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Clinical relevance of postoperative proteinuria for prediction of early renal outcomes after kidney transplantation

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Background: Proteinuria is associated with poor allograft and patient survival in kidney transplant recipients. However, the clinical relevance of spot urine protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR) as predictors of renal outcomes during the early postoperative period following kidney transplantation (KT) has not been determined.

Methods: This single-center retrospective cohort study included 353 kidney transplant recipients who underwent KT between 2014 and 2017 and were followed up for more than 3 years. Among them, 186 and 167 recipients underwent living donor KT and deceased donor KT, respectively. The PCR and ACR were measured during the immediate postoperative period (within 7 days postoperatively), before discharge (2–3 weeks postoperatively), and 3–6 months postoperatively.

Results: The median age of the patients was 51 years (interquartile range, 43–59 years), and 62.9% were male. An immediate postoperative PCR of ≥1 mg/mg was associated with old age, diabetes mellitus, high systolic blood pressure, delayed graft function, and donor factors (deceased donor KT, old age, and high serum creatinine concentrations). The PCR and ACR 3 to 6 months posttransplant were inversely associated with the estimated glomerular filtration rate at 1 year posttransplant. Deceased donor KT recipients with immediate postoperative PCR of ≥3 mg/mg showed a greater incidence of delayed graft function and lower estimated glomerular filtration rate before discharge than those with immediate postoperative PCR of <3 mg/mg.

Conclusion: Early postoperative proteinuria is a useful biomarker to predict early renal outcomes after KT.

Keywords: Delayed graft function, Kidney transplantation, Proteinuria, Renal outcome, Urine protein-to-creatinine ratio

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Introduction

Proteinuria is a marker of kidney injury and risk factor for progression to chronic kidney disease, cardiovascular disease, and mortality [1]. Several previous studies have reported that proteinuria is associated with poor allograft and patient survival [2–4], as well as an increased risk of cardiovascular disease in kidney transplant recipients (KTRs) [2,5,6]. In these studies, the prevalence of proteinuria after kidney transplantation (KT) ranged from 7.5% to 45%, depending on its definition; most previous studies measured proteinuria between 1 month and 1 year after KT [3,4,7].

Ischemia-reperfusion injury during KT causes renal tubular injury through an inflammatory process that can subsequently result in proteinuria [8]. Further, proteinuria induces kidney injury by causing tubules to release chemokines and cytokines, leading to interstitial inflammation and fibrosis [9,10]. Therefore, early postoperative proteinuria might reflect tubular injury and be an early indicator of poor renal outcomes after KT. However, the optimal timing for measurement of proteinuria in KTRs and the associations between early postoperative proteinuria and renal outcomes have not been determined.

We hypothesized that early postoperative proteinuria might reflect early renal outcomes in KTRs and investigated the clinical relevance of postoperative proteinuria, as assessed by the spot urine protein-to-creatinine ratio (PCR) and albumin-to-creatinine ratio (ACR), as a surrogate marker to predict early renal outcomes in KTRs.

Methods

Study population and variables

This single-center retrospective cohort study screened 474 adult patients (≥18 years old) who underwent KT between January 1, 2014 and December 31, 2017, at Samsung Medical Center, Sungkyunkwan University School of Medicine. A total of 353 patients were finally included after excluding patients for whom ACR or PCR measurements within 7 days posttransplant were unavailable. Baseline characteristics, such as age, sex, renal replacement therapy (RRT) modality before KT, causes of end-stage kidney disease (ESKD), body mass index (BMI), history of diabetes mellitus or cardiovascular disease, and donor information, including age, BMI, and serum creatinine at the time of KT, were obtained from electronic medical records. All patients were followed for 3 years after KT.

The immediate postoperative period was defined as postoperative days 1 to 7 after surgery. All PCRs and ACRs were measured using spot urine samples during the immediate postoperative period, prior to discharge, and 3–6 months after KT. Immediate postoperative PCR and ACR values were defined as the first PCR and ACR assessments within the immediate postoperative period. The PCR and ACR prior to discharge were defined as the last PCR and ACR during the hospital stay, usually 2 to 3 weeks postoperatively. The PCR and ACR at 3–6 months posttransplant were defined as the median values.

To evaluate correlations between spot urine PCR or ACR and 24-hour urine protein excretion within 1 month after KT, all values measured on the same day or the median spot urine PCR/ACR values calculated within 1 month from the time of initial 24-hour urine protein measurement were compared.

Ethics statement

This study complied with internationally accepted standards for research practice and reporting. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (No. 2019-08-112-002) in compliance with the Declaration of Helsinki, and the requirement for informed consent was waived.

Study outcomes

The primary outcome was early renal function as evaluated by the estimated glomerular filtration rate (eGFR) at 1 year posttransplant. The secondary outcome was delayed graft function (DGF) in deceased donor kidney transplant (DDKT) recipients. The presence of DGF was defined as an event in which RRT was required within 7 days posttransplant. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, which uses serum creatinine concentrations [11]. The eGFR prior to discharge was defined as the last eGFR measured during the hospital stay, and the eGFR at 3 to 6 months posttransplant was defined as the median eGFR value during this

period. Moreover, eGFRs at 1, 2, and 3 years posttransplant were defined as median eGFR values for the 9 to 15, 21 to 27, and 33 to 39 months intervals after KT, respectively.

Statistical analyses

Baseline characteristics are presented as numbers (percentages) for categorical variables and medians (interquartile ranges) or means ± standard deviations for continuous variables, as appropriate. Differences between groups were analyzed using the Wilcoxon rank-sum test or chi-square test. Logarithmic transformation of the postoperative PCR and ACR was performed because of the skewed distribution of these ratios. Univariable analyses were performed for postoperative PCR and ACR, using the eGFR as the outcome variable. Subsequently, multivariable regression analyses of the postoperative PCR and ACR were performed using models including covariates such as age, sex, donor status, donor serum creatinine, and acute rejection during the first 6 months after KT.

Statistical significance was set at a two-tailed p-value of 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows (released 2017, version 25.0; IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics and renal outcome depending on the degree of proteinuria in the immediate postoperative period

A total of 353 patients were analyzed to evaluate the degree of immediate postoperative proteinuria (Table 1). The median age of KTRs was 51 years (43–59 years), and 222 of the 353 patients (62.9%) were male. Diabetes mellitus was the most common cause of ESKD (112 of 353 KTRs, 31.7%).

We analyzed the cut-off value of the immediate postoperative PCR for predicting an eGFR of ≥60 mL/min/1.73 m^2 at 1 year postoperative using Youden's index method [12]. The best cut-off PCR value was 1.26 mg/mg (sensitivity, 68.8%; specificity, 45.9%). For ease of application in clinical practice, we used a PCR of 1 mg/mg (sensitivity, 60.6%; specificity, 53.3%) as a cut-off value, and divided the KTRs into two groups: the low-PCR (PCR < 1 mg/mg) and high-PCR groups (PCR ≥ 1 mg/mg).

The low- and high-PCR groups included 195 (55.2%) and 158 KTRs (44.8%), respectively. Compared to patients in the low-PCR group, patients in the high-PCR group were older (PCR ≥ 1 mg/mg vs. PCR < 1 mg/mg, 55 years [46–61 years] vs. 48 years [41–56 years]; p < 0.001) and had a higher prevalence of diabetes mellitus (39.9% vs. 26.2%, p = 0.008), higher systolic blood pressure (145 mmHg [134–157 mmHg] vs. 138 mmHg [125–150 mmHg], p = 0.001), higher incidence of DGF (22.2% vs. 2.1%, p < 0.001), and lower eGFR at 1 year posttransplant (64.3 ± 19.0 mL/min/1.73 m^2 vs. 69.2 ± 17.5 mL/min/1.73 m^2, p = 0.01). In addition, the proportion of deceased donors was greater (74.7% vs. 25.1%; p < 0.001), the donors were older (52 years [43–64 years] vs. 48 years [37–56 years], p < 0.001), and the donors' serum creatinine concentrations were greater (1.14 mg/dL [0.84–1.87 mg/dL] vs. 0.81 mg/dL [0.67–0.95 mg/dL], p < 0.001) in the high-PCR group than in the low-PCR group. The proportion of both sexes, BMI, and the causes of ESKD were comparable between the groups.

A lesser percentage of patients in the high-PCR group received ABO-incompatible (ABOi) grafts (17.1% vs. 33.8%, p < 0.001), but the presence of donor-specific antibodies was similar to that in the low-PCR group. Most ABOi grafts were from living donors (ABOi grafts from living donors vs. deceased donors were 80% vs. 18%, respectively). Patients in the high-PCR group received more antithymocyte globulin (ATG) monotherapy than basiliximab or ATG + rituximab as an induction therapy compared with those in the low-PCR group. Most patients (350 of 353) received tacrolimus, mycophenolate, and corticosteroids for initial maintenance therapy. Two patients received cyclosporine instead of tacrolimus, and one patient received sirolimus and corticosteroids. The high-PCR group tended to have a greater incidence of diabetes mellitus nephropathy and a shorter median interval to diagnosis after KT than the low-PCR group, although the difference was not statistically significant. The incidence of acute rejection or BK virus nephropathy and the diagnosis of posttransplant glomerular pathology, including recurrent or *de novo* glomerulonephritis, was similar between the two groups.

Serial follow-up evaluations of postoperative proteinuria and estimated glomerular filtration rate

The immediate postoperative PCR and ACR were much

Table 1. Characteristics of the study population

Characteristic	Total	Low-PCR group[a]	High-PCR group[b]	p-value
No. of patients	353	195	158	
Age (yr)	51 (43–59)	48 (41–56)	55 (46–61)	<0.001
Male sex	222 (62.9)	119 (61.0)	103 (65.2)	0.44
RRT modality before KT				0.17
Hemodialysis	265 (75.1)	139 (71.3)	126 (79.7)	
Peritoneal dialysis	30 (8.5)	20 (10.3)	10 (6.3)	
No dialysis	58 (16.4)	36 (18.5)	22 (13.9)	
Cause of ESRD				0.61
GN	97 (27.5)	54 (27.7)	43 (27.2)	
Diabetes mellitus	112 (31.7)	50 (25.6)	62 (39.2)	
Hypertension	33 (9.3)	24 (12.3)	9 (5.7)	
Cystic kidney disease	16 (4.5)	9 (4.6)	7 (4.4)	
Others	40 (11.3)	25 (12.8)	15 (9.5)	
Unknown	55 (15.6)	33 (16.9)	22 (13.9)	
BMI (kg/m^2)	22.7 (20.7–25.1)	22.7 (20.6–25.5)	22.6 (20.6–24.5)	0.34
Diabetes mellitus	114 (32.3)	51 (26.2)	63 (39.9)	0.008
Cardiovascular disease	27 (7.6)	12 (6.2)	15 (9.5)	0.314
SBP (mmHg)	141 (128–153)	138 (125–150)	145 (134–157)	0.001
DBP (mmHg)	83 (74–90)	83 (75–90)	83 (74–91)	0.88
Donor age (yr)	50 (38–60)	48 (37–56)	52 (43–64)	<0.001
Male donor	205 (58.1)	107 (54.9)	98 (62.0)	0.19
Donor height (cm)	167 (159–172)	165 (158–172)	167 (160–173)	0.26
Donor weight (kg)	66.0 (57.9–74.3)	66.2 (57.8–74.4)	66.0 (57.9–74.3)	0.90
Donor BMI (kg/m^2)	24.1 (21.7–26.3)	24.5 (22.1–26.3)	23.9 (21.5–26.3)	0.34
Donor serum creatinine (mg/dL)	0.89 (0.70–1.24)	0.81 (0.67–0.95)	1.14 (0.84–1.87)	<0.001
Donor status				<0.001
Living	186 (52.7)	146 (74.9)	40 (25.3)	
Deceased	167 (47.3)	49 (25.1)	118 (74.7)	
ABO incompatibility	93 (26.3)	66 (33.8)	27 (17.1)	<0.001
Donor-specific antibody	56 (15.8)	26 (13.5)	20 (12.9)	0.875
Induction therapy				<0.001
No induction	1 (0.3)	1 (0.5)	0 (0)	
ATG	218 (61.8)	104 (53.3)	114 (72.6)	
ATG + rituximab	73 (20.7)	50 (25.6)	23 (14.6)	
Basiliximab	60 (17.0)	40 (20.5)	20 (12.7)	
Basiliximab + rituximab	1 (0.3)	0 (0)	1 (0.6)	
Delayed graft function	39 (11.0)	4 (2.1)	35 (22.2)	<0.001
Acute rejection	129 (36.5)	79 (40.5)	50 (31.6)	0.10
Antibody-mediated rejection	25 (7.1)	17 (8.7)	8 (5.1)	0.18
BK virus nephropathy	21 (5.9)	11 (5.6)	10 (6.3)	0.79
Post-KT glomerular pathology	56 (15.9)	26 (13.3)	30 (19.0)	0.41
Focal segmental glomerulosclerosis	6 (1.7)	3 (1.5)	3 (1.9)	
IgA nephropathy	7 (2.0)	4 (2.1)	3 (1.9)	
Membranoproliferative GN	2 (0.6)	2 (1.0)	0 (0)	
Diabetic nephropathy	9 (2.5)	1 (0.5)	8 (5.1)	
CNI toxicity	13 (3.7)	7 (3.6)	6 (3.8)	
Others	19 (5.4)	9 (4.6)	10 (6.3)	
Interval from KT to diagnosis of glomerular pathology (day)	193 (145–408)	362 (14–414)	86 (15–398)	0.565
Treatment of ACEi/ARB within 1 year after KT	34 (9.6)	16 (8.2)	18 (11.4)	0.313

Data are expressed as number only, median (interquartile range), and number (%).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATG, antithymocyte globulin; BMI, body mass index; CNI, calcineurin inhibitor; DBP, diastolic blood pressure; ESRD, end-stage renal disease; GN, glomerulonephritis; IgA, immunoglobulin A; KT, kidney transplantation; PCR, spot urine protein-to-creatinine ratio; RRT, renal replacement therapy; SBP, systolic blood pressure.

[a]Patients with immediate postoperative PCR of <1 mg/mg. [b]Patients with immediate postoperative PCR of ≥1 mg/mg.

greater than the PCR and ACR before discharge and at 3 to 6 months postoperatively. The median PCR and ACR decreased from 0.87 mg/mg (0.52–1.98 mg/mg) and 373 μg/mg (183–1,258 μg/mg) during the immediate postoperative period to 0.22 mg/mg (0.52–0.87 mg/mg) and 52 μg/mg (26–127 μg/mg) and 0.13 mg/mg (0.10–0.21 mg/mg) and 19 μg/mg (13–39 μg/mg) prior to discharge and 3 to 6 months posttransplant, respectively (Fig. 1). The median eGFR values were 73.3 mL/min/1.73 m^2 (55.4–89.9 mL/min/1.73 m^2), 61.1 mL/min/1.73 m^2 (50.9–71.8 mL/min/1.73 m^2), and 66.4 mL/min/1.73 m^2 (54.0–79.9 mL/min/1.73 m^2) prior to discharge, at 3 to 6 months posttransplant, and at 1 year posttransplant, respectively. There were no significant differences between the eGFR values 1 and 3 years after KT (Fig. 1).

Correlations between 24-hour urine protein excretion and spot urine protein-to-creatinine ratio

We performed correlation analyses of spot urine PCR or ACR and 24-hour urine protein excretion in 333 patients who underwent a 24-hour urine protein measurement within 1 month posttransplant. The median spot urine PCR (R = 0.676, p < 0.001) and ACR (R = 0.728, p < 0.001) showed good correlation with 24-hour urine protein excretion (Fig. 2). Spot urine PCR measured on the same day was also correlated with 24-hour urine protein excretion (R = 0.610, p < 0.001).

Association between postoperative proteinuria and early renal outcome

The univariable linear regression analyses indicated that the eGFR at 1 year posttransplant was correlated with PCR and ACR in the immediate postoperative period, ACR prior to discharge, and PCR and ACR at 3 to 6 months posttransplant. After adjusting for sex, age, donor status (living vs. deceased), donor serum creatinine concentration, and acute rejection during the first 6 months after KT, the eGFR 1 year after KT was correlated with PCR and ACR at 3 to 6 months posttransplant (PCR: adjusted β coefficient, –13.771; p = 0.04; and ACR: adjusted β coefficient, –5.947; p = 0.002). In a multivariable analysis, the PCR and ACR measured less than 3 months posttransplant were not correlated with the eGFR 1 year after KT (Table 2).

We analyzed the PCR cut-off value at 3 to 6 months posttransplant for prediction of an eGFR of ≥60 mL/min/1.73 m^2 at 1 year posttransplant using Youden's index method [12]. The best PCR cut-off value was 0.158 mg/mg (sensitivity, 71.0%; specificity, 52.5%). In addition, according to the PCR cut-off value, we divided the patients into two groups: those with PCR of ≥0.2 mg/mg and <0.2 mg/mg at

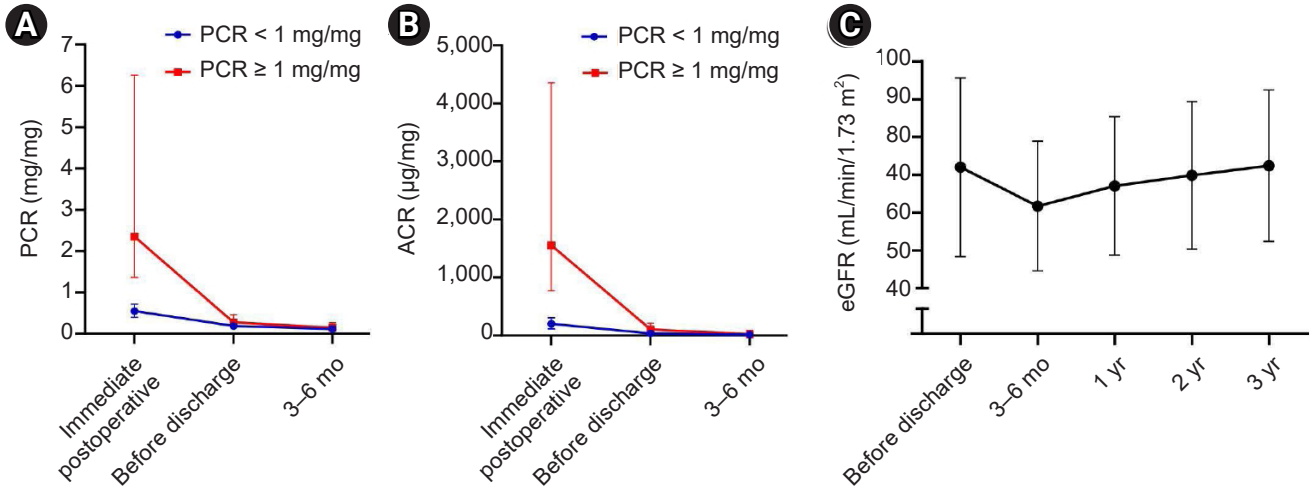

Figure 1. Serial follow-up measurements of postoperative proteinuria and eGFR. (A) Serial follow-up measurements of the spot urine PCR (median and interquartile range) after KT. (B) Serial follow-up measurements of the spot urine ACR (median and interquartile range) after KT. (C) Serial follow-up measurements of eGFR (mean ± standard deviation).
ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; PCR, protein-to-creatinine ratio.

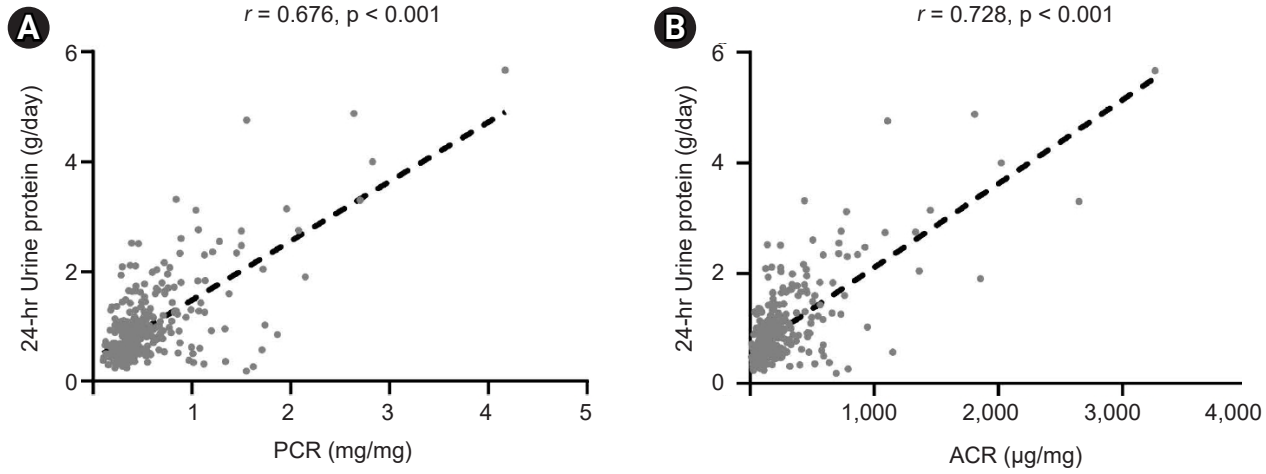

Figure 2. Correlations between spot urine PCR or ACR and 24-hour urine protein excretion. (A) Scatter plot of spot urine PCR and 24-hour urine protein excretion. (B) Scatter plot of spot urine ACR and 24-hour urine protein excretion.
ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio.

Table 2. Associations between postoperative proteinuria and early renal outcome (eGFR at 1 year after kidney transplantation)

Variable	Unadjusted		Adjusted[a]	
	β coefficient	p-value	β coefficient	p-value
PCR, immediately postoperation	−3.68	0.03	2.88	0.18
ACR, immediately postoperation	−3.53	0.01	1.72	0.33
PCR, before discharge	−4.73	0.18	−2.62	0.46
ACR, before discharge	−4.45	0.02	−2.39	0.23
PCR, 3–6 months posttransplant	−11.51	<0.001	−7.97	0.02
ACR, 3–6 months posttransplant	−8.62	<0.001	−6.68	0.001

Log transformation was performed for PCR (mg/mg) and ACR values (μg/mg).
ACR, spot urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; PCR, spot urine protein-to-creatinine ratio.
[a]Each model was adjusted for sex, age, recipient's diabetes mellitus and hypertension, donor status (living vs. deceased), donor serum creatinine concentration, delayed graft function, and acute rejection within 6 months after kidney transplantation using multivariable linear regression analyses.

3 to 6 months posttransplant, according to the definition of proteinuria in routine clinical practice. Patients with PCR of <0.2 mg/mg at 3 to 6 months posttransplant had similar eGFRs at 3 to 6 months posttransplant as those of patients with PCR of ≥0.2 mg/mg at 3 to 6 months posttransplant, but had greater eGFRs between 1 and 3 years posttransplant ($p < 0.001$) (Fig. 3).

Proteinuria in the immediate postoperative period as a surrogate marker for delayed graft function

We compared the incidence of DGF and the postoperative eGFR in DDKT recipients according to the degree of immediate postoperative proteinuria (Table 3). A total of 167 DDKT recipients were divided into two groups: 67 in the heavy proteinuria group (immediate postoperative PCR ≥ 3 mg/mg) and 100 in the control group (immediate postoperative PCR < 3 mg/mg). The incidence of DGF was significantly greater in the heavy proteinuria group than in the control group (control group vs. heavy proteinuria group, 12% vs. 39%; $p < 0.001$). After adjusting for age, sex, donor serum creatinine concentration, donor age, number of human leukocyte antigen mismatches, and presence of donor-specific antibodies, heavy proteinuria in the immediate postoperative period was still associated with DGF (adjusted odds ratio, 5.86; 95% confidence interval, 2.26– 15.16; $p < 0.001$). The heavy proteinuria group had lower postoperative eGFR within 1 month posttransplant than the control group (64.2 mL/min/1.73 m^2 [49.7–85.4 mL/min/1.73 m^2] vs. 49.6 mL/min/1.73 m^2 [35.8–66.5 mL/

min/1.73 m^2], p = 0.001). However, eGFR 1 year after DDKT was comparable between the groups.

The incidence of DGF and postoperative eGFR were also compared in living donor KT (LDKT) recipients according to the degree of proteinuria in the immediate postoperative period (Supplementary Table 1, available online). A total of 186 LDKT recipients were divided into two groups: 72 in the high-ACR group (immediate postoperative ACR ≥ 300 μg/mg) and 114 in the low-ACR group (immediate postoperative ACR < 300 μg/mg). The occurrence of DGF was reported in only one LDKT recipient, and no difference in postoperative eGFR between the groups was noted.

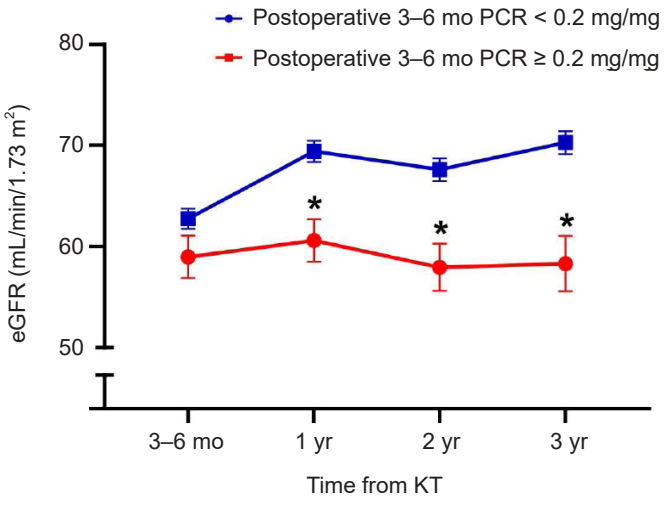

Figure 3. Serial follow-up measurements (for up to 3 years) of the postoperative eGFR according to the degree of proteinuria at postoperative 3 to 6 months after KT.
*p < 0.05, compared to patients with postoperative 3 to 6 months PCR of <0.2 mg/mg.
eGFR, estimated glomerular filtration rate; KT, kidney transplantation; PCR, protein-to-creatinine ratio.

Discussion

In this study, proteinuria at 3 to 6 months posttransplant was identified as a surrogate marker for prediction of early renal outcomes in KTRs. Compared to those with low PCRs during the immediate postoperative period, the KTRs with high PCRs were older and had a greater prevalence of diabetes mellitus and incidence of DGF, and higher systolic blood pressure and serum creatinine concentrations than the donors of the low-PCR group. Furthermore, we found a good correlation between 24-hour urine protein excretion and spot urine PCR or ACR during the first month posttransplant. In DDKT recipients, heavy proteinuria (PCR ≥ 3 mg/mg) during the immediate postoperative period was associated with a high incidence of DGF and low eGFR within 1 month of KT.

The severity of proteinuria after KT has been shown to be inversely associated with graft survival and favorable patient outcomes [2–4,13–19]. Similarly, a recent large cohort study demonstrated that the severity of proteinuria at 3 months, 1 year, 2 years, and 6 years after KT, as well as at the time of allograft biopsy, was inversely associated with graft survival [16]. In particular, proteinuria of >1 g/day was related to transplant glomerulopathy, microcirculatory inflammation, and *de novo* or recurrent glomerular disease diagnosed from both indication and protocol biopsies. Although the associations between proteinuria and graft survival or renal histology in the first 3 months after KT were weaker than those thereafter, our results were consistent with previous studies showing that proteinuria at 3 months after KT is a predictor of graft outcome [14,18,19].

Previous studies have reported that diabetes mellitus, hypertension, advanced recipient age, advanced donor age, extended criteria donor, and DGF were associated with

Table 3. Incidence of DGF and eGFR depending on the degree of immediate postoperative proteinuria in DDKT recipients

Variable	PCR (mg/mg)		p-value
	<3 (n = 100)	≥3 (n = 67)	
DGF	12 (12)	26 (39)	<0.001
eGFR, before discharge	64.2 (49.7–85.4)	49.6 (35.8–66.5)	0.001
eGFR, postoperative 3–6 months	58.5 (45.5–68.2)	52.6 (41.5–67.7)	0.38
eGFR, postoperative 1 year	62.8 (48.0–74.7)	60.0 (46.3–73.4)	0.74

Data are expressed as number (%) or median (interquartile range).
DDKT, deceased donor kidney transplantation; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; PCR, spot urine protein-to-creatinine ratio.

decreased allograft function [20–23]. The abovementioned factors were observed in the high-PCR group during the immediate postoperative period in our study. These results indicated that immediate postoperative PCR of ≥1 mg/mg may possibly indicate allograft damage and can be used as a surrogate marker to predict poor renal outcome after KT.

Currently, there is no consensus regarding the optimal method to assess the degree of proteinuria in KTRs [7]. Several studies have reported a high overall correlation between 24-hour urine protein or albumin excretion and spot urine PCR or ACR in KTRs (median correlation coefficient, 0.92; range, 0.772–0.998) [24–28], although one study showed only modest accuracy of spot urine PCR or ACR for prediction of 24-hour urine protein excretion despite high correlation between spot urine PCR or ACR and 24-hour urine protein excretion [29]. However, the correlation between 24-hour urine protein or albumin excretion and spot urine PCR or ACR within 1 month after surgery has not yet been reported. In the early postoperative period after KT, proteinuria from the native kidney [30], proteinuria due to tubular dysfunction as a result of ischemic-reperfusion injury, especially in the DDKT [31], and an increase in postoperative creatinine production due to high-dose corticosteroid treatment [32] may affect both the degree of proteinuria and accuracy of spot urine PCR or ACR. Our study demonstrated a good correlation between 24-hour urine protein excretion and spot urine PCR or ACR within 1 month posttransplant, and this may be valuable information for physicians and KTRs who experience difficulty in obtaining 24-hour urine collection.

In many previous KT studies, the timing of proteinuria measurement varied considerably, ranging from 1 month to 1 year after KT [3,4,7,13,14,33] and proteinuria during this period was associated with an increased risk of allograft dysfunction [4,13,14]. However, there were conflicting results regarding the prognostic value of proteinuria at 1 month after KT [4,14]. A few studies have evaluated the clinical value of proteinuria less than 1 month after transplant, and one among them showed an association between proteinuria measured 1 week posttransplant and graft function [15]; however, this study included only LDKT recipients, and proteinuria was assessed using 24-hour urine collection within 1 week posttransplant, but only by qualitative tests were used after 1 month [15]. Our study investigated the clinical value of quantitative measurement of urine protein excretion at different time points, including during the immediate postoperative period. The severity of proteinuria 3 to 6 months posttransplant was the most reliable predictive factor of eGFR 1 year posttransplant, regardless of the type of KT. Proteinuria occurring 3 to 6 months posttransplant may reflect irreversible allograft injury and can be considered a predictor of poor renal outcomes. In contrast, immediate postoperative proteinuria was not associated with allograft function at 1 year posttransplant. These results suggest that immediate postoperative proteinuria might reflect postoperative allograft injury, which is reversible in many cases and can be improved with adequate postoperative management.

Overall, DGF is the most important predictor of poor graft survival [20]. The main cause of DGF is tubular damage caused by ischemia-reperfusion injury [8]. We evaluated the potential value of proteinuria in the immediate postoperative period to predict DGF and renal function after KT, since the renal outcome may improve with an early diagnosis of DGF and appropriate therapeutic interventions. Heavy proteinuria (PCR ≥ 3 mg/mg) during the immediate postoperative period was associated with a high incidence of DGF and poor renal function within 1 month posttransplant in DDKT recipients. However, proteinuria in the immediate postoperative period was not associated with renal function as assessed 1 month posttransplant. These results suggest that immediate postoperative proteinuria may reflect tubular damage due to ischemia-reperfusion injury, which can be reversed with adequate postoperative management.

Our study had a few limitations. First, the composition of the study population might limit the generalizability of our results because this was a single-center study; however, the results are still clinically significant since we analyzed serial PCR and ACR assessments in an adequate number of both LDKT and DDKT recipients. Second, owing to the retrospective cohort study design, some unmeasured confounding factors may not have been addressed. Several key factors affecting allograft function were considered in the analyses to overcome this issue. Further multicenter prospective studies are necessary to validate our findings. Third, since we adopted renal function 1 year posttransplant as the primary outcome, long-term graft function could not be adequately evaluated. However, several studies have reported that renal function 1 year posttransplant

could reliably predict long-term graft survival [34,35]. Follow-up data spanning the interval from the immediate postoperative period to 3 years after KT were included in our study.

Despite the above limitations, we presented cut-off values for urine PCR during the immediate postoperative period and at 3 to 6 months posttransplant to predict eGFR 1 year after transplantation. These cut-off values could be very useful in identifying high-risk KTRs in clinical practice and indicate the need for more careful monitoring as well as appropriate management of renal function to improve renal outcomes in KTRs who have PCRs above the cut-off values. In addition, this study demonstrated a strong correlation between 24-hour urine protein excretion and spot urine PCR within 1 month posttransplant.

In conclusion, the degree of proteinuria 3 to 6 months posttransplant may be a good surrogate marker to predict allograft function 1 year posttransplant, and proteinuria during the immediate postoperative period may be a potential predictor of DGF in DDKT recipients. Therefore, early postoperative proteinuria can be considered as a biomarker to predict early renal outcomes in KTRs.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

Conceptualization: HRJ
Data curation: JJ, KP, HSL
Formal analysis: JJ, KP, KK
Investigation: JJ, KP, JEL, KK, WH, YGK, DJK, HRJ
Methodology: JJ, HRJ
Project administration: KWL, JEL, JBP, WH, YGK, DJK
Visualization: JJ, KP
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