Role of Serum and Urine Neutrophil Gelatinase-Associated Lipocalin as Biomarkers for Assessing Graft Function in Kidney Transplant Recipients

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Abstract

Background: The existing biomarkers used to promptly identify graft dysfunction post-kidney transplantation lack consistency. Neutrophil gelatinase-associated lipocalin (NGAL) appears to be promising as kidney injury biomarker for predicting graft dysfunction. However, both serum and urine NGAL levels demonstrate varying predictive values. Our study aimed to explore the potential of NGAL as a biomarker in predicting graft dysfunction in kidney transplant patients, including live and deceased donor recipients

Methods: A single-centered observational cohort study including live and deceased donor recipients was conducted between 2018 and 2022.Serum creatinine levels were monitored on daily, and creatinine reduction on day 2 (CRR2) and creatinine reduction on day 7(CRR7) were calculated. Recipients were categorized based on graft recovery into three distinct groups: delayed graft function (DGF), slow graft function (SGF), or immediate graft function (IGF). Analysis of serum and urine NGAL was conducted two hours after the transplant, and their predictive values were evaluated by the area under the curves (AUC).

Results: Among the 40 recipients,85% received transplant from live-related donors, while 15% received deceased donor transplants. DGF occurred in 10% (4/40), while 30% (12/40) exhibited SGF, and 60% (24/40) had IGF. Serum NGAL demonstrated higher sensitivity compared to urine NGAL. At a cut-off value of 678ng/ml (AUC=0.77),serum NGAL showed 90% sensitivity and 53% specificity, while urine NGAL had 70% sensitivity and74% specificity at a cut-off value of 489ng/ml (AUC= 0.72).

Conclusions: In our population, recipients with SGF or DGF consistently had elevated levels of serum and urine NGAL compared to those without graft dysfunction. Although serum NGAL showed higher sensitivity than urine NGAL in predicting graft dysfunction, both markers lacked the specificity needed for accurate predictions.

Keywords: Biomarker, Delayed graft function, Kidney transplantation, NGAL, Slow graft function

Introduction

Kidney transplantation is considered to be the preferred treatment for recipients with end-stage kidney disease as it offers improved long-term survival and a higher quality of life compared to dialysis. However, post-transplantation complications can occur, leading to allograft dysfunction and eventual graft failure. These complications can impose a significant health and economic burden.[1] Specifically, the early post-transplant complications can vary from slow graft function (SGF) and delayed graft function (DGF) to severe rejection of the transplanted kidney.[2]

DGF is defined by the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing (UNOS) as the need for dialysis within the first week of transplant and is associated with an extended hospital stay, a higher rejection risk, and poorer long-term survival of grafts.[1,3,4] Extended donor criteria (EDC) kidneys and kidneys donated after cardiac death (DCD) are notably more pronounced to experiencing DGF,[5,6] and its incidence varies from 4-10%,[7] in living donors to almost 19-70%,[8] in deceased donor kidney transplantation. Despite major advances in transplantation, DGF remains a major obstacle to good transplant outcomes, and currently, there is no effective treatment; however, early identification is warranted to provide swift therapeutic intervention and to limit further allograft injury. Whereas, slow graft function (SGF), an intermediate phenotype, is defined as a slower initial postoperative fall in serum creatinine without the requirement for dialysis.[9,10]

Clinically, DGF is described as a manifestation of acute kidney injury (AKI), with the most common cause being post-transplantation acute tubular necrosis (ATN).[11] Due to the significant impact of ATN and its subsequent development of DGF, finding an early biomarker of AKI with greater sensitivity and specificity is essential. Although serum creatinine is a conventional marker, it is nonspecific as many other factors may influence its reliability, and by the time an increase in serum creatinine is noticed, graft dysfunction would have already developed. Therefore, considerable efforts have been devoted to identifying potential novel biomarkers that could facilitate early detection of DGF. Among several putative biomarkers, Neutrophil gelatinase-associated lipocalin (NGAL) serves as an indicator of proximal tubular injury. It is a small class of secretory glycoproteins with a signal peptide of 20 amino acids at the N-terminal end and a "lipocalin" domain of 48–193 amino acids.[12] It is a protein comprised of 178 amino acids, and belongs to acute phase protein. In response to nephrotoxic injury the expression of NGAL is notably elevated in renal tubular cells, blood and urine. NGAL holds the capability to predict both the short- and long-term prognosis in transplant recipients, and perhaps even earlier detection of graft dysfunction.[13] The elevated production of NGAL by the tubular epithelium in DGF allografts is due to ischemia/reperfusion stress experienced by the transplanted kidney before organ withdrawal, during the period of ischemic storage, and subsequent reperfusion.[14] In previous studies, NGAL started to rise at 2 hours after injury, peaking at 8-12 hours and returned to normal after 24-48 hours, however data regarding the timeline of NGAL alterations in kidney allograft recipients remains limited.[15,16] Further the reliability of both serum and urine NGAL needs to be established and it is still unclear whether urine NGAL or serum NGAL is better at foretelling the onset of DGF. There is a sparsity of data on their role in transplant recipients from developing countries. Hence, we assessed the accuracy of both serum and urine NGAL in speculating DGF in our group of kidney transplant recipients.

Methods

This was a prospective observational cohort study from January 2018 to December 2022 at a tertiary care hospital in India. The study received approval from the Institutional Ethical Committee (IEC- 68/2017), and all participants provided informed consent. This study included recipients of either gender who were above 18 years of age and had received kidneys from living-related or deceased donors. All medical conditions that could interfere with NGAL measurement including active infection and sepsis were excluded. Reporting guidelines used for the study was STROBE.

The demographic data analysed included age, gender, and BMI were collected. The cause for renal failure, type of renal transplantation, and induction therapy used was included. The post-transplantation serum creatinine was measured daily and CRR2% and CRR7% were calculated on both day 2 and day 7. According to the graft function, recipients are categorized into immediate graft function (IGF), SGF, and DGF (Table 1). Serum and urine NGAL were quantitatively measured using a standardized one-step test kit. For urine NGAL analysis,8 ml of urine sample was collected and centrifuged at 3500rpm for 5min to avoid particulate matter and cell debris, and for serum NGAL 2.4 ml of blood was collected and serum was separated. Analysis was done in FIA8000 quantitative immune analyser (GP Getein, biotech, Inc.) which uses the colloidal gold immunochromatography principle to determine serum and urine NGAL levels.

Table1: Definitions of IGF, SGF, and DGF.

Definition	**Criteria**
Immediate graft function (IGF)	"Serum creatinine reduction on day 2 (CRR2) > 30% and creatinine reduction on day 7 (CRR7) > 70% post-transplant"

Slow graft function (SGF):	"All recipients with either serum creatinine reduction on day 2 (CRR2) ≤30% or serum creatinine reduction on day 7(CRR 7) ≤70% or ≤ 10%/day fall in creatinine in the first week post-transplant". CRR 2 = serum creatinine day 1 – day 2/day 1); CRR 7 = serum creatinine day 0 – day 7/day 0)
Delayed graft function (DGF)	"Recipients with graft dysfunction requiring haemodialysis within a week of transplantation"

The normality was assessed by the Shapiro test. For continuous data, the mean and standard deviation were used, while non-continuous variables were summarized using the median with the interquartile range. To compare the percentages of categorical variables, either the chi-square test or Fisher exact test was utilized. We used a t-test to compare the mean and Mann-Whitney U to compare the median of continuous variables. Receiver operating characteristic curve (ROC) analysis was employed to determine the optimal sensitivity and specificity of urine and serum NGAL in predicting/DGF. Analysis was done using SPSS 29.0.

Results

A total of 40 renal transplant recipients were included and analysed in the study, based on the defined inclusion criteria. Among these, 60% (n=24) had IGF whereas 10% (4/40) had DGF, 30% (12/40) exhibited SGF (*Figure 1).* Due to small sample size, we combined SGF and DGF groups for the analysis. The recipient cohort had an overall mean age of 40±11 years. Within the cohort, the mean age was 24±11.3 years and 34±11.2 years for IGF and SGF+DGF groups respectively. The overall mean age of the donors and recipients was 49 ± 10.6 and 40±11 years respectively, and the majority (n=36; 83.7%) of transplant recipients were males with 78.6% (n=22) in IGF and 87.5% (n=14) in the SGF+DGF groups as shown in *Table 2*. Chronic glomerulonephritis (CGN) was found to be the leading cause of renal failure in both groups. There were on average 3/6 HLA mismatches in this study across both groups.

Overall, 34/40 (85%) in our cohort underwent live-related renal transplantation. Cadaveric transplant were significantly higher in the SGF+DGF group(p=0.04) and live related kidney transplant were higher in the IGF group(p=0.001) (*Table2*). The induction agents used were ATG, ATG-F, and Basiliximab. The majority received Basiliximab (60.5%), and there was no difference in the use of induction agents between groups(p>0.05). The mean serum creatinine value was significantly higher in SGF+DGF group compared to SGF(p=0.01) *(Table 2).*

Table 2: Baseline characteristics of the transplant recipients.

Variables	**Total (n=40)**	**IGF (n=24)**	**SGF+DGF (n=16)**	***p*-value**
Recipient Age* (years)	40±11	24±11.3	34±11.2	0.6
Recipient gender (males), n (%)	36 (83.7)	22 (78.6)	14 (87.5)	0.7
Donor Age* (years)	49 ± 10.6	42 ± 8.3	45 ± 10.7	0.8
Chronic glomerulonephritis, n (%)	28 (70)	18 (75)	10 (62.5)	0.3
HLA mismatches*	3.3 ± 1.3	3.3 ± 1.0	3.3 ± 1.2	0.6
Type of renal transplantation, n (%)				
Cadaveric	6(15)	2(8.3)	4(25)	**0.04**
Live donor	34(85)	22(91.6)	12(75)	**0.01**
Induction agents, n (%)				
ATG	7(17.5)	2(8)	5(31.2)	0.9
ATG-F	9(22.5)	4(12.5)	5(31.2)	0.2
Basiliximab	24(60.5)	18(45.8)	6(37.5)	0.4
Serum creatinine*, mg/dl				
Day 1	3.9±1.6	2.8±1.2	5.2±1.8	**0.01**
Day 2	2.3± 0.8	1.6±0.6	5.0±1.9	**0.01**
Day 7	1.5±0.7	1.3±0.4	3.7±1.2	**0.01**

** Mean ±Standard deviation*

In our study, we analysed the median serum and urine NGAL concentration at 2 hours post-transplantation. In those with SGF+DGF, both serum and urine NGAL were higher compared to the IGF group (807 vs 620 ng/ml, p=0.02; 590 vs 476 ng/ml, p=0.04) *(Table 3).*

Table 3: Serum and urine NGAL at 2 hours post-transplantation.

NGAL, ng/ml	IGF	SGF+DGF	*p*-value
Serum NGAL*, ng/ml	620 (184.78-2586.6)	807(317-1662)	0.02
Urine NGAL*, ng/ml	476 (226-1734)	590(365-240.9)	0.04

*NGAL: neutrophil gelatinase-associated lipocalin, * Median ± IQR*

Serum NGAL demonstrated a sensitivity of 90% and specificity of 53% at a cut-off value of 678 ng/ml. The area under the ROC curve was 0.77 *(Figure 1).* While urine NGAL showed 70% sensitivity and 74% specificity at cut-off 489 ng/ml, the area under the ROC curve was 0.72 *(Figure 2).* Thus, in our cohort, serum NGAL was more sensitive than urine NGAL in predicting SGF/DGF, however, as far as specificity was considered both were found to be non-specific.

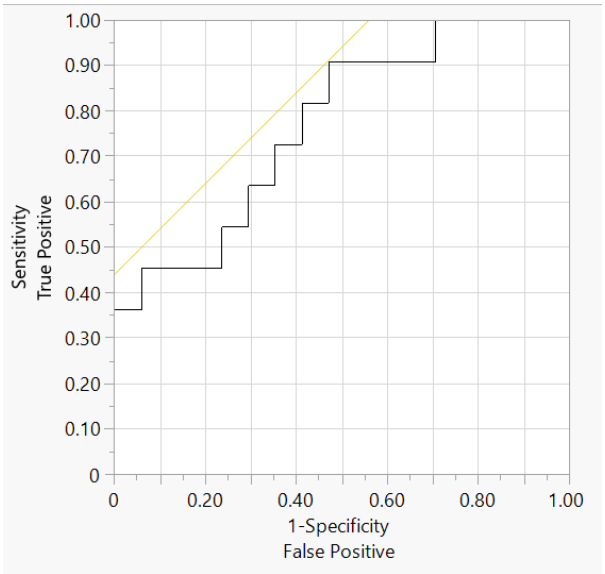

Figure 1: Receiver operating-characteristic curves for serum NGAL at 2 hours post-transplantation for predicting graft function in SGF+DGF group.

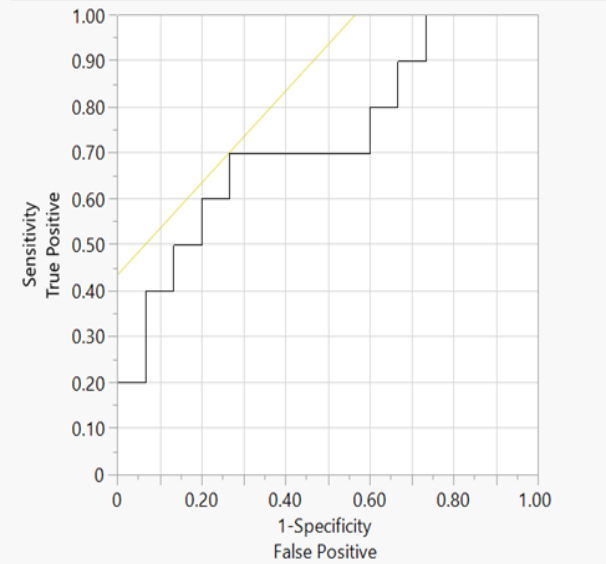

Figure 2: Receiver operating-characteristic curves for urine NGAL at 2 hours post-transplantation for predicting graft function in SGF+DGF group.

Discussion

NGAL (lipocalin-2) is a small group of secretory glycoproteins comprising 20 amino acids at the N-terminal end followed by a "lipocalin" domain of 48–193 amino acids.[12] Initially, NGAL was identified as a component of neutrophil granules, however, it is also secreted from several human tissues including hepatocytes, and gastrointestinal and pulmonary tract cells.[17] According to reports, it participates in several pathways, including apoptosis, bacteriostasis, proliferation, and regeneration of renal tubule epithelial cells.[14] NGAL levels exhibit a significant increase in case of proximal tubular injury. As a result, studies have highlighted the usefulness of both urine and serum NGAL in various clinical conditions of AKI, including cardiac surgery,[18] and contrast-induced AKI after cardiac cauterization,[19] however, in the context of DGF post-renal transplantation, the predictability varies based on the literature review.[20] To effectively detect DGF in kidney transplant recipients, clinicians must know when to detect NGAL which usually rises 2 hours after the injury, peaks at 8–12 hours, and reaches baseline after 24–48 hours.[21] In this study, we conducted a quantitative comparison of the predicting ability of serum and urine NGAL in recipients who underwent live-related as well as cadaveric renal transplantation and subsequently developed SGF or DGF eventually.

In our study, we analysed a total of 40 renal transplant recipients. 60% (n=24) had IGF whereas 40% (n=16) of cases were found to have SGF+DGF. These findings share similarities with the study by Hall IE et al.[21] In their study, a total of 91 recipients were analysed, of which 50/91 (54.9%) recipients had deceased donors and 34/91 (37.3%) had DGF, 33/91 (36.2%) had SGF, and 24/91 (26.3%) had IGF. Pourmand G et al.[22] analysed 29 post-transplant recipients wherein 8/29 (27.6%) recipients developed DGF which is similar to our study.

In this study, Basiliximab was the induction agent (n=24; 60.5%) used predominantly in both groups. The study by Maier et al,[23] which included 170 recipients wherein the majority were given Basiliximab as the induction agent in both the IGF group (83/118 (70%)) and DGF group (45/52 (87%)) which is identical to our study. Inconsistent with these, in Hall IE et al.[21] study ATG was used predominantly (56%) as the induction agent. The variation in the induction agents observed in studies may be attributed to the lack of uniformity in the choice of induction agents among practicing nephrologists and many recipient and donor-related factors influence the choice of induction agent before transplantation.

In the present study, we found that the median concentration of both serum and urine NGAL were higher in the SGF+DGF group compared to the IGF group. This aligns with previous studies wherein serum NGAL levels were reported 436 ng/ml at less than 6 hours of transplantation,[24] and urine NGAL was reported 560ng/ml on day 1 post transplant.[25] Further, Hollmen,[24] reported DGF Predictability was best in the group where sample was drawn in less than 6 hours. Pourmand G et al. also demonstrated that serum NGAL predicts DGF during the early post-transplantation period (p =0.005), further, serum NGAL was the only significant independent predictor of DGF based on the multivariate analysis (p=0.039).[22] In our study the choice of measuring NGAL at 2-hour post transplantation is considered to be significant due to the critical phase where significant changes in NGAL production occurs, reflecting the initial response to renal injury. By quantifying NGAL at this point offers valuable insights into the early stages of kidney injury, aiding timely detection and management.

In the current study, serum NGAL showed 90% and 53% sensitivity and specificity respectively with a cut-off of 678ng/ml (AUC=0.77), while urine NGAL showed 70% and 74% sensitivity and specificity with a cut-off of 489ng/ml (AUC=0.72) suggesting that in our cohort, serum NGAL was more sensitive than urine NGAL in predicting SGF/DGF but were nonspecific.This can be explained by the fact that the predictability of urine NGAL might be affected by frequent occurrence of oliguria and anuria in the post-operative period.[15,16] In the metanalysis by Li et al,[20] including a total of 1036 recipients from 8 observational studies on urine NGAL and 6 studies on serum NGAL observed that the composite AUC for urine NGAL was 0.91 (95% CI, 0.89–0.94) with 88% sensitivity and 81% specificity, and the composite AUC for serum NGAL was 0.95 (95% CI, 0.93–0.97) with 91% sensitivity and 86% specificity, thus suggesting both urine and serum NGAL being valuable biomarkers for early prediction of DGF.

The urine and serum NGAL source varies as the serum NGAL comes from the systematic pool, most urine NGAL is produced by the distal nephron rather than being filtered from the blood, therefore, theoretically, it was anticipated that urine NGAL would represent kidney injury better than serum NGAL.[26] In Li et al meta-analysis, however, demonstrated that serum NGAL displayed a definite increase in sensitivity and a marginal increase in specificity compared to urine NGAL which was also supported by Buemi's study,[27] which compared the predictive abilities of serum and urine NGAL for DGF in 97 recipients and found that serum NGAL had higher AUC values

than urine NGAL suggesting it to be a better predictor for DGF. One of the potential explanations was that a variety of variables including urine concentration and glomerular filtration rate could influence urine NGAL levels, decreasing urine NGAL predictive power, which was useful for most of the clinicians because, in addition to having better predictive ability, serum NGAL would be more practical for kidney transplant recipients who experienced severe oliguria or even anuria after surgery.

The variation in sensitivity and specificity from different studies is due to multiple factors like differences in population, race, methods of estimation, and sampling timings post-transplant. We have summarised the existing studies, and various cut-off values on both serum and urine NGAL for predicting renal graft dysfunction in *Table 4*. We need large-scale multicentre prospective studies with serial monitoring of NGAL with the timing of collection to identify cutoff values of both serum and urine NGAL for predicting DGF.

Table 4: Overview of studies analysing NGAL in predicting DGF.

Study	Sample size	Sampling Time	Cut off value(ng/ml)	AUC	sensitivity	specificity	Clinical significance
Serum NGAL							
Pezeshgi,[28] (2016)	37	6hrs and 12hrs	6hrs-309 12hrs-317	0.68 0.97	66 100	64 92	12hrs NGAL plasma NGAL showed higher predictability compared to serum creatinine
Cantaluppi,[29] (2015)	50	24hour	532	0.94	90.9	80.6	Significantly higher levels of NGAL in the DGF group than in the non-DGF group
Hollmen,[24] (2015)	176	<6hours,7-12hours and >12hours	<6hrs-436 7-12hrs-420 >12hours-420	1.00 0.86 0.92	100 94 91	100 73	DGF Predictability was best in the group where sample was drawn in less than 6 hours
Lee,[30] (2012)	59	Day 1,5, and 14 post transplantation. ROC was compared with IL-18 and SCr	233.3	0.86	78.6	77.8	The AUC of NGAL on day 1 was higher than IL-18 and creatinine. On days 5 and 14, the AUC values were not significant to predict DGF
Urine NGAL							
John,[31] (2016)	79	48hours	120	0.80	75	71	NGAL at 48 hours predicted DGF
Cui,[32] (2015)	129	At 4,12,24,48and 72 hours. ROC was compared with IL-18 and SCr	4h-521.7 12h-559.2 24h-688.3 48h-295.2 72h-297.4	4h-0.78 12h-0.80 24r-0.83 48h-0.89 72h-0.86	4h-80.0 12h-80.0 24h-70.0 48h-80.0 72h-80.0	4h-68.7 12h-68.7 24h-93.7 48h-96.9 72h-100	The specificity was increased with time, but sensitivity does not show any change. AUC was higher to 0.984 with 100% sensitivity and 96.9% specificity in the combination panel of NGAL+ IL-18 and SCr
J Kanter,[33] (2013)	38	At days 1,3,6 and 10 post-transplantations Compared the ROC between days 1 and 3	1day-128 3day-124	0.71 0.91	85.7 80	61.5 83	Day 3 uNGAL performed better predictability than day1
Hollmen,[25] (2011)	176	Day 1 Post-transplant	560	0.74	65	74	Day 1 uNGAL predicted early and prolonged DGF that led to the worst graft survival
Our study	40	2hrs	sNGAL-678ng/ml uNGAL-489ng/ml	0.77 0.72	90 70	53 74	sNGAL demonstrated higher sensitivity compared to urine NGAL.However, both appeared to lack specificity.

**DGF-delayed graft function, IL-18- Interleukin-18, SCr- serum creatinine, u NGAL- urinary NGAL, sNGAL-serum NGAL.*

Our study was conducted in a single center limiting the external validity to other centers with different settings and the sample size is relatively small. We conducted only single serum and urine measurements and did not include serial monitoring of NGAL over time. We did not compare the performance of NGAL with other potential biomarkers, which could provide a more comprehensive understanding of their predictive abilities.

Conclusion

In our population, serum and urine NGAL were significantly elevated in renal transplant recipients with SGF/DGF. The serum NGAL was more sensitive than urine NGAL for predicting SGF/DGF but both appear to be non-specific. However, the optimum NGAL cut-off value for clinical application will need to be determined by more large-scale prospective cohort studies.

Author Contribution

All authors have substantially contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity

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References

1. Wu WK, Famure O, Li Y, Kim SJ. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. Kidney Int 2015 Oct;88(4):851-858. . Published online 24 Jun 2015.

2. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. Lancet 2004 Nov;364(9447):1814-1827. .

3. Tapiawala SN, Tinckam KJ, Cardella CJ, Schiff J, Cattran DC, Cole EH, et al. Delayed graft function and the risk for death with a functioning graft. J Am Soc Nephrol 2010 Jan;21(1):153-161. .

4. Butala NM, Reese PP, Doshi MD, Parikh CR. Is delayed graft function causally associated with long-term outcomes after kidney transplantation? Instrumental variable analysis. Transplantation 2013 Apr;95(8):1008-1014. .

5. Barreda Monteoliva P, Redondo-Pachón D, Miñambres García E, Rodrigo Calabia E. Kidney transplant outcome of expanded criteria donors after circulatory death. Nefrologia (Engl Ed) 2022;42(2):135-144. English Edition.

6. Querard AH, Le Borgne F, Dion A, Giral M, Mourad G, Garrigue V, et al. Propensity score-based comparison of the graft failure risk between kidney transplant recipients of standard and expanded criteria donor grafts: Toward increasing the pool of marginal donors. Am J Transplant 2018 May;18(5):1151-1157. .

7. Querard AH, Foucher Y, Combescure C, Dantan E, Larmet D, Lorent M, et al. Comparison of survival outcomes between Expanded Criteria Donor and Standard Criteria Donor kidney transplant recipients: a systematic review and meta-analysis. Transpl Int 2016 Apr;29(4):403-415. .

8. Melih KV, Boynuegri B, Mustafa C, Nilgun A. Incidence, Risk Factors, and Outcomes of Delayed Graft Function in Deceased Donor Kidney Transplantation. Transplant Proc 2019 May;51(4):1096-1100. .

9. Boom H, Mallat MJ, de Fijter JW, Zwinderman AH, Paul LC. Delayed graft function influences renal function but not survival. Transplant Proc 2001;33(1-2):1291. .

10. Moore J, Shabir S, Chand S, Bentall A, McClean A, Chan W, et al. Assessing and comparing rival definitions of delayed renal allograft function for predicting subsequent graft failure. Transplantation 2010 Nov;90(10):1113-1116. .

11. Lechevallier E, Dussol B, Luccioni A, Thirion X, Vacher-Copomat H, Jaber K, et al. Posttransplantation acute tubular necrosis: risk factors and implications for graft survival. Am J Kidney Dis 1998 Dec;32(6):984-991. .

12. Chakraborty S, Kaur S, Guha S, Batra SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. Biochim Biophys Acta 2012 Aug;1826(1):129-169.

13. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003 Oct;14(10):2534-2543. .

14. Pajek J, Škoberne A, Šosterič K, Adlešič B, Leskošek B, Bučar Pajek M, et al. Non-inferiority of creatinine excretion rate to urinary L-FABP and NGAL as predictors of early renal allograft function. BMC Nephrol 2014 Jul;15:117. .

15. Fonseca I, Oliveira JC, Almeida M, Cruz M, Malho A, Martins LS, et al. Neutrophil gelatinase-associated lipocalin in kidney transplantation is an early marker of graft dysfunction and is associated with one-year renal function. J Transplant 2013;2013:650123. .

16. Chakraborty S, Kaur S, Tong Z, Batra SK, Guha S. Neutrophil gelatinase associated lipocalin: structure, function and role in human pathogenesis. InTech; 2011 Oct 5.

17. Kjeldsen L, Johnsen AH, Sengeløv H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. J Biol Chem 1993 May;268(14):10425-10432. .

18. Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, et al. Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. Am J Kidney Dis 2015 Dec;66(6):993-1005. .

19. Zhou F, Luo Q, Wang L, Han L. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. Eur J Cardiothorac Surg 2016 Mar;49(3):746-755. .

20. Li YM, Li Y, Yan L, Wang H, Wu XJ, Tang JT, et al. Comparison of urine and blood NGAL for early prediction of delayed graft function in adult kidney transplant recipients: a meta-analysis of observational studies. BMC Nephrol 2019 Aug;20(1):291. .

21. Hall IE, Yarlagadda SG, Coca SG, Wang Z, Doshi M, Devarajan P, et al. IL-18 and urinary NGAL predict dialysis and graft recovery after kidney transplantation. J Am Soc Nephrol 2010 Jan;21(1):189-197. .

22. Pourmand G, Emamjomeh B, Gooran S, Namdari F, Mehrsay A, Dehghani S, Mashhadi R, Aghaii M, Bagherpour F, Heidari F, Ashtari S. The Predictive value of serum NGAL for the diagnosis of Delayed Graft Function in kidney transplantation.

23. Maier HT, Ashraf MI, Denecke C, Weiss S, Augustin F, Messner F, et al. Prediction of delayed graft function and long-term graft survival by serum and urinary neutrophil gelatinase-associated lipocalin during the early postoperative phase after kidney transplantation. PLoS One 2018 Jan;13(1):e0189932. .

24. Hollmen ME, Kyllönen LE, Merenmies J, Salmela KT. Serum neutrophil gelatinase-associated lipocalin and recovery of kidney graft function after transplantation. BMC Nephrol 2014 Jul;15:123. .

25. Hollmen ME, Kyllönen LE, Inkinen KA, Lalla ML, Salmela KT. Urine neutrophil gelatinase-associated lipocalin is a marker of graft recovery after kidney transplantation. Kidney Int 2011 Jan;79(1):89-98. .

26. Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, et al. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. Kidney Int 2009 Feb;75(3):285-294. .

27. Buemi A, Musuamba F, Frederic S, Douhet A, De Meyer M, De Pauw L, et al. Is plasma and urine neutrophil gelatinase-associated lipocalin (NGAL) determination in donors and recipients predictive of renal function after kidney transplantation? Clin Biochem 2014 Oct;47(15):68-72. .

28. Pezeshgi A, Abedi Azar S, Ghasemi H, Kamali K, Esmaeilzadeh A, Hajsalimi B, et al. Role of plasma neutrophil gelatinase-associated lipocalin as an emerging biomarker of acute renal failure following kidney transplantation and its correlation with plasma creatinine. J Renal Inj Prev 2016 Mar;5(2):98-103. .

29. Cantaluppi V, Dellepiane S, Tamagnone M, Medica D, Figliolini F, Messina M, et al. Neutrophil Gelatinase Associated Lipocalin Is an Early and Accurate Biomarker of Graft Function and Tissue Regeneration in Kidney Transplantation from Extended Criteria Donors. PLoS One 2015 Jun;10(6):e0129279. .

30. Lee EY, Kim MS, Park Y, Kim HS. Serum neutrophil gelatinase-associated lipocalin and interleukin-18 as predictive biomarkers for delayed graft function after kidney transplantation. J Clin Lab Anal 2012 Jul;26(4):295-301. .

31. Nieto-Ríos JF, Serna-Higuita LM, Ocampo-Kohn C, Aristizábal-Alzate A, Vélez-Echeverry C, Vanegas-Ruiz JJ, et al. Neutrophil gelatinase-associated lipocalin as an early predictor of delayed graft function. Biomedica 2016 Jun;36(2):213-219. .

32. Cui LY, Zhu X, Yang S, Zhou JS, Zhang HX, Liu L, et al. Prognostic Value of Levels of Urine Neutrophil Gelatinase-associated Lipocalin and Interleukin-18 in Patients With Delayed Graft Function After Kidney Transplantation. Transplant Proc 2015 Dec;47(10):2846-2851. .

33. Kanter J, Beltran S, Molina D, Vallecillo J, Sancho A, Gavela E, et al. Urinary neutrophil gelatinase-associated lipocalin after kidney transplantation: is it a good biomarker to assess delayed graft function? Transplant Proc 2013 May;45(4):1368-1370. .