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Serum and urinary biomarkers for predicting acute kidney injury after partial nephrectomy

Abstract

Purpose: The purpose of this study was to evaluate the ability of specific biomarkers to predict acute kidney injury (AKI) after partial nephrectomy.

Methods: A prospective study of 89 patients undergoing partial nephrectomy was conducted in the First Affiliated Hospital of Fujian Medical University. The patients were divided into two groups according to AKI status: an AKI group and non-AKI group. Receiver operator characteristic (ROC) curves were generated and the areas under the curve (AUCs) were compared.

Results: Twenty-eight subjects (31.5%) developed AKI while sixty-one subjects (68.5%) did not. Vascular clamping time in the AKI group was longer than that in the non-AKI group (29 ± 17 min vs. 24 ± 9 min, $P = 0.042$). Eight patients (28.6%) received blood infusion in the AKI group compared with five patients (8.2%) in the non-AKI group ($P = 0.021$). The area under ROC curve for AKI prediction was 0.792 [95% confidence interval (CI) 0.697 to 0.888, $P < 0.000$] for serum cystatin C 24 hours after surgery and 0.756 (95% CI 0.656 to 0.857, $P < 0.000$) for serum cystatin C 48 hours after surgery. Multivariate regression analysis showed transfusion [Hazard ratio (HR) 3.712, $P = 0.044$] and 24 hours serum cystatin C (HR 41.594, $P = 0.001$) correlated with AKI.

Conclusions: Postoperative serum cystatin C may be an early predictor for AKI after partial nephrectomy. Transfusion may be an independent risk factor for AKI after partial nephrectomy

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Partial nephrectomy is considered the preferable treatment for small renal cell carcinoma tumors, resulting in equivalent oncological outcomes but better preservation of renal function and improved overall survival compared with radical nephrectomy [1, 2]. Interruption of renal blood flow through temporary renal artery occlusion is widely carried out during partial nephrectomy. This maneuver may improve visibility, aid in hemostasis and allow for adequate closure of the parenchymal defect; however, this may also cause renal ischemia reperfusion injury, which may induce postoperative acute kidney injury (AKI) [3]. Many studies have demonstrated that impaired renal function may increase postoperative non-cancer associated mortality [4, 5].

Current criteria for AKI diagnosis and classification depend highly on serum creatinine (SCr) changes [6]; however, many studies have indicated that SCr is not a sensitive biomarker for detection of early AKI [7]. Although early AKI diagnosis could trigger early initiation of supportive measures and novel therapeutic strategies [8], the diagnosis of AKI is often delayed until the SCr level increases.

Several clinical indicators are presently used to predict AKI after cardiac surgery and renal disease, including serum or urinary cystatin C [9]. Serum β_2 microglobulin may also be an early indicator for acute kidney ischemia (based on data from animal models) and urinary concentrations of β_2 microglobulin are measured to evaluate percutaneous nephrolithotomy-induced kidney damage [10]. As a result of such evidence supporting the use of biomarkers to indicate or predict kidney damage, the extent of AKI in patients undergoing partial nephrectomy was quantitatively assessed by measuring novel serum and urinary biomarkers. In addition, these novel biomarkers were evaluated for their ability to predict renal dysfunction during the postoperative period.

Methods

Patients

The present study was performed from January 2013 to December 2013. The study was approved by our institutional review board and all patients provided written informed consent. Eighty-nine patients underwent partial nephrectomy for right or left renal carcinoma. The criteria for inclusion in this study included tumors size <7 cm and normal contralateral renal function. Normal contralateral renal function was defined as differential renal function of > 40% as determined by radionuclide scintigraphy. Exclusion criteria were prior bilateral partial nephrectomy, preoperative combined with chronic renal disease (defined as GFR <60 mL/min/1.73 m² for three months

or more, with or without kidney damage), patient age <18 years old and preoperative use of drugs such as aminoglycosides, aspirin and angiotension converting enzyme inhibitors, which are known to cause renal toxicity.

Anesthesia technique

Upon entering the operating room, patients underwent an ECG, and noninvasive blood pressure and pulse oxygen saturation monitoring were performed. Anesthesia induction included 1.5 mg/kg propofol, 4 μ g/kg fentanyl and 0.15 mg/kg cisatracurium. Ventilation was performed following successful endotracheal intubation to maintain ET CO_2 concentration between 35 and 45 mmHg.

Surgical technique

All surgical procedures were performed by the same surgical team. All surgeons applied a standard 11th rib flank approach with the patient in the full flank position. After mobilizing the kidney, the ureter and vascular pedicle were identified and isolated on a vascular loop. The kidney surface was cooled with ice slush saline before renal artery clamping. Tumor enucleation involved circumferential incision, followed by blunt dissection between the fibrous pseudocapsule and renal parenchyma. Samples of the remaining renal parenchyma at the tumor bed were sent for intraoperative frozen section analysis to verify a tumor-free margin. Open blood vessels or collection ducts were sutured and an argon beam coagulator was used to seal the exposed renal parenchyma. The pedicle clamp was removed and clamp-time was recorded. The kidney was inspected for bleeding or urinary leakage prior to closure.

Biomarkers assay and sample collection

Biomarkers examined included serum cystatin C, serum creatinine, serum β_2 microglobulin (β_2 MG), urine β_2 microglobulin, urine microalbuminuria (MALB) and urine α_1 -microglobulin (α_1 MU). Serum and urine samples were collected from all patients before surgery, and 24 and 48 hours after renal pedicle clamp removal. Serum cystatin C level was detected by enzyme-linked immunosorbent assay (ELISA). Estimation of serum β_2 MG was also carried out by ELISA. Enzymatic assay was used to measure serum creatinine concentration. Urine β_2 MG, urine MALB, and urine α_1 MU levels were measured by immunoassay.

Endpoints and groups

The designated endpoint for the study was postoperative AKI. AKI was defined as an increase SCr >50% or by 0.3 mg% from baseline in 48 hours. Patients were divided into two groups according to endpoint: an AKI group and a group without diagnosed AKI.

Data collection and definitions

Data were obtained from the medical records for each patient in the study and were classified as preoperative, perioperative and postoperative data. Preoperative data included patient characteristics such as age, gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI), smoking history, alcohol intake history and previous medical history of high blood pressure, diabetes and kidney disease. Perioperative hypotension was defined as a decrease of mean blood pressure (MAP) higher than 20% over 5 min. When it occurred, fluids or vasopressors such as intravenous infusion of dopamine were given as needed. The perioperative data included surgery duration, estimated blood loss, perioperative blood transfusion, intraoperative colloid and crystalloid fluid volume, intraoperative vasopressors use and duration of clamping of the renal vessels. Duration of hospital stay was also recorded.

Statistical analysis

All data were analyzed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL). The chi-square test or Fisher exact test, were used as appropriate for categorical variables, while the Wilcoxon or Kruskal-Wallis test were applied for continuous variables. Repeated measurement data analysis was per-

formed for changes of serum cystatin C, serum or urinary $\beta 2$ microglobulin concentration, urinary MALB and $\alpha 1$ MU concentration over time. The receiver operating characteristics (ROC) curve was applied to assess the ability of biomarkers to identify AKI. Biomarkers were considered to show excellent predictive ability when AUC-ROC (the area under the curve of the receiver operating characteristic) was between 0.90 and 1.00, good prediction when AUC-ROC was between 0.80 and 0.89, average prediction when AUC-ROC was between 0.70 and 0.79, and poor prediction when AUC-ROC was between 0.50 and 0.69. Receiver operating characteristic analyses were used to estimate the best thresholds in order to maximize sensitivity and specificity. Univariate logistic regression analysis was used to compare AKI against individual preoperative, intraoperative, and postoperative variables, respectively. Multivariate analysis with the conditional backward method was performed to determine the odds ratio (OR) based on multiple logistic regressions of variables found to be significant or with a P value < 0.2 in the univariate analysis. Multivariate logistic regression models were used to determine variables that were independently correlated with postoperative AKI. Differences were considered to be statistically significant when P < 0.05.

Results

Demographics

Table 1 shows baseline characteristics of the designated groups. Twenty-eight patients suffered from AKI. No patients required continuous renal replacement therapy (CRRT), and no fatalities occurred during surgery. The patients in the AKI group had higher preoperative urine MALB (P = 0.046) and $\alpha 1$ MG

FIGURE 1. Changes in serum cystatin C in both AKI and non-AKI groups. ** P < 0.001 between groups; * P < 0.001 compared to respective baseline. Values are presented as the mean $\pm$ SE.

FIGURE 2. Changes in serum $\beta 2$ microglobulin in AKI and non-AKI groups. * P < 0.01 compared to respective baseline. Values are presented as the mean $\pm$ SE.

($P = 0.007$) concentrations than those in the non-AKI group. The duration of renal hilum blockage in the AKI group was greater than that in the non-AKI group (29 ± 17 min *vs* 24 ± 9 min, $P = 0.042$). Eight patients (28.6%) in the AKI group and five patients (8.2%) in the non-AKI group received a blood transfusion during surgery ($P = 0.021$).

Changes in AKI biomarkers

Changes in AKI biomarkers are shown in Figures 1-6. The prediction efficiency of AKI biomarkers is shown in Table 2. The AUC of 24 hours postoperative serum cystatin-C was 0.792 (95% CI 0.697-0.888, $P < 0.001$). Other 24 hours postoperative biomarkers exhibited poor predictive ability for AKI. The

AUC of 48 hours postoperative serum cystatin-C was 0.756 (95% CI 0.656-0.857, $P < 0.001$), though other 48 hours postoperative biomarkers were poor predictors of AKI.

Sensitivity and specificity of serum cystatin-C prediction for AKI

The sensitivity of 24 hours postoperative serum cystatin-C prediction was 0.714, the specificity was 0.738 and the threshold was 0.98 mg/L. The sensitivity of 48 h postoperative serum cystatin-C prediction was 0.679, the specificity was 0.656 and the threshold was 1.005 mg/L.

FIGURE 3. Change of urinary $\beta 2$ microglobulin in both AKI and non-AKI groups. * $P < 0.01$ compared to respective baseline. Values are presented as the mean $\pm$ SE.

FIGURE 4. Changes in urinary MALB in both AKI and non-AKI groups. ** $P = 0.046$ between groups. * $P < 0.001$ compared to respective baseline. Values are presented as the mean $\pm$ SE.

FIGURE 5. Figure. 5 Changes in urine $\alpha 1$ MG in both AKI and non-AKI groups. ** $P = 0.007$ between groups. * $P < 0.001$ compared to respective baseline. Values are presented as the mean $\pm$ SE.

FIGURE 6. Changes in serum creatinine in both AKI and non-AKI group. ** $P < 0.001$ between groups. * $P < 0.001$ compared to baseline creatinine. Values are presented as the mean $\pm$ SE.

TABLE 1. Characteristics of patients with AKI compared with those without AKI

Characteristics	AKI group (N = 28)	No AKI group (N = 61)	P value
Demographic data			
Age (years)	51 ± 13	48 ± 11	0.363
Sex			0.630
Male	20	39	
Female	8	22	
Body mass index	24.9 ± 2.8	24.1 ± 2.8	0.213
Smoking	11	23	1.000
Alcohol	6	6	0.182
Kidney disease	1	1	0.533
Diabetes mellitus	3	5	0.103
Hypertension	10	19	0.808
Surgical factors			
Colloid fluids (mL)	1107 ± 393	1121 ± 416	0.880
Crystalloid fluids (mL)	1896 ± 510	1775 ± 478	0.280
Urine output (mL)	854 ± 1171	673 ± 445	0.263
Estimate blood loss (mL)	304 ± 542	212 ± 203	0.251
Clamping time (min)	29 ± 17	24 ± 9	0.042
Operative time (min)	169 ± 57	149 ± 40	0.058
Hospital stay (days)	14 ± 6	13 ± 4	0.374
Transfusion	8	5	0.021
Intraoperative vasopressors use	16	26	0.255
Baseline serum Cr (μmol/L)	67.7 ± 19.8	71.7 ± 12.9	0.255
Baseline serum Cys-C (mg/L)	0.95 ± 0.17	0.92 ± 0.19	0.556
Baseline urinary MALB (mg/L)	25.6 ± 59.1	10.3 ± 3.8	0.046
Baseline urinary α1MG (mg/L)	10.6 ± 9.4	6.9 ± 3.1	0.007
Baseline serum β2MG (mg/L)	1.71 ± 0.53	1.71 ± 0.60	0.986
Baseline urine β2MG (mg/L)	0.41 ± 1.34	0.26 ± 0.77	0.485

TABLE 2. Performance characteristics of biomarkers to predict AKI

Renal Markers	AUC-ROC (95% CI)	P value
At 24 hours after partial nephrectomy		
Serum cystatin C	0.792 (0.697-0.888)	< 0.001
Serum β2 microglobulin	0.565 (0.425-0.704)	0.329
Urine MALB	0.451 (0.326-0.592)	0.839
Urine α1MG	0.545 (0.407-0.684)	0.496
Urine β2 microglobulin	0.575 (0.447-0.703)	0.258
At 48 hours after partial nephrectomy		
Serum cystatin C	0.756 (0.656-0.857)	< 0.001
Serum β2 microglobulin	0.525 (0.386-0.665)	0.701
Urine MALB	0.487 (0.360-0.613)	0.839
Urine α1MG	0.521 (0.383-0.659)	0.754
Urine β2 microglobulin	0.561 (0.424-0.697)	0.358

Independent risk factors for postoperative AKI

Univariate analysis identified independent risk factors for AKI including preoperative MALB and α1MG concentration, duration of surgery, duration of clamping, blood transfusion, post-operative 24 hours serum cystatin C concentration and post-operative 24 hours serum β2 microglobulin concentration. Multiple regression analysis showed that risk factors for post-operative AKI included required blood transfusion ($P = 0.044$) and 24 hours postoperative serum cystatin C concentration ($P = 0.001$) (Table 3-5).

Discussion

In this study, serum cystatin C was found to be a predictive biomarker for postoperative AKI and blood transfusion was found to be a risk factor for postoperative AKI during partial nephrectomy. Partial nephrectomy is considered the primary treatment for small renal carcinoma tumors with equivalent oncological outcomes, better preservation of renal function and improved overall survival compared with radical nephrectomy [11, 12]. During partial nephrectomy, the renal hilum is

TABLE 3. Univariate and multivariate analysis to identify preoperative factors correlated with postoperative AKI

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.018 (0.980-1.058)	0.360		
Gender	1.410 (0.533-3.729)	0.488		
BMI	1.109 (0.942-1.306)	0.213		
Smoking history	1.069 (0.427-2.678)	0.887		
Alcohol history	2.500 (0.727-8.595)	0.146	2.961 (0.726-12.088)	0.130
Kidney disease history	2.222 (0.134-36.866)	0.577		
Diabetes mellitus history	1.344 (0.298-6.066)	0.701		
Hypertension history	1.228 (0.478-3.157)	0.670		
Baseline serum Cr	0.982 (0.952-1.013)	0.254		
Baseline serum Cys-C	2.091 (0.183-23.861)	0.553		
Baseline urinary MALB	1.106 (1.021-1.198)	0.014	1.083 (0.993-1.182)	0.072
Baseline urinary α 1MG	1.118 (1.013-1.233)	0.026	1.079 (0.967-1.204)	0.176
Baseline serum β 2MG	0.993 (0.452-2.181)	0.986		
Baseline urinary β 2MG	1.161 (0.756-1.784)	0.496		

TABLE 4. Univariate and multivariate analysis to identify intraoperative factors correlated with postoperative AKI

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Estimate blood loss	1.001 (0.999-1.002)	0.301		
Transfusion	4.480 (1.311-15.304)	0.017	3.712 (1.036-13.301)	0.044
Operative time	1.012 (1.002-1.022)	0.020	1.007 (0.996-1.019)	0.223
Clamping time	1.054 (1.006-1.104)	0.026	1.041 (0.992-1.092)	0.102
Urinary output	1.000 (1.000-1.001)	0.300		

clamped, which reduces blood loss and improves accessibility of the surgical field. Despite these benefits, renal ischemia-reperfusion injury induced by clamping the renal hilum can lead to postoperative acute renal injury. In the present study, postoperative AKI was determined by chart review using the established Acute Kidney Injury Network (AKIN) criteria [13]. Using these criteria, postoperative AKI is defined as an increase in serum creatinine of 50% from baseline. Our study found that twenty-eight patients suffered postoperative AKI,

which was greater than that reported by Fergany *et al.* [14]. Prolonged clamping time in our study may account for this difference. In our study, patients with or without AKI had the same duration of hospital stay, which was not the case in other studies [15, 16].

Cystatin C has shown great clinical potential as a biomarker of AKI in critically ill patients and cardiac surgery patients [17, 18]. One recent study found that cystatin C was highly correlated with the development of AKI [19]. Similarly,

TABLE 5. Univariate and multivariate analysis to identify postoperative factors correlated with postoperative AKI

	Univariate		Multivariate	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
24 hour serum Cys-C	41.594 (4.802-360.253)	0.001	41.594 (4.802-360.253)	0.001
24 hour urinary MALB	0.999 (0.996-1.003)	0.638		
24 hour urinary α 1MG	1.007 (0.995-1.019)	0.247		
24 hour serum β 2MG	2.198 (1.004-4.809)	0.049	1.154 (0.491-2.713)	0.742
24 hour urinary β 2MG	1.018 (0.991-1.045)	0.189	0.996 (0.958-1.036)	0.841

in our present study, multivariate analysis results showed that elevated serum cystatin C levels were significantly correlated with the postoperative occurrence of AKI. This may be due to serum cystatin C's importance as an ideal glomerular filtration marker. A biomarker must have the capacity to differentiate between pre-renal azotemia and cellular injury, as therapies for these two conditions differ considerably.

During partial nephrectomy, the use of the renal hilum clamp can induce renal ischemia reperfusion injury. A recent retrospective study of 362 patients with solitary kidneys who underwent partial nephrectomy with the utilization of warm ischemia suggested that each minute of warm ischemia time was associated with a 6% (hazard ratio 1.06, $P < 0.001$) greater risk of acute renal failure and 4% (hazard ratio 1.04, $P = 0.03$) greater risk of stage IV CKD during follow-up [20]. This may be true for AKI. Serum cystatin C may therefore be a good indicator for AKI during partial nephrectomy and have the capacity to differentiate between prerenal azotemia and cellular injury.

Previous studies have shown that β 2 microglobulin is a more sensitive marker of renal tubular injury in comparison with serum creatinine levels; therefore, β 2 microglobulin has been advocated as an early marker of tubular injury [21, 22]. Urinary β 2 microglobulin has also been used to measure kidney tubular damage after shock wave lithotripsy (SWL) [23]. Important considerations for using urinary β 2 microglobulin as a renal injury assessment tool are that it is a simple, non-invasive measurement and that longitudinal tracking of its levels is straightforward and convenient. The results of this study revealed that neither serum nor urinary β 2 microglobulin were predictive early biomarkers for postoperative AKI. In nephropathy models, urinary β 2 microglobulin was identified as a potential early biomarker for renal tubular injury; however, serum or urinary β 2 microglobulin may not be useful as early biomarkers for AKI in partial nephrectomy. Recently, microalbuminuria concentration was considered as an early important

biomarker for kidney injury in nephropathy [24]; however, our study found no differences in urinary microalbuminuria and α 1 MU, suggesting these biomarkers may also not be early predictors for postoperative AKI in partial nephrectomy.

Despite the interesting results obtained in our study, the small number of enrolled patients limited the strength of these observations. Larger studies will be necessary to confirm our findings. Secondly, problems exist in using creatinine as a marker of AKI: it is insensitive to minor changes in kidney function and is affected by other factors. While renal biopsy may be the gold standard for diagnosing AKI, it is invasive and impractical in most clinical settings. Limiting the generalizability of our findings is the fact that patients with baseline chronic kidney disease were excluded from the study. Moreover, biomarkers were not measured at earlier points. Future studies with larger patient numbers will help confirm the findings of the present study and shed more light on the association between AKI and partial nephrectomy. Despite the limitations of this study, postoperative serum cystatin C shows promise as an early predictor for AKI after partial nephrectomy and transfusion may be an independent risk factor for AKI after partial nephrectomy.

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