

# Increased serum cystatin C is a predictive factor for renal outcome in non-cardiac critically ill patients

Tadashi Kaneko, Ryosuke Tsuruta, Shunji Kasaoka, Takashi Miyauchi, Motoki Fujita, Yoshikatsu Kawamura, Tsuyoshi Maekawa

## Abstract

**Objective:** Serum cystatin C has been reported as a specific predictor of renal function and renal outcome in cardiac disease patients. In this study, serum cystatin C was measured in non-cardiac critically ill patients. We found that serum cystatin C was a predictive marker of renal dysfunction (RD) in these patients.

**Methods:** The study design was a retrospective, single-medical-center analysis conducted in the intensive care unit of a university hospital. Two hundred fifty-nine critically ill patients were included in this study. RD was defined as a two-fold increase in the serum creatinine level or a requirement for renal replacement therapy (RRT) on the last ICU day. Serum cystatin C, estimated

glomerular filtration rate (eGFR), APACHE II score, sequential organ failure assessment (SOFA) score, and vital signs on admission were analyzed using a logistic regression model and receiver operating characteristic (ROC) analysis.

**Results:** APACHE II score ( $p=0.007$ ) and serum cystatin C ( $p=0.020$ ) were significant risk factors for RD. The ROC analysis showed that a serum level of cystatin C greater than 1.50 mg/L had specificity for RD above 90%.

**Conclusions:** Serum cystatin C is a predictive marker of RD in non-cardiac critically ill patients.

**Key words:** Blood purification, renal replacement therapy, renal outcome, chronic kidney disease.

## Introduction

Cystatin C is a 122-amino-acid, 13 kDa protein that is a member of the family of competitive inhibitors of lysosomal cysteine proteinases. (1) Serum cystatin C is a useful tool

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From Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, Japan (Tadashi Kaneko, Ryosuke Tsuruta, Shunji Kasaoka, Takashi Miyauchi, Motoki Fujita, Yoshikatsu Kawamura, and Tsuyoshi Maekawa).

### Address for correspondence:

Tadashi Kaneko  
Advanced Medical Emergency and Critical Care Center  
Yamaguchi University Hospital  
1-1-1 Minamikogushi Ube, Yamaguchi, Japan  
Tel: +81-836-2343  
Fax: +81-836-2344  
E-mail: kaneyui-ygc@umin.ac.jp

employed in cardiac disease patients to measure kidney function, (2,3) and it may be a risk factor for cardiac events, including heart failure, coronary artery disease, and diastolic dysfunction, with or without chronic heart disease. (4-11) The estimated glomerular filtration rate (eGFR) of serum creatinine is also an established tool employed in measuring kidney function in cardiac disease patients. (12)

More than 30% of critically ill patients exhibit acute kidney injury (AKI) as a complication which is related to renal outcome. (13) Renal replacement therapy (RRT) is a convenient tool for the management of AKI in a critical care setting; however, the current RRT indications and treatment protocols are insufficient. (14) Cardiac disease data suggest that serum cystatin C and eGFR may be markers of kidney function in critically ill patients who do not suffer from

cardiac disease, and they may be used to identify groups with a high risk of renal outcome.

In the present study, we investigated whether serum cystatin C and eGFR were predictive markers of renal outcome in non-cardiac critically ill patients.

## Methods

### *Subjects*

The protocol of this clinical study was approved by the Institutional Review Board of our university. The study was designed as single-center retrospective analysis, covering the period from July 2006 to April 2008. Over this period, our emergency medical center admitted 1,284 critically ill patients. The patient enrollment procedure is shown in **Figure 1**. We excluded patients younger than 15 years of age, those with cardiac disease, and those whose stay in the intensive care unit (ICU) was shorter than 2 days. Serum cystatin C was measured in 302 of the remaining 619 cases. In our center, most of the cases whose initial serum creatinine exceeded 3.0 mg/dl underwent RRT or were placed on hemodialysis on the day of admission; therefore, we excluded an additional 43 cases that fit these parameters. As a result, the final number of patients enrolled in the present study was 259 (**Figure 1**). The details of this retrospective study were posted on the web site of our center from November 2008 to March 2009, without receiving any requests (from patients or their families) to exclude data from the analysis.

In this study, renal dysfunction (RD) was defined as a two-fold increase in the serum creatinine level measured on the last day spent at the ICU compared with the level on the first day, or as the performance of RRT because of oliguria. The 259 enrolled patients were divided into two groups: the RD group (23 cases) and the non-RD group (236 cases). Age, gender, vital signs on admission, APACHE II score, sequential organ failure assessment (SOFA) score, history of hypertension and diabetes mellitus, serum cystatin C, and eGFR were compared between the two groups by logistic regression analysis using a stepwise method. Significant parameters were investigated and their relationship with RD was assessed using the receiver operating characteristic (ROC) analysis. Serum creatinine was eliminated from the logistic regression and ROC analyses because of its direct

correlation with the study outcome (i.e., RD).

### *Sample collection*

Serum cystatin C was measured within 72 h of admission and eGFR was calculated for serum creatinine measured on the same day. During the study period, it was only possible to measure cystatin C on weekdays.

### *Assays*

Serum cystatin C was analyzed using a colloidal gold immunoassay (Nescote GC Cystatin C, Alfresa Pharma Corporation, Osaka, Japan). eGFR was calculated using a modified diet in renal disease (MDRD) formula. (15,16) The MDRD formula was adapted to Japanese patients. (17)

### *Statistical analyses*

Statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as medians and interquartile ranges, and categorical variables are expressed as counts and percentages. Statistical comparisons of continuous variables were analyzed using the Mann-Whitney *U* test, where appropriate. Statistical comparisons of categorical variables were analyzed using the chi-square test, where appropriate. A multivariate logistic regression analysis was performed using a stepwise procedure to identify significant factors. Sensitivity and specificity were calculated using ROC curves. The threshold of significance was set at  $p < 0.05$ .

## Results

The characteristics of the 259 patients are listed in **Table 1**. Compared with the non-RD group, patients in the RD group had a higher heart rate, APACHE II score, and SOFA score, and a lower eGFR. The non-RD group had a higher rate of hypertension history. Higher rates of RRT and ICU mortality were recorded in the RD group.

**Table 2** lists the results of logistic regression analysis using a stepwise procedure. The objective variable was defined as RD. Explanatory variables were defined as age, gender, history of hypertension, history of diabetes mellitus,

vital signs on admission, APACHE II score, SOFA score, cystatin C, and eGFR. The APACHE II score and cystatin C were significant factors with unfavorable odds ratios for avoiding RD ( $p=0.007$  and  $0.020$ , respectively). A history of hypertension was a significant factor with a favorable odds ratio for avoiding RD ( $p=0.031$ ).

**Figure 2** shows the ROC curve of serum cystatin C. **Table 3** shows the area under the ROC curve (AUC), and the sensitivity and specificity of each cutoff value. The AUC of serum cystatin C was  $0.607$  ( $p=0.089$ ), and a cystatin C level  $>1.50$  mg/L was the cutoff value ( $>90\%$  specificity).

**Table 4** compares the group of patients with cystatin C  $>1.50$  mg/L against the group with cystatin C  $<1.50$  mg/L. RD, RRT, and ICU mortality were significantly different between the two groups ( $p<0.001$ ).

## Discussion

We used a logistic regression model to demonstrate that the APACHE II score and serum cystatin C were risk factors for RD (a two-fold increase in the serum creatinine level or a requirement for RRT) (**Table 2**). Serum cystatin C was an encouraging biomarker of RD in non-cardiac critically ill patients. Previous studies showed that cystatin C was a reliable predictor of GFR in patients with cardiac dysfunction of any severity and of AKI in post-cardiac-surgery patients; (3,18) therefore, cystatin C predicts latent low renal function and acute renal failure. Here, we found that cystatin C was a more adequate predictor than eGFR. Acute renal failure in critically ill patients is reportedly a component of multiple organ dysfunction; therefore, it is reasonable that the APACHE II score, which is an indicator of systemic status, should be strongly correlated with RD. (19,20) A history of hypertension was a favorable factor for RD in the present study population; however, this result cannot be easily explained, as hypertension is a risk factor for chronic kidney disease. (21) Therefore, the finding warrants confirmation in a different population.

ROC analysis of cystatin C as a marker of RD did not yield a satisfactory AUC value ( $0.607$ ) in the present study population (**Figure 2**). It has been reported that classification based on serum cystatin C correlates with mortality, cardiovascular events, and incidence of heart failure in

coronary heart disease. (22) The ROC analysis enabled us to define the cutoff value of cystatin C at which the specificity for RD was  $>90\%$  (i.e.,  $1.50$  mg/L), although the sensitivity at this cutoff value was only  $34.8\%$  (**Table 3**). Classification of patients using a cystatin C cutoff of  $1.50$  mg/L revealed a significant difference ( $>20\%$  difference) in RD, RRT, and ICU mortality rate ( $p<0.001$ ) between the groups (**Table 4**). These results suggest that a cystatin C level  $>1.50$  mg/L may be treated as the cutoff value for the identification of patients at high risk of low renal function. An indication of RRT and hemodialysis should be considered for these patients, as highly related to the mortality (**Table 4**).

In the present study,  $23\%$  of patients with cystatin C  $>1.50$  mg/L received RRT, whereas only  $1\%$  of patients with cystatin C  $<1.50$  mg/L received RRT (**Table 4**). Previous studies have shown that RRT for acute renal failure may improve mortality and renal outcome, (23-25) while other studies failed to find any improvement. (26-28) Consequently, there are no indicators for the prophylactic RRT strategy for these acute renal failure or AKI patients. The present serum cystatin C data delineated the RD high-risk group, which may represent the group of patients suitable for prophylactic RRT. It should be noted that prophylactic RRT is not recognized as a common strategy to protect renal function in critically ill patients. In contrast, several studies have reported that the human atrial natriuretic peptide (which has been listed as a candidate prophylactic treatment for patients at high risk of low renal function) has a beneficial effect on renal function; (29,30) therefore, the roles of RRT and human atrial natriuretic peptide in the treatment of renal failure should be considered in clinical practice.

In the current clinical setting, serum creatinine is used as an indicator of renal failure; however, it was recently reported that cystatin C was more sensitive and detectable earlier than serum creatinine and blood urea nitrogen. (31) Therefore, serum cystatin C may be a new marker of renal function. In the present study, we showed that serum cystatin C may reflect renal function in non-cardiac critically ill patients. Future studies are required to investigate whether the daily routine measurement of serum cystatin C improves renal outcome.

Finally, serum cystatin C is eligible as a predictor of RD and as an indicator of RRT for non-cardiac critically ill patients; however, a prospective study using a large number of non-

cardiac critically ill patients will be necessary to confirm the applicability of serum cystatin C as a biomarker to predict renal function and disease outcome.

## Conclusions

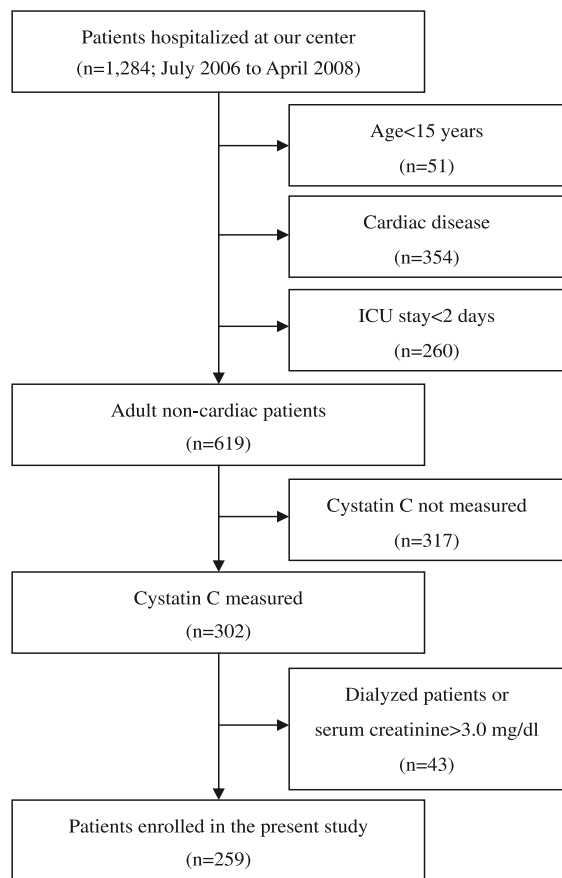
Serum cystatin C significantly predicted RD and enabled the identification of non-cardiac critically ill patients who

required RRT. Serum cystatin C may predict renal function in non-cardiac critically ill patients.

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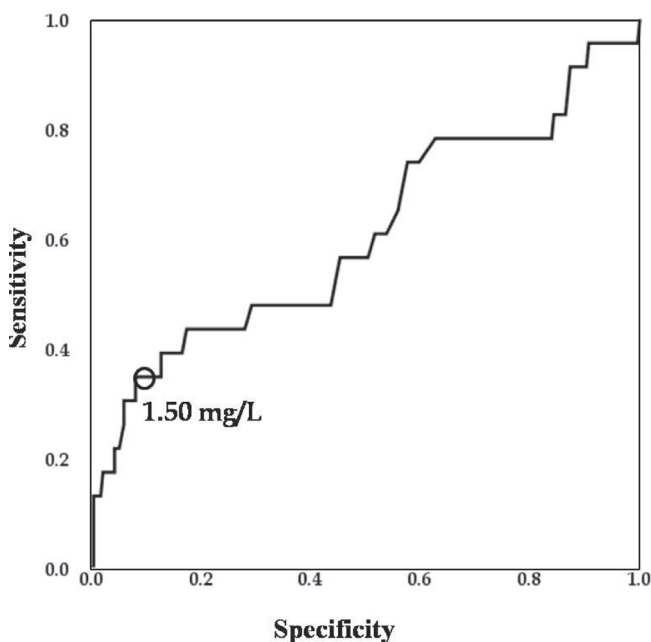
We are grateful to the staff, nurses, and medical residents at our emergency and critical care center. We also thank Masako Ueda for her assistance with paper work.

**Figure 1.** The patient enrollment procedure



Legend: Our center admitted 1,284 cases from July 2006 to April 2008. Patients who were younger than 15 years of age, had cardiac disease, and whose stay in the ICU was shorter than 2 days were excluded from this study. Serum cystatin C was measured in 302 of the 619 remaining cases. In our center, cases whose serum creatinine was >3.0 mg/dl had RRT, and chronic renal failure patients were placed on hemodialysis on the day of admission; therefore, 43 of these cases were excluded from the study. The final number of patients enrolled in this study was 259.

**Figure 2.** The ROC curve of serum cystatin C for AKI and RRT



Legend: The areas under the ROC curve, and the sensitivity and specificity are listed in **Table 3**. A cystatin C level >1.50 mg/L was associated with a specificity >90%.

**Table 1.** Patient characteristics

Variable	RD (n=23)	Non-RD (n=236)	p value
Age (years)	68 (49-75)	64 (51-73)	0.626
Male (%)	12 (52%)	132 (56%)	0.729
History of hypertension	5 (22%)	127 (54%)	0.003
History of diabetes mellitus	6 (26%)	60 (25%)	0.856
Serum creatinine			
On admission	1.09 (0.66-1.41)	0.69 (0.54-0.85)	0.003
At leave of ICU	1.91 (1.34-2.24)	0.64 (0.51-0.78)	<0.001
On admission			
Systolic BP (mmHg)	130 (95-153)	135 (112-158)	0.367
Diastolic BP (mmHg)	80 (50-88)	75 (60-90)	0.660
Heart rate (/min)	105 (93-118)	95 (76-110)	0.014
Respiratory rate (/min)	18 (14-20)	20 (16-24)	0.190
Body temperature (°C)	36.3 (35.2-37.1)	36.5 (35.8-37.2)	0.436
APACHE II score	25 (15-30)	13 (8-20)	<0.001
SOFA score	7 (4-9)	4 (2-6)	<0.001
Cystatin C (mg/l)	0.81 (0.72-1.88)	0.77 (0.65-1.08)	0.089
eGFR (ml/min/1.73 m <sup>2</sup> )	52 (31-86)	83 (64-104)	0.001
RRT	9 (39%)	0 (0%)	<0.001
Length of ICU stay (days)	13 (6-23)	12 (7-17)	0.496
ICU mortality (%)	12 (52%)	12 (5%)	<0.001
Stroke	2 (9%)	88 (37%)	
Sepsis	6 (26%)	13 (6%)	
Post cardiac arrest	4 (17%)	16 (7%)	
Gastrointestinal	0 (0%)	12 (5%)	
Aortic dissection	0 (0%)	13 (6%)	
Pneumonia	1 (4%)	5 (2%)	
Trauma	7 (30%)	50 (21%)	
Others	3 (13%)	39 (17%)	

Legend: Values are medians (interquartile range); eGFR was calculated using a MDRD

**Table 2.** Logistic regression analysis of RD using a stepwise method

Variable	p value	Odds ratio
APACHE II score	0.007	1.066 (1.017-1.116)
Cystatin C	0.020	2.033 (1.120-3.688)
History of hypertension	0.031	0.300 (0.100-0.893)

**Table 3.** ROC analysis of cystatin C and eGFR for RD

Variable	Area under the ROC curve	Cutoff value (mg/L)	Sensitivity (%)	Specificity (%)
Cystatin C	0.607	0.50	95.7	4.7
		0.75	60.9	46.2
		1.00	43.5	73.3
		1.25	39.1	85.2
		1.50	34.8	90.7
		1.75	30.4	93.2

**Table 4.** Renal outcome and mortality categorized using a cutoff value of 1.50 mg/L serum cystatin C

Variable	Cystatin C<1.50 mg/L (n=229)	Cystatin C>1.50 mg/L (n=30)	p value
RD	15 (7%)	8 (27%)	<0.001
RRT	2 (1%)	7 (23%)	<0.001
Length of ICU stay	13 (7-17)	11 (7-20)	0.983
ICU mortality	16 (7%)	8 (27%)	<0.001

Legend: Values are medians (interquartile range)

## References

1. Dharmidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney functions: a meta-analysis. *Am J Kidney Dis* 2002;40:221-6.
2. Levin A. Cystatin C, serum creatinine, and estimates of kidney function: searching for better measures of kidney function and cardiovascular risk. *Ann Intern Med* 2005;142:586-8.
3. Codognotto M, Piccoli A, Zaninotto M, Mion M, Vertolli U, Tona F, et al. Cystatin C in heart failure is nothing more than a bystander of glomerular filtration. *J Nephrol* 2007;20:219-27.
4. Ix JH, Shlipak MG, Chertow GM, Ali S, Schiller NB, Whooley MA. Cystatin C, left ventricular hypertrophy, and diastolic dysfunction: data from the Heart and Soul Study. *J Card Fail* 2006;12:601-7.
5. Arimoto T, Takeishi Y, Niizeki T, Takabatake N, Okuyama H, Fukui A, et al. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail* 2005;11:595-601.
6. Moran A, Katz R, Smith NL, Fried LF, Sarnak MJ, Seliger SL, et al. Cystatin C concentration as a predictor of systolic and diastolic heart failure. *J Card Fail* 2008;14:19-26.
7. Muntner P, Mann D, Winston J, Bansilal S, Farkouh ME. Serum cystatin C and increased coronary heart disease prevalence in US adults without chronic kidney disease. *Am J Cardiol* 2008;102:54-7.
8. Wang J, Sim AS, Wang XL, Salonikas C, Moriatis M, Naidoo D, et al. Relations between markers of renal function, coronary risk factors and the occurrence and severity of coronary artery disease. *Atherosclerosis* 2008;197:853-9.
9. Niccoli G, Conte M, Della Bona R, Altamura L, Siviglia M, Dato I, et al. Cystatin C is associated with an increased coronary atherosclerotic burden and a stable plaque phenotype in patients with ischemic heart disease and normal glomerular filtration rate. *Atherosclerosis* 2008;198:373-80.
10. Tang WH, Van Lente F, Shrestha K, Troughton RW, Francis GS, Tong W, et al. Impact of myocardial function on cystatin C measurements in chronic systolic heart failure. *J Card Fail* 2008;14:394-9.
11. Sarnak MJ, Katz R, Stehman-Breen CO, Fried LF, Jenny NS, Psaty BM, et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med* 2005;142:497-505.
12. Garcia A, Hermida J, Tutor JC. Estimation of the glomerular filtration rate from serum creatinine and cystatin C with regard to therapeutic digoxin monitoring. *J Clin Pharmacol* 2007;47:1450-5.
13. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008;23:1203-10.
14. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7-20.
15. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994;330:877-84.
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-70.
17. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007;11:41-50.
18. Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Dragun D, et al. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery—a prospective cohort study. *Crit Care Med* 2009;37:553-60.
19. Eachempati SR, Wang JC, Hydo LJ, Shou J, Barie PS. Acute renal failure in critically ill surgical patients: persistent lethality despite new modes of renal replacement therapy. *J Trauma* 2007;63:987-93.
20. Brar H, Olivier J, Lebrun C, Gabbard W, Fulop T, Schmidt D. Predictors of mortality in a cohort of intensive care unit patients with acute renal failure receiving continuous renal replacement therapy. *Am J Med Sci* 2008;335:342-7.
21. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007;71:159-66.
22. Ix JH, Shlipak MG, Chertow GM, Whooley MA. Association of cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: data from the Heart and Soul Study. *Circulation* 2007;115:173-9.
23. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. *Lancet* 2000;356:26-30.
24. Schiff H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002;346:305-10.
25. Saudan P, Niederberger M, De Seigneux S, Romand J, Pugin J, Perneger T, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006;70:1312-7.
26. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med* 2002;30:2205-11.
27. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM. Standard versus high-dose CVVHDF for ICU-related acute renal failure. *J Am Soc Nephrol* 2008;19:1233-8.
28. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7-20.
29. Mitaka C, Kudo T, Jibiki M, Sugano N, Inoue Y, Makita K, et al. Effects of human atrial natriuretic peptide on renal function in patients undergoing abdominal aortic aneurysm repair. *Crit Care Med* 2008;36:745-51.
30. Swärd K, Valsson F, Odencrans P, Samuelsson O, Ricksten SE. Recombinant human atrial natriuretic peptide in ischemic acute renal failure: a randomized placebo-controlled trial. *Crit Care Med* 2004;32:1310-5.
31. Song S, Meyer M, Türk TR, Wilde B, Feldkamp T, Assert R, et al. Serum cystatin C in mouse models: a reliable and precise marker for renal function and superior to serum creatinine. *Nephrol Dial Transplant* 2009;24:1157-61.