Proteinuria predicts postcardiotomy acute kidney injury in patients with preserved glomerular filtration rate

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Objective: Acute kidney injury is a common and serious problem after cardiac surgery. Postoperative acute kidney injury is independently associated with in-hospital mortality and long-term morbidity, even after adjustment for comorbid diseases. Chronic kidney disease has been recognized as a strong risk factor of acute kidney injury after cardiac surgery. The association between proteinuria and postcardiotomy acute kidney injury in patients with preserved glomerular filtration rate remains uncertain.

Methods: Patients with an estimated glomerular filtration rate greater than 60 mL/min/1.73 m² who underwent cardiac surgery between January 2003 and December 2007 in a tertiary medical center were retrospectively analyzed. Dipstick urinalysis was performed before surgery. Proteinuria was categorized into negative, trace, 1+, 2+, or 3+. Postoperative acute kidney injury was defined by the Acute Kidney Injury Network criteria. Multinomial logistic regression was used to clarify whether proteinuria is an independent risk factor of postoperative acute kidney injury.

Results: A total of 1246 patients were included in this study, with a mean estimated glomerular filtration rate of 80 ± 13 mL/min/1.73 m². Proteinuria was present in 290 patients (23.4%). Postoperative acute kidney injury developed in 434 patients (34.8%), and 36 patients (2.9%) required renal replacement therapy. Proteinuria was independently associated with all stages of postcardiotomy acute kidney injury and dialysis-requiring acute kidney injury. The crude risk of acute kidney injury was greater in patients with a higher grade of proteinuria. In subgroup analysis for gender, diabetes, and surgical type, preoperative proteinuria remains a strong risk factor of acute kidney injury after cardiac surgery.

Conclusions: Urine analysis is usually neglected before cardiac surgery despite the fact that proteinuria is the earliest manifestation of kidney dysfunction. In the current study, we show that urine protein is strongly and independently associated with postoperative acute kidney injury in subjects with preserved estimated glomerular filtration rate. These data suggest that such a relatively simple and clinically easy to use tool as a urinary dipstick may be useful to identify patients at high risk of acute kidney injury before cardiac surgery. (*J Thorac Cardiovasc Surg* 2015;149:894-9)

See related commentary on pages 900-1.

Acute kidney injury (AKI) is a common and serious complication after cardiac surgery. It is independently associated with not only short-term but also long-term adverse outcomes.¹⁻⁴ Emerging evidences have suggested that

even small changes in serum creatinine levels after cardiac surgery are associated with significant effects on mortality.⁵⁻⁷ Therefore, identification of the high-risk patients followed with appropriate intervention plays a critical role in improving the clinical outcome of cardiac surgery. Preoperative renal dysfunction usually is the most important determinant of postoperative AKI, and serum creatinine is routinely measured as a marker of renal function.^{8,9} Although clinicians have long recognized proteinuria to be the earliest manifestation of kidney dysfunction, the prognostic significance of the presence and severity of proteinuria was hindered among patients with preserved glomerular filtration rate (GFR).

Community-based studies by James and colleagues¹⁰ and Grams and colleagues¹¹ have shown that the presence of proteinuria is associated with an increased risk of subsequent AKI among patients with estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m². Both studies confirmed the prognostic value of proteinuria in the development of AKI despite normal serum creatinine. In addition, the association among proteinuria, adverse renal outcomes, and mortality in patients undergoing

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Abbreviations and Acronyms

AKI = acute kidney injury
 AKIN = Acute Kidney Injury Network
 eGFR = estimated glomerular filtration rate
 GFR = glomerular filtration rate
 IABP = intra-aortic balloon pump
 RRT = renal replacement therapy

percutaneous coronary intervention¹² and coronary artery bypass surgery¹³ has been reported. However, the prognostic significance of proteinuria on postcardiotomy AKI in patients with preserved eGFR has remained unknown. The current study assesses the impact of preoperative proteinuria on AKI after cardiac surgery in subjects with eGFR greater than 60 mL/min/1.73 m².

MATERIALS AND METHODS

Study Subjects

This is a retrospective cohort study approved by the institutional review board. All consecutive adult patients who underwent cardiac surgery with

cardiopulmonary bypass from January 1, 2003, to December 31, 2008, at Taipei Veterans General Hospital entered this study. Patients who were on maintenance dialysis or who underwent heart transplantation were ineligible for this study. Patients with preoperative eGFR less than 60 mL/min/1.73 m² were also excluded (Figure 1).

Data Collection

Demographic and clinical data, such as age, gender, body weight, body mass index, diabetes, and left ventricular ejection fraction, were obtained from medical records. Hemoglobin, serum creatinine, and albumin were measured before surgery. Duration of cardiopulmonary bypass, preoperative treatment of intra-aortic balloon pump (IABP), and types of operation were obtained from surgical records.

Baseline Urine Protein and Acute Kidney Injury

A urine sample was collected during a 3-day period before surgery. The presence of proteinuria was determined using an automatic dipstick analyzer (CLINITEK Atlas; Siemens Healthcare Diagnostics, Eschborn, Germany). The degree of proteinuria was semiquantified as negative, trace (protein 15-30 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), or 3+ (>300 mg/dL).

Preoperative eGFR was calculated by the Cockcroft–Gault formula as follows for men: $(140 - \text{age}) \times (\text{body weight in kilograms}) / (72 \times \text{serum creatinine})$. In women, the value was multiplied by 0.85.¹⁴ Blood chemistries were checked with a 24-hour interval after operation.

FIGURE 1. Patient selection flow. *GFR*, Glomerular filtration rate.

TABLE 1. Baseline characteristics of study patients

Variable	(n = 1246)
Demographic data	
Male gender	963 (77.3%)
Age (y)	61.5 ± 15.5
Body mass index (kg/m ²)	24.3 ± 3.6
Diabetes	329 (26.5%)
LV ejection fraction	51.0% ± 13.5%
Surgery type	
CABG	705 (56.6%)
Valve	476 (38.2%)
CABG + valve	73 (5.8%)
Others	193 (15.5%)
Perioperative parameter	
Urgent surgery	177 (14.2%)
Preoperative IABP	88 (7.1%)
Bypass time (min)	153 ± 71
Biochemical data	
Hemoglobin (g/dL)	11.2 ± 1.8
Albumin (g/dL)	3.6 ± 0.7
Creatinine (mg/dL)	0.9 ± 0.2
eGFR (mL/min/1.72 m ²)	80 ± 13

CABG, Coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LV, left ventricle.

AKI was defined and categorized into 3 stages by the Acute Kidney Injury Network (AKIN) criteria.¹⁵

Indication for Renal Replacement Therapy

The indications for renal replacement therapy (RRT) were as follows: oliguria (urine output <240 mL/12 hours) despite fluid resuscitation and intravenous diuretic treatment, severe hyperkalemia greater than 6.5 mmol/L, severe acidosis (pH <7.2), or pulmonary edema. The decision to initiate or terminate RRT was determined by the consulting nephrologists.

Statistical Analysis

Normally distributed continuous data were expressed as mean ± standard deviation. Statistical analysis was performed with SPSS 15.0 software (IBM, Chicago, Ill). To identify risk factors for different stages of postoperative AKI, a multinomial logistic regression model was performed. To identify independent risk factors for dialysis-requiring AKI, a binominal multivariate logistic stepwise regression model was used. Risk factors with a *P* value less than .1 in univariate analysis were entered into the multivariate analysis, and a logistic assumption was tested for all continuous variables in this model. All probabilities were 2 tailed.

RESULTS

Basic Characteristics of Study Population

During the 6-year study period, 2285 consecutive patients underwent cardiac surgery with cardiopulmonary bypass at Taipei Veterans General Hospital. After excluding patients receiving maintenance dialysis and heart transplantation, 1246 patients with baseline eGFR greater than 60 mL/min/1.73 m² were included in the study. The clinical characteristics of the study cohort are shown in Table 1. Patients' mean age was 61.5 ± 15.5 years and mean baseline eGFR was 80 ± 13 mL/min/1.73 m². The distribution

FIGURE 2. Distribution plot of eGFR in study population. eGFR, Estimated glomerular filtration rate.

plot of eGFR is shown in Figure 2; 26.5% (n = 330) of the subjects were diabetic.

Acute Kidney Injury Incidence Stratified by Category of Proteinuria

A total of 23.4% of patients (n = 290) had preoperative proteinuria. The overall incidence rate of AKI was 34.8% (n = 434), including 26.2% (n = 326) in AKIN stage 1, 3.6% (n = 45) in AKIN stage 2, and 5% (n = 63) in AKIN stage 3. Only 36 patients (2.9%) required RRT after surgery. The crude risk of AKI was greater in patients with proteinuria. When stratified into groups of dipstick negative, trace, 1+, 2+, or 3+, there was a stepwise increase in incidence of postcardiotomy AKI with greater levels of proteinuria (Table 2).

Multinomial Logistic Regression Model for Postoperative Acute Kidney Injury

Independent risk factors for all stages of postoperative AKI were high body mass index, low serum albumin, longer bypass time, urgent surgery, requirement of preoperative IABP or extracorporeal membranous oxygenation, and presence of proteinuria. Diabetes was an independent risk factor for developing AKIN stage 1 but not for higher stages. On the other hand, lower eGFR was a risk factor

TABLE 2. Cross table between preoperative proteinuria and postcardiotomy acute kidney injury

		Category of proteinuria					Total
		Negative	Trace	1+	2+	3+	
AKIN	No	587	81	97	43	4	812
	Stage 1	213	25	53	22	13	326
	Stage 2	17	5	11	8	4	45
	Stage 3	22	6	22	8	5	63
Total		839	117	183	81	26	1246

Pearson chi-square *P* < .0001, likelihood ratio *P* < .0001. AKIN, Acute Kidney Injury Network.

for developing AKIN stage 3 but not for lower stages. The incremental possibility of developing AKI paralleled with incremental severity of proteinuria (Table 3).

Multivariate Logistic Regression Model for Acute Kidney Injury Requiring Renal Replacement Therapy

Independent risk factors of dialysis-requiring AKI were urgent surgery, requirement of preoperative IABP, lower eGFR, and presence of proteinuria. The incremental possibility of developing RRT-requiring AKI also paralleled with incremental severity of proteinuria (Table 4).

Subgroup Analysis

To validate the risk of proteinuria for postoperative AKI in various patient populations, we performed subgroup

TABLE 3. Risk factors for postcardiotomy acute kidney injury

AKIN stage	OR	P value	Lower 95% CI	Upper 95% CI
AKIN stage 1 (n = 326)				
Body mass index	1.068	.001	1.028	1.109
LV ejection fraction (%)	1.120	.790	0.487	2.576
Hemoglobin (mg/dL)	0.937	.087	0.870	1.009
Albumin (g/L)	0.698	.000	0.575	0.846
Bypass time (min)	1.006	.000	1.004	1.008
Age (y)	1.001	.868	0.988	1.015
eGFR (mL/min)	0.993	.079	0.985	1.001
Male gender	1.535	.005	1.136	2.074
Diabetes	1.319	.041	1.011	1.721
Urgent surgery	2.512	.000	1.650	3.822
IABP	2.041	.008	1.202	3.465
ECMO	1.433	.447	0.566	3.629
Proteinuria (negative proteinuria as reference)				
Proteinuria trace	3.408	.001	1.667	6.967
Proteinuria 1+	3.489	.000	1.770	6.878
Proteinuria 2+	5.408	.000	2.652	11.029
Proteinuria 3+	3.850	.000	2.044	7.251
AKIN stage 2 (n = 45)				
Body mass index	0.962	.474	0.864	1.070
LV ejection fraction (%)	0.881	.910	0.096	8.048
Hemoglobin (mg/dL)	0.962	.698	0.792	1.169
Albumin (g/L)	0.508	.010	0.304	0.849
Bypass time (min)	1.007	.003	1.002	1.011
Age (y)	1.058	.006	1.016	1.101
eGFR (mL/min)	1.019	.054	1.000	1.040
Male sex	1.005	.990	0.450	2.245
DM	1.461	.285	0.729	2.926
Urgent surgery	2.294	.090	0.878	5.996
IABP	4.845	.001	1.951	12.029
ECMO	5.866	.006	1.642	20.963
Proteinuria (negative proteinuria as reference)				
Proteinuria trace	2.858	.110	0.788	10.370
Proteinuria 1+	11.437	.001	2.710	48.275
Proteinuria 2+	4.926	.018	1.318	18.403
Proteinuria 3+	12.882	.000	3.753	44.223

(Continued)

TABLE 3. Continued

AKIN stage	OR	P value	Lower 95% CI	Upper 95% CI
AKIN stage 3 (n = 63)				
Body mass index	1.095	.008	1.024	1.172
LV ejection fraction (%)	1.053	.942	0.261	4.242
Hemoglobin (mg/dL)	0.917	.184	0.808	1.042
Albumin (g/L)	0.600	.003	0.427	0.841
Bypass time (min)	1.009	.000	1.005	1.012
Age (y)	0.995	.686	0.971	1.020
eGFR (mL/min)	0.946	.000	0.931	0.961
Male sex	0.949	.837	0.579	1.556
Diabetes	1.525	.084	0.944	2.462
Urgent surgery	4.719	.000	2.573	8.655
IABP	4.178	.000	2.147	8.129
ECMO	23.757	.000	9.545	59.131
Proteinuria (negative proteinuria as reference)				
Proteinuria trace	3.189	.006	1.402	7.252
Proteinuria 1+	5.044	.000	2.216	11.485
Proteinuria 2+	10.558	.000	3.891	28.651
Proteinuria 3+	13.733	.000	6.107	30.883

Model fitting $P < .0001$, goodness for fit $P = .006$, likelihood ratio test for proteinuria $P < .0001$. AKIN, Acute Kidney Injury Network; CI, confidence interval; DM, diabetes mellitus; ECMO, extracorporeal membranous oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LV, left ventricular; OR, odds ratio.

analysis for gender, diabetes, and surgical type. Proteinuria (urine dipstick greater than trace) remained a risk factor for all stages of postoperative AKI in all prespecified subgroups (Figure 3).

DISCUSSION

In previous investigations,¹⁰⁻¹³ an equal importance of both eGFR and proteinuria in the assessment of AKI has been found. Our results extended this association across the full range of proteinuria and to all cardiac surgery, even in patients with an eGFR greater than 60 mL/min/1.73 m². This was the first study to quantify the graded relationship between proteinuria and risk of postcardiotomy AKI among patients with preserved eGFR. It showed a graded increase in the hazards of AKI along the worsening proteinuria categories, measured by using standard urinary dipstick, in patients undergoing cardiac surgery. This association was essentially unaltered despite extensive statistical adjustment for gender, traditional cardiac risk factors, diabetes mellitus, or modality of surgery.

The mechanisms of postcardiotomy AKI are multifactorial. Intraoperative hypotension, ischemia-reperfusion injury of cardiopulmonary bypass, oxidative stress, activation of inflammatory cytokines, and postoperative low cardiac output have been speculated as the causes.¹⁴⁻¹⁹ The final event is tubular damage and GFR decline. Accordingly, it is well accepted that patients with lower GFR are more vulnerable to these insults, and consequently kidney damage develops after the operation.

TABLE 4. Risk factors for dialysis-requiring acute kidney injury after cardiac surgery (n = 36)

Parameters	Unadjusted				Multivariate adjusted			
	OR	95% CI	95% CI	P value	OR	95% CI	95% CI	P value
Age (per 10 y)	1.19	0.91	1.57	.203				
Body mass index	0.99	0.95	1.04	.770				
Male gender	1.85	0.71	4.80	.207				
Diabetes	1.30	0.59	2.50	.590				
Urgent surgery	3.25	1.71	6.16	<.001	3.14	1.70	5.79	<.001
LV ejection fraction (per 10%)	0.56	0.12	2.68	.470				
Preoperative IABP	2.73	1.38	5.37	.004	3.15	1.63	6.07	.001
Bypass time (per 10 min)	1.00	1.00	1.01	.131				
Hemoglobin (mg/dL)	0.92	0.79	1.06	.256				
Albumin (mg/dL)	0.71	0.48	1.04	.081				
eGFR (mL/min/1.72 m ²)	0.95	0.94	0.96	.021				
Urine protein by dipstick				<.001				<.001
Negative	1				1			
Trace	1.29	0.47	3.59	.619	1.22	0.44	3.325	.701
1+	2.82	1.33	5.99	.007	3.31	1.60	6.83	.001
2+	5.72	2.76	11.87	<.0001	6.33	3.13	12.83	<.0001
3+	9.57	4.49	20.42	<.0001	11.22	5.40	23.30	<.0001

CI, Confidence index; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LV, left ventricle; OR, odds ratio.

On the contrary, proteinuria reflects an altered glomerular filtration barrier integrity rather than an altered GFR. As the earliest manifestation of glomerular damage, proteinuria may be present in the setting of a normal GFR, such as diabetes, hypertension, and glomerular disease. Thus, the casual relationship between proteinuria and AKI needs to be explored. There are several possible explanations. At first, proteinuria is the earliest

manifestation of glomerular damage; “damaged kidneys” have a higher possibility of further injury during operation. Another possible explanation is systemic endothelial cell injury.²⁰⁻²² Because proteinuria is strongly accepted as a surrogate marker of endothelial dysfunction, proteinuria in patients undergoing cardiac surgery might reflect systemic endothelial dysfunction, making kidneys less able to tolerate hemodynamic changes during

FIGURE 3. Subgroup analysis of proteinuria in postoperative AKI. AKI, Acute kidney injury; CABG, coronary artery bypass grafting; DM, diabetes mellitus; RRT, renal replacement therapy.

operation and eventually developing postoperative AKI. Regardless of the causes, proteinuric patients undergoing cardiac surgery may benefit from closer surveillance.

Previous epidemiologic studies consistently showed that proteinuria predicted mortality in populations with and without diabetes or cardiovascular disease.^{23,24} Likewise, we showed that the association of proteinuria with AKI was similar between diabetic and nondiabetic subjects, despite diabetes being well known as a strong independent risk factor for AKI. It is plausible that the potential impact of diabetes mellitus might be due to the coexisting proteinuria.

Study Limitations

At first, this study was conducted at a single center, which may limit the use of its results to other centers. However, the mortality rate and incidence of AKI found in our population compared well with those from prior studies.^{3,5,13} Second, the standard urinary dipstick, an inexpensive and simple tool to identify the presence of proteinuria, is also a relatively insensitive marker of urinary protein excretion. Whether microalbuminuria may represent a more sensitive test to identify persons at increased risk of AKI after cardiac surgery requires further evaluation in future studies. Third, to focus the prognostic impact of “postcardiotomy acute kidney injury” by AKIN criteria, AKI occurring 48 hours after surgery was not entered in the analysis, although this might increase the predictive power of mortality. Fourth, as is true in retrospective and observational studies, several potential risk factors for AKI were not investigated, such as intraoperative hypotension and degree of hemodilution.

CONCLUSIONS

There was a graded association between the severity of preoperative proteinuria and the risk of AKI after cardiac surgery. The finding that even a small amount of proteinuria from a simple urine dipstick may serve as a “low eGFR equivalent” to identify a hitherto neglected subset of at-risk individuals has therapeutic implications. These results also underscore that the current staging system of chronic kidney disease based primarily on the eGFR without fully incorporating the severity of concomitant proteinuria can be improved. It is important that future studies address whether medications that decrease proteinuria might be associated with a decrease in mortality in patients undergoing cardiac surgery or whether proteinuria is simply a marker of early kidney disease or endothelial dysfunction.

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