5 years (range:17-59 years), and 21 of them (72.4%) were male. Eight (27.6%) recipients developed DGF in the study. No significant difference was found between "DGF" and "non-DGF" patients in terms of demographic and clinical characteristics before transplantation (p-value>0.05). However, in terms of findings, the mean duration of hospitalization was significantly lower in the "non-DGF" group compared to patients in the "DGF" group (18.2±7.05 vs. 27.6±15.2 days, p-value=0.029).

Postoperative biomarkers

To demonstrate differences in the expression of biomarkers, serum NGAL, serum Cr and urine output was measured postoperative day 1 to 7. Table 2 shows mean±SD values of serum NGAL, serum Cr and urine output levels from postoperative day 1 to 7, and findings of serum Cr in months 1, 3, and 6 following transplantations in DGF non-DGF groups. Plasma NGAL level at early hours of post-transplantation (1143.4±231.6 vs. 761.3±356.1 ng/ml, p-value=0.009) and day 7 (574.13±290.71 vs .220.45±67.78 ng/ml, p-value=0.007) was significantly higher in patients with DGF than those without DGF; while it was not significantly different among the groups before transplantation (p-value=0.822). The serum Cr levels from postoperative days 1 to 3 were not significantly different between the two groups of patients. However, significantly higher serum Cr was observed in post-transplantation day four and after that in patients with DGF than those without DGF (p-value<0.05). Also, urine output on the first day after transplantation was significantly lower in the "DGF" group than those patients in the "non-DGF" group (1658.7±1398.7 vs. 3746.5±2610.7 ml p-value=0.043). No statistically significant difference was found between the groups regarding serum Cr level in months 1, 3, and 6 following transplantations (p-value>0.05).

Prediction of DGF by serum NGAL

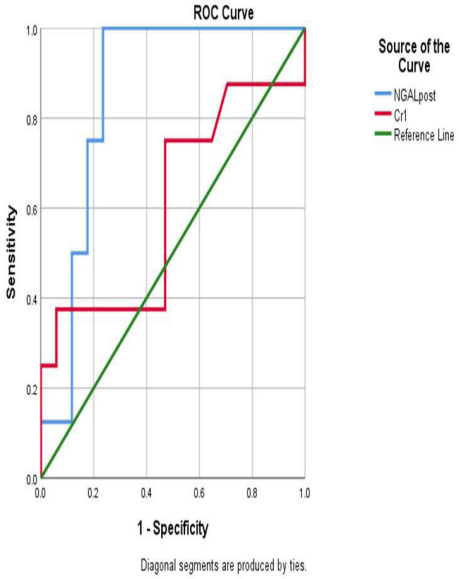

Figure 1. Regarding the AUC, serum NGAL could predict DGF highly accurately at postoperative days compared to serum Cr.

To assess the predictive value of serum NGAL vs. serum Cr to detect DGF, we compared the area under the ROC curves (AUCs). Table 3 shows the AUC and cutoff point of serum NGAL, Cr, and urine output at days 1 to 7 following transplantation for predicting DGF. ROC analysis showed that the AUC for predicting DGF using serum NGAL at early hours of post-transplantation were (0.839, 95% CI: 0.69-0.98, p-value=0.005) compared to serum Cr (0.607, 95% CI: 0.34-0.86, p-value=0.398) and urine output (0.747, 95% CI: 0.555-0.939, p-value=0.045) at the first day following transplantation. However, the AUC for Serum Cr after operative is highest at days 4 to 7, with a highly accurate prediction of DGF. The cutoff point of 884.64 (ng/ml) for serum NGAL at postoperative had a sensitivity of 100% and specificity of 76.5% and 232.98 (ng/ml) at day 7, had a sensitivity of 100% and specificity of 75%. While the cutoff point of 1075 (ml) for urine output at day one following transplantation had a sensitivity of 80% and specificity of 50%. Regarding the AUC, serum NGAL could predict DGF highly accurately at postoperative days compared to serum Cr (Figure. 1).

Multivariate analysis for predicting DGF

Concerning NGAL expression, univariate and multivariate analyses were performed to determine independent parameters for DGF. Univariate analysis showed that the age (p-value=0.967), sex (p-value=0.848), duration of dialysis (p-value=0.933), type of donor (p-value=0.607), serum Cr and urine output at day one after transplantation (p-value=0.252 and 0.064) were not predictive of DGF. However, post-transplantation serum NGAL and level of serum Cr at day four following transplantation were independent predictors of DGF (Table 4). However, in multivariate analysis, only post-transplantation serum NGAL was a significant independent predictor of DGF (OR: 0.996, 95% CI: 0.993-1.000, p-value=0.039).

Discussion

Diagnosis of DGF is usually made by elevated serum Cr, which is a late signal of kidney injury. Early prediction and treatment are essential for a better outcome. Therefore, it would be ideal to find a marker better than Cr to predict acute kidney injury (24,25). We compared the serum NGAL with serum Cr as predictive biomarkers for DGF following kidney transplantation. The study showed that serum NGAL after transplantation was more useful than absolute or percentage of serum Cr decrease in predicting DGF. In both ROC and multivariable analyses, serum NGAL was superior to serum Cr in predicting early DGF. We have shown that absolute values of serum NGAL on the first hours of post-transplantation correspond with DGF, whereas Serum Cr values at these times poorly differentiate between groups. Besides, the results revealed that better accuracy and predictive power of serum Cr occurred at four or more days after transplantation. The absolute value of serum Cr on the post-transplantation day 1 and 4 for predicting DGF resulted in AUCs was (0.607, 95%CI: 0.346-0.868, p-value=0.398) and (0.770, 95%CI: 0.562-0.977 p-value=0.029), respectively. Therefore, serum NGAL detects DGF 1 to 3 days earlier than serum Cr after transplantation. Furthermore, urine output at 24 hours after transplantation had modest diagnostic performance AUC (0.747, 95% CI: 0.555-0.939, p-value=0.045).

A meta-analysis study indicated that rine and serum/plasma NGAL was valuable biomarkers for early identification of Delayed graft function (DGF) in renal transplantation, and blood NGAL was superior to urine NGAL in early prediction of DGF (26). Moreover, measuring urine NGAL during the first 6 hours after admission or surgery with a cutoff point of 50 mg/dL provides the optimum diagnostic value in detecting AKI in children (27). In 2009, Michael Haase and colleagues showed that the NGAL level was a useful prognostic tool concerning the prediction of renal replacement therapy initiation and in-hospital mortality (28, 29).

The accuracy and predictive power of serum Cr was affected by many parameters such as age, sex and muscle mass, protein metabolism, volume of distribution, and drugs (30). Furthermore, the ability of creatinine to detect functional impairment is less than 50% (31). Several studies have been evaluated the role of urine or serum NGAL in predicting DGF after kidney transplantation, compared with traditional biomarkers such as serum Cr and urine output (32,34). Similar to our study, they showed that NGAL level was more helpful than serum Cr in early predicting DGF. In contrast, Mahdavi-Mazdeh et al., (35) reported ROC curve and AUCs of serum NGAL and serum Cr levels on the first post-transplantation day had similar significance in predicting DGF. However, they showed that the highest AUC (0.82) was attributed to

Table 4. Univariate and multivariate analysis of risk factors for predicting DGF

Variables	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.999	0.941-1.060	0.969	-	-	-
Sex	0.833	0.130-5.350	0.848	-	-	-
Duration of dialysis	0.993	0.942-1.047	0.800	-	-	-
Type of donor	0.679	0.155-17.47	0.679	-	-	-
Serum NGAL	0.996	0.992-0.999	0.022	0.996	0.993-1.000	0.039
Serum Cr, day 1	0.811	0.568-1.160	0.252	-	-	-
Serum Cr, day 4	0.627	0.415-0.948	0.027	0.667	0.417-1.064	0.089
Urine output, day 1	1.000	1.000-1.001	0.064	-	-	-

DGF: delayed graft function, CI: confidence interval, OR: odds ratio, NGAL: neutrophil gelatinase-associate lipocalin

serum NGAL at 24 hours (p-value=0.002). Parikh et al., (33) in 53 transplant patients from living and deceased donors, found a better AUC (0.9) for urine NGAL in the prediction of DGF than serum Cr. While Mojtahedzadeh et al., (36) in 69 transplant patients from deceased donors found a relative fall in serum Cr had higher AUC (0.821 vs. 0.790) than urine NGAL at 24 hours post-transplantation in the prediction of DGF. In contrast to our findings, some of the previous studies showed that NGAL level in early postoperative hours was not able to differentiate patients with DGF from those with non-DGF (35,36). Lebkowska et al., (37) found a significant decrease in serum NGAL as early as 24 hours after transplantation before the serum Cr level decreases. Two studies demonstrated that 48 hours urine NGAL showed larger AUCs and better sensitivity and specificity than those of early hours after transplantation (38, 39).

NGAL is a good predictor of early AKI post OLT, although there is significant variation in the published results. Standardized definitions of AKI and rigorous data reporting should be shown to establish its clinical usefulness and limitations (40, 41). A systematic review and meta-analysis found that urine levels of IL18 and NGAL from patients with cirrhosis discriminate between those with ATN and other types of kidney impairments, so these biomarkers might be used to determine prognosis and select treatments for patients with cirrhosis (42, 43). Plasma and urine NGAL were evaluated and compared in some studies to investigate their performance to predict DGF (31, 32, 44). In some studies, plasma NGAL showed higher sensitivity and slightly higher specificity than those of urine NGAL, which supported the superiority of plasma NGAL over urine NGAL in predicting DGF within 24 hours following kidney transplantation (44). Hollmen et al., (31) found a higher AUC value of serum NGAL (AUC, 0.85) compared to urine NGAL (AUC, 0.74). However, Maier et al., (32) reported higher AUC (0.74) of urine NGAL compared to serum NGAL (0.73) at 24 hours post-transplantation to predict DGF. These contradictory findings may be due to differences in study designs or sample size. Therefore, a large prospective kidney transplantation cohort with different sampling time points is required to illustrate the features of NGAL in predicting the risk of DGF.

The small sample size is the main limitation of this study, so further studies in larger cohorts are necessary to confirm our results. The small sample size also limited our ability to evaluate meaningfully between different variables and examine important patient subgroups. Also, due to the low sample size, a multivariate analysis of the combination of the two biomarkers was not possible. Another limitation of this study was the unavailability of cold ischemia time.

Conclusions

In conclusion, the study showed that the superior serum NGAL to serum Cr is an early predictor of graft function and DGF. Serum NGAL at the early hours after transplantation also demonstrates excellent potential for predicting DGF with fair sensitivity and specificity. While measuring serum Cr at 24 hours, post-transplantation did not help diagnose DGF. Our findings emphasize the promising role that NGAL serum can play as an early indicator of DGF.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no potential competing or conflict of interest.

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Ethics statement

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.

VCR.REC.1397.173) and the patients were enrolled after giving written informed consent.

Data availability

Data will be provided on request.

Abbreviations

AKI	Acute kidney injury
ARF	Acute renal failure
Cr	Creatinine
DGF	Delayed graft function
GODT	Global observatory donation and transplantation
NGAL	Neutrophil gelatinase-associated lipocalin

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