Original Article

The value of cystatin C and urinary and serum neutrophil gelatinase-associated lipocalin during the perioperative period of renal transplantation

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Background: The perioperative management of renal transplantation is complex. Our research aimed to study the clinical value of cystatin-C (Cys-C) and urinary and serum neutrophil gelatinase-associated lipocalin (NGAL) during the perioperative period of renal transplantation.

Methods: We collected the clinical information of 47 renal transplantation patients. Urine and serum samples were collected daily until the second week and then weekly until discharge to determine serum NGAL (s-NGAL), urine NGAL (u-NGAL), serum creatinine (s-Cr), and Cys-C levels. Receiver-operating characteristic (ROC) analysis was used, and the area under the curve (AUC) was compared to evaluate the accuracy of the diagnosis of delayed graft function (DGF). Multivariable analysis was used to find the association between the markers and renal function at discharge.

Results: In our research, the value of Cys-C, serum NGAL, and urine NGAL were higher in DGF group. In the ROC analysis, Cys-C had the highest AUC (0.939) compared with s-NGAL (0.909), u-NGAL (0.856), and s-Cr (0.747). Multivariable analysis showed that Cys-C levels in the first week after the operation and cold ischemia time were independently associated with estimated glomerular filtration rate (eGFR) at discharge ($P<0.05$).

Conclusions: Our results showed that Cys-C, serum NGAL, and urine NGAL could reflect renal function sensitively. Cys-C had the highest sum of sensitivity and specificity at 4.77 mg/L, with a sensitivity of 0.818 and specificity of 0.889. The Cys-C level during the first week after the operation was independently associated with eGFR at discharge and could predict the short-term prognosis of renal transplantation patients.

Keywords: Renal transplantation; delayed graft function (DGF); cystatin-C (Cys-C); neutrophil gelatinase-associated lipocalin (NGAL)

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Introduction

Renal transplantation is the best method for the treatment of end stage of renal disease (ESRD). Patients do not need dialysis after a successful kidney transplant. Benefiting from the efficient system of donors after cardiac death (DCD), the number of renal transplants is rising rapidly in China. The surgical technique for renal transplantation has constantly improved and is now a mature technology. However, the management of the perioperative period is very complicated. Delayed graft function (DGF) is one of the most common complications after renal transplantation, and it is the main problem of successful transplantation. DGF can increase the incidence of acute rejection and decrease the survival time of the allograft (1). In our clinical practice, DGF is diagnosed depending on urine volume, Cr, and the need for dialysis. Early diagnosis of DGF and timely intervention are very important. However, there is currently no valuable indicator to evaluate renal status during the perioperative period.

Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein found in neutrophils, and recent research has confirmed its function in evaluating renal performance. It is markedly increased after ischemic, septic, or nephrotoxic injury of the kidney (2). Other research found that urine NGAL levels were higher in DGF patients. Serum and urinary NGAL may thus be useful early predictors of DGF after kidney transplantation (3,4). Moreover, NGAL is produced in the renal tubule cells and will rise rapidly immediately after acute kidney injury. This can easily be detected in urine samples (5).

Cystatin-C (Cys-C) is an endogenous cysteine proteinase inhibitor, independent of gender, age, and muscle mass of the individual. Cys-C in the blood is cleared only by glomerular filtration, and this feature gives its exclusive sensitivity to glomerular filtration rate (GFR) changes (6). Some researchers have shown that Cys-C is superior to serum creatinine in the assessment of renal function (7). Other recent investigation has indicated that cystatin C might become a sensitive marker in the early diagnose of renal injury (8).

Our study aimed to study the function of NGAL and Cys-C to assess DGF and predict the short-term prognosis of renal transplantation patients.

Methods

This study was performed at the First Affiliated Hospital of Soochow University, Suzhou, China. Our research was a retrospective analysis approved by the medical ethics committee of the First Affiliated Hospital of Soochow University (Number 38). We collected the information of the patients from June 2016 to July 2017. All the patients were first time recipients of renal transplantation, needed because of ESRD. This study comprised 47 patients. The mean age of the patients was 44 years old.

Laboratory methods

Urine and serum samples were collected on the morning following the operation, nearly 3 to 12 hours after renal transplantation, then daily during the 1st week following the operation, and then at 14 and 21 days after operation. Serum creatinine was examined preoperatively, daily until the 2nd week, and then weekly until discharge.

NGAL was measured with an NGAL kit (Getein Biotech, China) with a detection range of 50–5,000 ng/mL. If the value of the sample was higher than 5,000 ng/mL, we diluted the sample 2 times. If the value was lower than 50 ng/mL, we marked it 50 ng/mL. NGAL measurements were performed using a dry immunofluorescence method. Cys-C was measured with cystatin C kit (Meikang Biotech, China); at the same time points, NGAL was measured. The test method was latex-enhanced immunoturbidimetry. The laboratory technician was blinded to patient information. Creatine was tested with enzymatic creatine-2 reagents (Siemens Healthcare Diagnostics Inc., Canada); the test is based on an enzyme method.

Definitions

DGF was defined as the requirement for dialysis within the first 7 days after renal transplantation, due to the poor recovery of the graft. Situations such as hyperkalemia and hypervolemia were excluded (9). Non-DGF was defined as no dialysis requirement within the first week after renal transplantation (10).

S-NGAL means the NGAL in serum and u-NGAL means the NGAL in the urine. S-Cr means the creatinine in serum.

Estimated GFR was calculated using the correction formula known as the Chinese population corrected MDRD, which has better accuracy of the true GFR in Chinese renal transplantation patients (11).

The standard of discharge was when renal function and the concentration of antirejection drugs were stable.

There were no infections such as urinary tract infection or pneumonia. The wound healed well, and the internal stent was extracted.

Statistical analysis

Statistical analysis was done using SPSS 19.0. The diagrams of the changes in the variables were drawn with Graphpad 7.0. Normality was evaluated for each variable by the Kolmogorov-Smirnov test. The data are summarized as the mean and standard deviation (SD) for variables with a normal distribution or as the median and 25^{th}–75^{th} quartiles (interquartile range) for variables with a skewed distribution. Comparisons between continuous variables were made using either the *t*-test or the Mann-Whitney test, according to the data. Categorical variables are presented as percentages. The Chi-square test was used to compare the differences in the categorical variables. Receiver-operating characteristic (ROC) curves and area under the curve (AUC) were used for determining the efficiency and cut-off point of s-NGAL, u-NGAL, Cys-C, and s-Cr, in diagnosing DGF. All the analyses were two-tailed with a significance level of 0.01. The best cut-off values for biomarkers and s-Cr were chosen according to the maximum sum of sensitivity and specificity. Multivariable analysis was used to describe the independent association of s-NGAL, u-NGAL, Cys-C, and s-Cr with e-GFR at discharge.

Results

Patient characteristics

Basic clinical characteristics of the renal transplantation patients are shown in *Table 1*. Before the research period, 1 patient suffered from bleeding, and the allograft was resected. Forty-seven patients were enrolled in the study. Among these patients, 11 patients suffered DGF. At basic levels, the 2 groups were compared in terms of donor condition and recipient condition. We used the Kolmogorov-Smirnov test to confirm the normality of the data. Apart from BMI and urine volume before renal transplantation, the other data were normally distributed. There were no differences between the 2 groups except for cold ischemia time (P<0.01) and urine volume before renal transplantation (P<0.01).

Differences in s-NGAL, u-NGAL, Cys-C, s-Cr, and eGFR between the DGF and non-DGF groups

The differences in the biomarkers between the two groups are listed in *Table 2* and *Table 3*. We checked the normality of the data first. All the s-NGAL and Cys-C data were normally distributed. However, the u-NGAL, s-Cr, and eGFR data were not normally distributed. We then used the *t*-test to compare the difference in s-NGAL and Cys-C; the data are shown as the mean ± SD. We used the Mann-Whitney test to compare the difference in u-NGAL, s-Cr, and eGFR; the data are shown as the median (interquartile range). S-NGAL concentrations were markedly higher in the DGF group, except for the time point on the 14^{th} day (P>0.05). The u-NGAL, Cys-C, and s-Cr levels were markedly higher in the DGF group at all time points (P<0.05). The e-GFR level was markedly higher in the non-DGF group at the time of discharge (P<0.01).

The longitudinal changes in u-NGAL, s-NGAL, Cys-C, and s-Cr were drawn with Graphpad 7.0 and are shown in *Figure 1*. The longitudinal changes in Cr (*Figure 1B*), s-NGAL (*Figure 1C*), and u-NGAL (*Figure 1D*) were characterized by an initial rapid decline and then a slow decrease in the following days in both the DGF and non-DGF groups. The curves for the DGF group were above the curves of the non-DGF group at all points. The change in Cys-C was the same in the non-DGF group. However, the change in Cys-C in the DGF group was different.

The decrease in Cys-C was slower in the DGF group than the non-DGF group (*Figure 1A*). We doubt that this was associated with the addition of calcineurin inhibitors (CNIs). We then investigated the longitudinal changes in Cys-C before and after the addition of CNIs. The results are provided in *Figure 2*. There was a small rise after the addition of CNIs and then a rapid decline on the 3^{rd} day in the DGF group. However, there was no rise in the non-DGF group.

ROC analysis of s-NGAL, u-NGAL, Cys-C, and s-Cr for predicting DGF

The predictive value of s-NGAL, u-NGAL, Cys-C, and s-Cr was evaluated with ROC curves. The results are shown in *Figure 3*, *Table 4*, and *Table 5*. *Table 4* shows the AUC and P value for the four indicators on the 1^{st} after the operation.

Table 1 Baseline clinical characteristics between DGF and non-DGF group

Variable	DGF	Non-DGF	P
Total	11	36	
Recipient			
Age (years)	39.6±10.5	40.8±10.2	0.748
Male (%)	6 (54.5)	22 (61.1)	0.737
BMI (kg/m^2)	20.9 (17.5–26.0)	21.3 (16.2–28.6)	0.714
Cause of ESRD, n (%)			
Glomerulonephritis	2 (18.2)	14 (38.9)	
IgA renal disease	1 (9.1)	6 (16.7)	
Polycystic kidney	1 (9.1)	3 (8.3)	
Diabetic nephropathy	2 (18.2)	4 (11.1)	
Others	5 (45.5)	9 (25)	
Urine volume before RT	72 (0–200)	333 (0–1,600)	0.004*
Blood type, n (%)			
A	0 (0)	12 (33.3)	
B	3 (27.3)	9 (25)	
AB	2 (18.2)	3 (8.3)	
O	6 (54.5)	12 (33.3)	
Pre-transplant therapy, n (%)			0.56
Peritoneal dialysis	3 (27.3)	7 (19.4)	
Hemodialysis	8 (72.7)	26 (72.2)	
Others	0 (0)	3 (8.3)	
Dialysis time (month)	55.5±30.7	40.4±37.5	0.233
Serum Cr before RT	987.5±187.8	969.8±330.2	0.866
Donor			
Age (years)	43.3±5.4	41.3±5.6	0.295
S-Cr (μmol/L)	130.7±36.4	107.7±33.9	0.059
Cold ischemia time(hours)	17.0±4.1	13.4±3.8	0.009*
CDC	2.9±0.9	2.6±0.7	0.256
HLA mismatch number	5.0±1.0	5.0±0.9	0.931
PRA (%)			
Negative percentage	100	100	
Induction regimen, n (%)			0.31
ATG-F	8 (72.7)	19 (52.8)	
Basiliximab	3 (27.3)	17 (47.2)	
Immunosuppression drug, n (%)			
Steroids	11 (100.0)	36 (100.0)	
CNIs			0.367
Tacrolimus	8 (72.7)	31 (86.1)	
Cyclosporine A	3 (27.3)	5 (13.9)	

*P<0.05. DGF, delayed graft function; non-DGF, prompt graft function; BMI, body mass index; ESRD, end stage of renal disease; CDC, complement dependent cytotoxicity; HLA, human leukocyte antigen; PRA, panel reactive antibody; ATG-F, anti-thymocyte globulin; CNIs, calcineurin inhibitors.

S-NGAL, u-NGAL, and Cys-C were accurate in predicting DGF, while s-Cr was not (P>0.01); Cys-C shows the largest AUC (0.939). The cut-off values for s-NGAL, u-NGAL, and Cys-C were chosen according to the maximum sum of sensitivity and specificity (*Table 5*). The data in the table contain the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). S-NGAL had the highest sensitivity at 1,025.86 ng/mL (sensitivity: 0.909; specificity: 0.778; PPV: 0.556; NPV: 0.966). U-NGAL had the highest specificity at 1,787.8 ng/mL (sensitivity: 0.727; specificity: 0.972; PPV: 0.889; NPV: 0.921). Cys-C had the highest sum of sensitivity and specificity at 4.77 mg/L (sensitivity: 0.818; specificity: 0.889; PPV: 0.692; NPV: 0.941).

The predictive value of s-NGAL, u-NGAL, Cys-C, and s-Cr for predicting renal function at discharge

The predictive values of s-NGAL, u-NGAL, Cys-C, and s-Cr were tested with multivariable analysis. In multivariable linear regression models, we incorporated 12 variables including recipient sex, age, BMI, s-Cr before the operation, CDC, cold ischemia time, acute rejection, drug poisoning, s-NGAL, u-NGAL, Cys-C, and s-Cr after the operation. The s-NGAL, u-NGAL, Cys-C, and s-Cr values during the first 7 days after operation were analyzed. We used the eGFR at the time of discharge as the prognostic value. The results are shown in *Table 6*. Our research shows that the values of Cys-C on days 1, 3, 4, 5, 6, and 7 after

Table 2 The differences of s-NGAL and Cys-C between DGF and non-DGF group

Variable (days after operation)	DGF (mean ± SD)	Non-DGF (mean ± SD)	P
s-NGAL (ng/mL)			
1st day	1,680.0±830.8	801.2±352.5	0.006*
2nd day	1,671.7±835.1	530.1±276.7	0.001*
3rd day	856.3±373.9	475.8±360.8	0.004*
4th day	595.0±233.3	306.1±212.5	0.000*
5th day	488.0±221.7	287.1±199.0	0.006*
6th day	525.6±194.7	300.0±217.2	0.004*
7th day	600.8±309.3	316.5±257.5	0.004*
14th day	560.1±365.1	372.1±196.0	0.128
21st day	497.4±330.1	310.1±209.7	0.029*
Cys-C (mg/L)			
1st day	5.8±1.1	3.3±1.1	0.000*
2nd day	5.6±1.2	2.7±1.0	0.000*
3rd day	5.5±1.0	2.5±1.0	0.000*
4th day	5.6±1.2	2.5±1.1	0.000*
5th day	5.8±1.3	2.6±1.2	0.000*
6th day	5.7±1.3	2.5±1.2	0.000*
7th day	5.5±1.4	2.4±1.1	0.000*
14th day	3.9±1.4	2.1±1.0	0.000*
21st day	3.5±1.4	1.9±0.7	0.004*

*P<0.05. DGF, delayed graft function; non-DGF, prompt graft function; s-NGAL, neutrophil gelatinase associated lipocalin in serum; Cys-C, cystatin-C.

operation were independently associated with eGFR at discharge (P<0.01). Cys-C and eGFR are negatively related. The value of s-Cr on day 2 was independently associated (negative relationship) with eGFR at discharge (P<0.01). Cold ischemia time of the organ was independently associated (negative relationship) with eGFR at discharge (P<0.05).

Table 3 The differences of Cr, u-NGAL and e-GFR between DGF and non-DGF group

Variable (days after operation)	DGF, media [IQR]	Non-DGF, media [IQR]	P
s-Cr (μmol/L)			
1st day	1,010 [819–1,140]	540 [411–742]	0.014*
2nd day	892 [612–1,043]	267 [201–538]	0.000*
3rd day	722 [602–797]	159 [127–370]	0.000*
4th day	526 [426–761]	140 [109–234]	0.000*
5th day	512 [371–690]	117 [97–163]	0.000*
6th day	557 [297–616]	96 [92–133]	0.000*
7th day	389 [331–681]	93 [89–137]	0.000*
14th day	260 [183–404]	108 [93–127]	0.000*
21st day	224 [159–452]	113 [90–134]	0.000*
Discharge	135 [98–148]	99 [77–116]	0.004*
u-NGAL (ng/mL)			
1st day	2,622.5 [1,072–5,436]	369.4 [176.3–747.3]	0.000*
2nd day	2,189.5 [1,448.0–5,028.2]	140.9 [66.3–369.3]	0.000*
3rd day	1,749 [1,022–3,021]	94.9 [50.0–199.3]	0.000*
4th day	1,438.4 [830.0–1,520.8]	64.2 [50.0–110.8]	0.000*
5th day	887.0 [255–2,586.3]	52.2 [50.0–79.1]	0.000*
6th day	599.1 [388.9–2,205.9]	51.3 [50.0–96.7]	0.000*
7th day	522.0 [386.7–1,800]	56.0 [50.0–77.0]	0.000*
14th day	242.0 [89.1–1,376.6]	56.9 [50.0–85.1]	0.005*
21st day	102.0 [79.8–770.5]	58.6 [50.0–74.5]	0.002*
e-GFR [mL/(min·1.73 m^2)]			
Discharge	85.2 [62.3–106.1]	56.5 [44.1–70.5]	0.000*

*P<0.05. DGF, delayed graft function; non-DGF, prompt graft function; s-Cr, serum creatinine; u-NGAL, neutrophil gelatinase associated lipocalin in urine; e-GFR, estimated glomerular filtration rate.

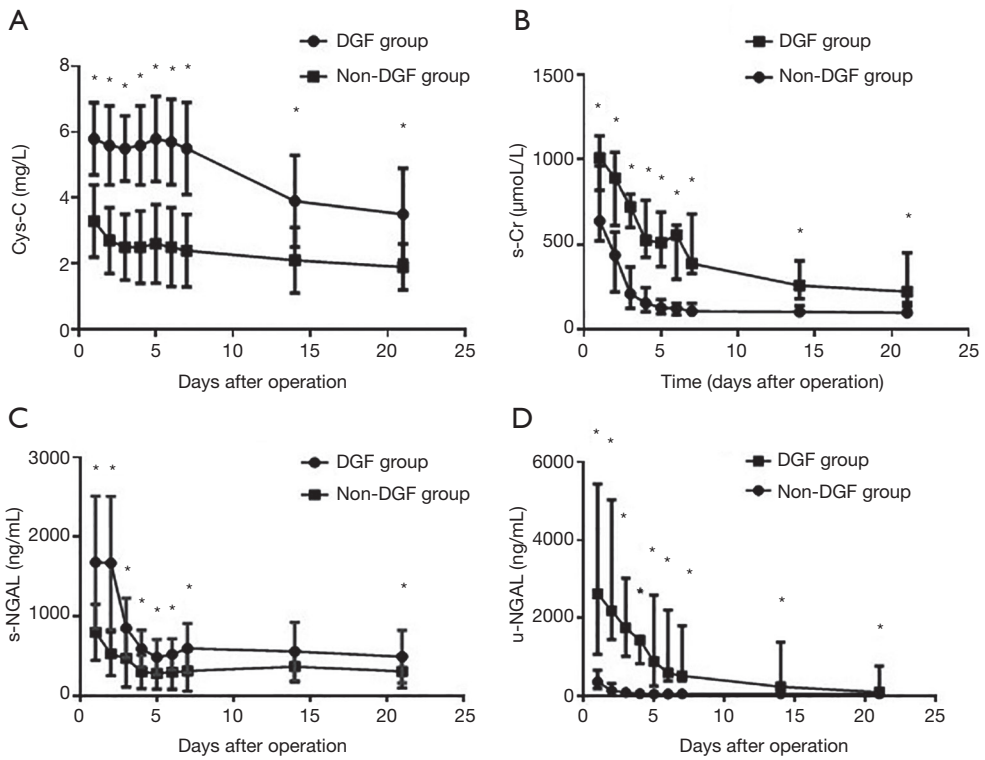

Figure 1 The longitudinal changes of cystatin-C (Cys-C), serum creatinine (s-Cr), serum neutrophil gelatinase-associated lipocalin (s-NGAL), urinary neutrophil gelatinase-associated lipocalin (u-NGAL) between delayed graft function (DGF) and prompt graft function (non-DGF) group. *P<0.05.

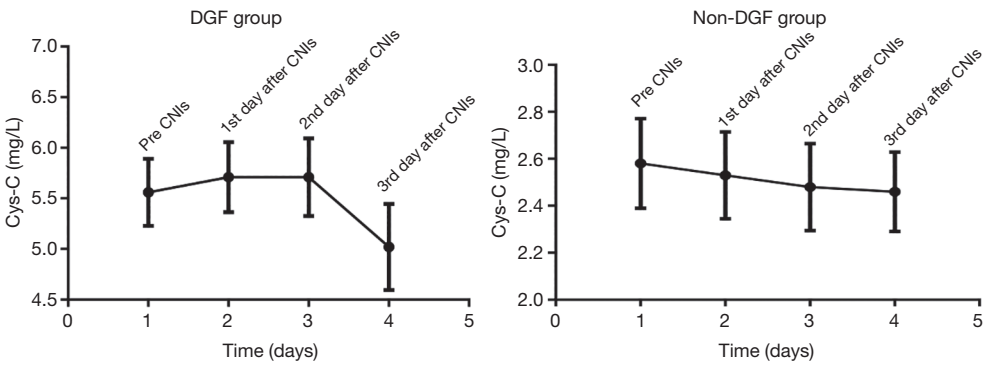

Figure 2 The longitudinal changes of cystatin-C (Cys-C) before and after the addition of calcineurin inhibitors (CNIs). DGF, delayed graft function; non-DGF, prompt graft function.

Discussion

DGF is a common complication after renal transplantation. The diagnostic criteria of DGF depend on the need for dialysis, diuresis, and serum creatinine level (12). Some research has tried to find predictive models to help diagnose the condition, but they were not so efficient due to the complex influences and poor accuracy (1). New markers have been developed in recent years to evaluate renal status after renal transplantation. NGAL and Cys-C are both new measures of the study. More and more research has been done to study their function during the perioperative period of renal transplantation. However, little research has

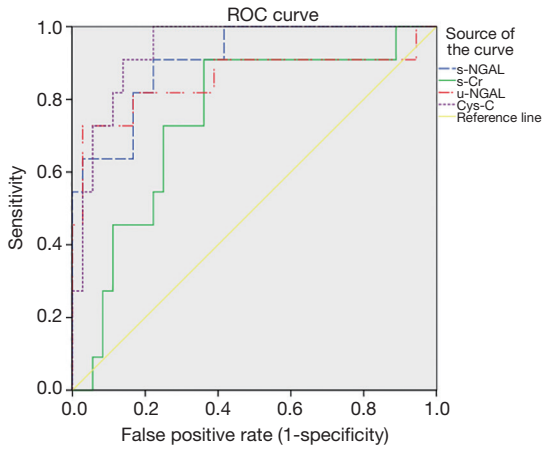

Figure 3 The ROC curve of serum neutrophil gelatinase-associated lipocalin (s-NGAL), urinary neutrophil gelatinase-associated lipocalin (u-NGAL), cystatin-C (Cys-C) and serum creatinine (s-Cr) for predicting delayed graft function (DGF).

Table 4 The AUC and P value of s-NGAL, Cr, u-NGAL, Cys-C

Biomarker	AUC (95% confidence interval)	P
s-NGAL	0.909 (0.817–1.000)	0.000*
u-NGAL	0.856 (0.688–1.000)	0.000*
Cys-C	0.939 (0.874–1.000)	0.000*
s-Cr	0.747 (0.583–0.912)	0.014*

*P<0.05. AUC, area under the curve; s-NGAL, serum neutrophil gelatinase-associated lipocalin; s-Cr, serum creatinine; u-NGAL, urinary neutrophil gelatinase-associated lipocalin; Cys-C, cystatin-C.

compared the differences between them. Our study found the following: (I) s-NGAL, u-NGAL and Cys-C could reflect renal function sensitivity and that the patients in the DGF group were more sensitive to CNIs as reflected by Cys-C; (II) Cys-C had the highest sum of sensitivity and specificity at 4.77 mg/L, with a sensitivity of 0.818 and a specificity of 0.889; (III) Cys-C can predict the short-term prognosis of renal transplantation patients.

Cys-C is a polypeptide chain with 120 amino acids and can only be filtered by the glomerulus. It is reabsorbed by the proximal tubule (13). In the past, Cys-C was used to assess the GFR. Recently, a few researchers have begun to study the function as a predictor of renal injury. Some research shows that Cys-C is not superior to creatinine for the detection of acute renal dysfunction (14), while other research shows that Cys-C can predict renal injury (15). Our findings indicate that Cys-C can not only predict DGF but can also predict renal function at discharge, as the efficiency was superior to creatinine and NGAL. Other investigations have compared the value of creatinine on the 2nd day or the 3rd day after operation for predicting DGF; however, we think the most useful value is obtained the 1st day after the operation, because the patient may receive dialysis on subsequent days. When we studied the longitudinal change of Cys-C, we found that the decrease in Cys-C was not very obvious. Then, we compared the changes in Cys-C before and after the use of CNIs. We found that there was a small rise in Cys-C in the DGF group after the use of CNIs and then a rapid decline. This may mean that DGF patients are more sensitive to the nephrotoxicity of CNIs and can recover quickly. This phenomenon supports the point of a kidney transplant guideline recommending that CNIs not be delayed until the graft has recovered (16).

NGAL was isolated for study in the 1990s (17). Until recently, the functions of NGAL were not well understood. Recent research shows that NGAL levels rise immediately after kidney injury and thus can be used as a marker of renal dysfunction. An increasing number of studies have begun to examine its function in renal injury, especially after renal transplantation, and have yielded promising results. Almost all the findings show it is a better indicator than creatinine (3,9,15,18), and our research is in line with this. We discovered that both the NGAL in serum and urine were higher in the DGF group at all the time points; it declined over time in both groups but was continuously higher in the DGF group. Although NGAL is not as good as Cys-C in predicting DGF, urine NGAL is noninvasive, and this constitutes the main advantage of u-NAGL.

Additionally, at the point of the maximum sum of sensitivity and specificity, s-NGAL had the highest sensitivity, and u-NGAL had the highest specificity. Some researchers have studied the predictive function of NGAL. Jafari *et al*. (18) found that plasma NGAL levels at 2, 24, and 96 hours after transplantation could predict graft loss at 3 months. Fonseca *et al*. (10) concluded that u-NGAL levels were associated with prognosis at 1 year. Our research studied the predictive function of NGAL and found it was inferior to Cys-C.

In this study, we did not examine the samples before renal transplantation because of the urgency to operate and because a few renal failure patients lacked urine. We chose the sample collected on the first morning after the transplantation as the first value because we thought it was the most practical to collect.

Table 5 Sensitivity, specificity, and predictive values for delayed graft function (DGF)

Biomarker	Cut-off value	Sensitivity	Specificity	PPV	NPV
s-NGAL	1,025.85 ng/mL	0.909	0.778	0.556	0.966
u-NGAL	1,787.8 ng/mL	0.727	0.972	0.889	0.921
Cys-C	4.77 mg/L	0.818	0.889	0.692	0.941

The values of predictive values were calculated at the max sum of sensitivity and specificity. PPV, positive predictive value; NPV, negative predictive value; s-NGAL, serum neutrophil gelatinase-associated lipocalin; u-NGAL, urinary neutrophil gelatinase-associated lipocalin; Cys-C, cystatin-C.

Table 6 Significant factors associated with eGFR at discharge after kidney transplantation

Variable	Regression coefficient	P	95% CI
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 1			
Cys-C	−8.424	0.001	−13.363 to −3.485
Cold ischemia time	−2.156	0.023	−4.004 to −0.31
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 2			
s-Cr	−0.048	0.000	−0.068 to −0.023
Cold ischemia time	−2.12	0.017	−3.976 to −0.438
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 3			
Cys-C	−10.977	0.000	−15.363 to −6.591
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 4			
Cys-C	−9.969	0.000	−13.87 to −6.067
Cold ischemia time	−1.739	0.041	−3.4 to −0.078
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 5			
Cys-C	−10.595	0.000	−14.302 to −6.889
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 6			
Cys-C	−9.656	0.000	−13.485 to −5.827
Cold ischemia time	−1.723	0.044	−3.393 to −0.052
Model with s-NGAL, u-NGAL, Cys-C and s-Cr at day 7			
Cys-C	−10.684	0.000	−14.588 to −6.781

s-NGAL, serum neutrophil gelatinase-associated lipocalin; u-NGAL, urinary neutrophil gelatinase-associated lipocalin; Cys-C, cystatin-C; s-Cr, serum creatinine.

Some studies have shown that these markers can predict the prognosis of three months and one year after kidney transplantation (10,18). However, Pezeshgi *et al*. (3) showed that serum and urinary NGAL had no relationship with graft loss rate and patient death rate after kidney transplantation. Many factors can influence renal function, and long-term prognosis is complicated to evaluate. Our research explored the function of Cys-C and NGAL in predicting the short-term prognosis which is simple and practical. We found that the value of Cys-C on days 1, 3, 4, 5, 6 and 7 after operation were independently associated with eGFR, the same as cold ischemia time. To our knowledge, this has never been reported before.

Similar to the other study (10), we found that cold ischemia time was associated independently with renal function at discharge. We also found that cold ischemia

time in the DGF group was longer than that in the non-DGF group. Cold ischemia time is one of the most important causes of DGF, and it can aggravate renal ischemia-reperfusion injury (19). Going forward, we will try to shorten the cold ischemia time to improve the prognosis of renal transplantation. Furthermore, we will introduce the use of a hypothermic machine perfusion system to reduce ischemia-reperfusion injury (20).

Our research still had some limitations. We did not obtain s-NGAL, u-NGAL, and Cys-C levels before renal transplantation. As a next step, we will obtain these values when the patients come for matching. Furthermore, there were only 47 participants in the study, which is a small number. We will expand the sample size and continue to confirm our findings in our following work. As the number of cases increases and follow-up time prolongs, we will study the relationship between these markers and long-term prognosis in the future.

Conclusions

Our research found that Cys-C, s-NGAL, and u-NGAL could accurately reflect the renal function after renal transplantation. Cys-C had the highest sum of sensitivity and specificity at the point of 4.77 mg/L with a sensitivity of 0.818 and a specificity of 0.889 compared with s-NGAL and u-NGAL. The value of Cys-C of the first week after the operation was independently associated with eGFR at discharge and can predict the short-term prognosis of renal transplantation patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the medical ethical committees of the First Affiliated Hospital of Soochow University.

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