Does preoperative serum creatinine affect the early surgical outcomes of acute Stanford type A aortic dissection?

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Abstract

Background: Acute Stanford type A aortic dissection is a lethal disease requiring surgery. Evidence regarding the effects of preoperative creatinine in mortality is limited, and few studies have evaluated the effect of postoperative dialysis treatment on it.

Methods: In this cohort study, we continuously recruited 632 surgical patients who were treated for acute type A aortic dissection in our hospital between January 2015 and May 2017. The preoperative level of serum creatinine was measured. All patients were followed up after surgery for 30 days to determine early mortality.

Results: The 30-day mortality after surgery increased with elevated levels of preoperative serum creatinine. Median (interquartile range) serum creatinine levels in survivors were 9.61 μmol/dL (7.28-12.62 μmol/dL) versus 13.41 μmol/dL (10.28-20.63 μmol/dL) in death ($p < 0.01$). Adjusted odds ratios for increasing per μmol/dL serum creatinine were 1.09 (95% confidence interval, 1.03-1.15). We also found that the effect of preoperative creatinine on 30-day mortality was diminished by dialysis treatment after surgery.

Conclusion: Preoperative serum creatinine predicts outcome in patients undergoing surgery for Stanford type A aortic dissection, and postoperative dialysis treatment can reduce its hazard.

Keywords: Aortic dissection; Creatinine; Mortality

1. INTRODUCTION

Acute aortic dissection is a rare and lethal cardiovascular disease that has an annual incidence of three to four per hundred thousand. In two-thirds of patients with acute aortic dissection, it is the ascending aorta that is affected, which is classified as Stanford type A.[1] With the advancement of surgical techniques, the intraoperative mortality of acute type A aortic dissection (AAAD) is reduced to around 5%, but compared with surgery for other cardiac conditions, the postoperative early mortality and the incidence of complications is still high.[2] Risk scoring system for cardiac surgery such as European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) has been found unsuitable for prognosis prediction of AAAD.[3] Therefore, many risk models for AAAD have been created, and preoperative creatinine level or renal function is often included as a variable in these models.

Previous studies have addressed the relationship between preoperative renal function and the prognosis of aortic diseases,[4,5] but these studies involved few AAAD patients and not many studies have assessed the effect of postoperative dialysis as a confounding factor. The aim of this study is to research the independent effect of the preoperative level of serum creatinine (SCr) on postoperative mortality risk based on the largest single-center AAAD sample in northern China.

2. METHODS

2.1. Study design

This study was designed as a retrospective cohort study that continuously collected data on AAAD patients who underwent surgery in Anzhen Hospital from January 2015 to May 2017. All patients were diagnosed by computed tomography angiography (CTA) or ultrasound cardiogram (UCG). Preoperative creatinine levels were measured using blood samples obtained within 48 hours before surgery. Demographic data, timing of surgery, cardiopulmonary bypass (CPB) factors, surgical methods, heart function, and continuous renal replacement therapy (CRRT) were obtained as surrogate markers of adverse outcomes. All patients were followed up for 30 days after surgery. All-cause 30-day mortality was defined as the end point. All data related to the study were obtained after approved by the ethics committee of Anzhen Hospital.

2.2. Related definitions

This study included only AAAD patients treated with operation, which means surgery was underwent within 7 days of the onset. Variables of surgical modalities included Bentall, and total arch replacement was combined with a stented elephant trunk (TARSET) implant procedure,[6] and those who did not undergo

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Bentall underwent ascending aortic replacement, Wheat or David's surgery. Selective cerebral perfusion with a flow rate of 5-10 mL/kg·min was performed in all patients undergoing TARSET surgery, and circulatory arrest or low-flow perfusion was performed in the lower half of the body. Preoperative critical state was defined as the presence of any of the following events: ventricular fibrillation, preoperative ventilation, preoperative inotropic support, or preoperative systolic blood pressure below than 90 mmHg. Perioperative estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI formula.[7] Postoperative acute renal failure (ARF) is diagnosed according to the Risk, Injury, Failure, Loss, and End-stage renal failure (RIFLE) criteria,[8] from which the GFR was estimated to have decreased by at least 25% in the 48- to 72-hour period after surgery. Demographic data included age, gender, height, and weight. Medium to large pericardial effusion was defined as the depth of pericardial effusion at any location more than 5 mm under ultrasound evaluation.

2.3. Statistical analysis

All analyses were performed using statistical packages R (The R Foundation; http://www.Rproject.org version 3.1.2). Continuous variables were expressed as mean ± SD or median (quartile range). Categorical variables were expressed in frequency or as a percentage. One-way analysis of variance (ANOVA) test, Kruskal-Wallis H test, and chi-square test (categorical variables) were used to determine any statistical difference between different groups. Multivariate models were used to evaluate the associations between baseline SCr and 30-day mortality. We established unadjusted, mildly adjusted, and fully adjusted models. We performed subgroup analyses with generalized additive model (GAM) and using likelihood ratio test to check whether the relationship is stable in different populations. The relationship between SCr and 30-day mortality was fitted with a smooth curve adjusted for confounding variables. Two-piecewise linear regression model was used to examine the threshold effect of the smoothing plot. Results of the logistic regressions model are presented as the odds ratio (OR) and the 95% confidence interval (CI). Statistical significance was defined as $p < 0.05$.

3. RESULTS

A total of 632 AAAD patients were recruited into the study. Fifteen patients were excluded because of incomplete data or lost in the 30-day follow-up, and 10 patients were excluded for preoperative dialysis. The final cohort of 609 consisted of 160 women and 449 men, aged 48.36 ± 11.04 years old, and the median preoperative SCr level was 100.10 μmol/L (interquartile range, 75.10-133.60). A total of 78 deaths (12.8%) occurred during the follow-up. Postoperative complications in the deaths include multiple organ dysfunction (MODS) (n = 13), respiratory failure (n = 20), sepsis (n = 11), cerebral infarction or hemorrhage (n = 46), cardiovascular adverse events (n = 34), and ARF (n = 43). Creatinine levels between the death and survival groups

Table 1

Characteristics of patients stratified by SCr quartiles

SCr group[a] (μmol/L)	<75.1 (n = 152)	75.1-100.1 (n = 152)	100.1-133.6 (n = 151)	>133.6 (n = 154)	*p*
Baseline characteristics					
Age, y	49.41 (11.22)	47.49 (11.10)	47.80 (10.79)	48.71 (11.07)	0.549
Gender					*<0.001*
Women	81 (53.29%)	33 (21.71%)	28 (18.54%)	18 (11.69%)	
Men	71 (46.71%)	119 (78.29%)	123 (81.46%)	136 (88.31%)	
Height, cm	168.56 (6.94)	172.19 (8.69)	172.36 (7.44)	171.50 (6.71)	*<0.001*
Weight, kg	71.17 (11.18)	76.57 (12.19)	77.19 (12.86)	80.81 (13.41)	*<0.001*
Previous aortic surgery	4 (2.63%)	0 (0.00%)	1 (0.66%)	0 (0.00%)	*0.034*
EF, %	62.12 (5.90)	61.99 (6.07)	61.72 (5.94)	61.18 (6.10)	0.638
Medium to large pericardial effusion	3 (2.65%)	2 (1.65%)	9 (7.63%)	10 (8.33%)	*0.036*
Aortic insufficiency					*0.003*
No	25 (22.12%)	37 (30.83%)	23 (19.49%)	26 (21.67%)	
Mild	43 (38.05%)	35 (29.17%)	49 (41.53%)	61 (50.83%)	
Moderate	17 (15.04%)	21 (17.50%)	30 (25.42%)	21 (17.50%)	
Severe	28 (24.78%)	27 (22.50%)	16 (13.56%)	12 (10.00%)	
Preoperative critical state	10 (6.58%)	14 (9.21%)	16 (10.60%)	16 (10.39%)	0.601
Operative characteristics					
CPB time, min	202.95 (45.18)	201.78 (51.30)	210.73 (46.38)	228.38 (62.31)	*<0.001*
Bentall procedure	61 (40.40%)	76 (50.00%)	65 (43.05%)	59 (38.56%)	0.196
TARSET procedure	88 (57.89%)	99 (65.13%)	113 (74.83%)	121 (78.57%)	*<0.001*
Early outcomes					
Postoperative CRRT	10 (6.58%)	11(7.24%)	14 (9.27%)	54 (35.06%)	*<0.001*
ARF	49 (32.24%)	39 (25.66%)	46 (30.46%)	60 (38.96%)	0.093
Sepsis	1 (0.66%)	1 (0.66%)	3 (1.99%)	7 (4.55%)	*0.046*
Cardiovascular adverse events	3 (1.97%)	9 (5.92%)	14 (9.27%)	26 (16.88%)	*<0.001*
Respiratory failure	2 (1.32%)	4 (2.63%)	5 (3.31%)	15 (9.74%)	*0.001*
Nervous system complications	5 (3.29%)	13 (8.55%)	18 (11.92%)	34 (22.08%)	*<0.001*
MODS	1 (0.66%)	2 (1.32%)	1 (0.66%)	9 (5.84%)	*0.003*
Thirty-day mortality	5 (3.29%)	13 (8.55%)	21 (13.91%)	39 (25.32%)	*<0.001*

Continuous variables are presented as mean (SD) while categorical variables are presented as n (%).

The italics were statistically significant ($p < 0.05$).

ARF = acute renal failure; CPB = cardiopulmonary bypass; CRRT = continuous renal replacement therapy; EF =eject fraction; MODS = multiple organ dysfunction; SCr = serum creatinine; TARSET = total arch replacement combined with stented elephant trunk implant procedure.

[a]According to quartile division.

showed significant differences (Supplementary Table 1, http://links.lww.com/JCMA/A47).

Patients were divided into four groups according to SCr baseline quintiles (quartile 1-quartile 4, Q1-Q4). Across all quartiles, there are statistical differences in height, weight, gender, CPB time, surgical methods, degree of aortic regurgitation, medium to large pericardial effusion, aortic surgery history, postoperative CRRT treatment, 30-day mortality, and all kinds of complications. Taller, male AAAD patients who received a TARSET procedure or have mild aortic regurgitation tend to have higher preoperative SCr. Meanwhile, the highest SCr quartile group had a higher risk of 30-day mortality, ARF, sepsis, respiratory failure, cardiovascular adverse events, and MODS. The 30-day mortality rates and ARF incidence rate for Q1, Q2, Q3, and Q4 were 3.29%, 8.55%, 13.91%, and 25.32% and 32.24%, 25.66%, 30.46%, and 38.96%, respectively (Table 1).

Univariate analysis demonstrated that increased SCr, longer CPB time, TARSET procedure, and CRRT were significant predictors for 30-day mortality. Meanwhile, factors such as age, gender, height, weight, pericardial effusion, and preoperative critical state were not related to 30-day postoperative death (Table 2).

The multivariate regression analysis indicated that preoperative SCr was independently associated with 30-day mortality (Table 3). The unadjusted model showed a 11.8% increase in the risk of 30-day mortality for increasing 10 μmol/L SCr (OR = 95%, CI, 1.079-1.159), when adjusted by potential confounders, the risk of 30-day mortality increased by 8.5% for every 10 μmol/L increase of SCr (OR = 95%, CI, 1.027-1.146). In a second set of multivariable analyses, adjusted ORs for higher quartiles of SCr (Q2, Q3, Q4) were compared with the lowest quartile (Q1), which were 2.035 (95% CI, 0.456-9.072), 4.339 (95% CI, 1.029-18.297), and 5.785 (95% CI, 1.352-24.747), respectively. These findings indicate a strong correlation between preoperative SCr and 30-day mortality.

Table 2

Univariable analysis for 30-day mortality

	OR (95% CI)	*p*
SCr, 1 μmol/dL increment	1.12 (1.08-1.16)	*<0.001*
Postoperative CRRT	12.95 (7.56-22.21)	*<0.001*
Postoperative AFR[a]	3.09 (1.90-5.02)	*<0.001*
Baseline characteristics		
Age, 1 y increment	1.02 (1.00-1.04)	0.081
Male	0.96 (0.56-1.65)	0.889
Previous aortic surgery	…	0.983
Height, 1 cm increment	0.98 (0.95-1.02)	0.317
Weight, 1 kg increment	0.99 (0.97-1.01)	0.308
Preoperative critical state	0.97 (0.42-2.22)	0.942
Aortic insufficiency		
No	Ref.	
Mild	1.21 (0.58-2.52)	0.616
Moderate	1.41 (0.61-3.27)	0.421
Severe	1.26 (0.53-3.02)	0.603
Medium to large pericardial effusion	1.88 (0.67-5.24)	0.227
EF < 50%	…	0.986
Operative characteristics		
CPB time, 1 min increment	1.01 (1.01-1.02)	*<0.001*
Bentall procedure	0.67 (0.41-1.10)	0.111
TARSET procedure	5.25 (2.36-11.64)	*<0.001*

The italics were statistically significant ($p < 0.05$).

ARF = acute renal failure; CI = confidence interval; CPB = cardiopulmonary bypass; CRRT = continuous renal replacement therapy; EF = eject fraction; GFR = Glomerular filtration rate; OR = odds ratio; SCr = serum creatinine; TARSET = total arch replacement combined with stented elephant trunk implant procedure.

[a]Postoperative ARF is defined as GFR decreased by at least 25% in the 48- to 72-hour period after surgery.

In subgroup analysis, we found that the effect values of SCr as a predictor of 30-day mortality are significantly different according to the height, aortic insufficiency, Bentall procedure, and CRRT (*p* for interaction = 0.0475, 0.0234, 0.0256, and 0.0007, respectively). There was no significant difference in other confounding subgroups (*p* for interaction > 0.05). In not performing postoperative CRRT subgroup, the adjusted OR for increasing 10 μmol/L SCr is 1.15 (95% CI, 1.09-1.22), while in performing postoperative CRRT subgroup, the adjusted OR is 1.01 (95% CI, 0.97-1.06) (Supplementary Table 2, http://links.lww.com/JCMA/A47). This result shows that postoperative CRRT treatment can reduce the adverse effect of high baseline SCr level on 30-day mortality.

A smooth curve was fitted (Fig. 1) and clearly illustrates that the 30-day mortality risk was increased with the increasing preoperative SCr level. Moreover, the relationship between preoperative SCr and postoperative mortality was nonlinear (log likelihood ratio = 0.016). The knot point of the curve was at SCr = 25.49 μmol/dL. The slope of the curve steep (β = 1.16, 95% CI, 1.07-1.25) on the left side of the knot point and the slope on the right side of knot point are relatively gentle (β = 0.94, 95% CI, 0.83-1.06). After stratification for the variable of whether or not postoperative CRRT was performed, we found that postoperative CRRT treatment significantly reduced the risk of death by 30 days. The stratified fit curve shows an interesting result. When SCr is lower than 260 μmol/L, the survival rate of patients without postoperative dialysis is higher. When SCr is higher than 260 μmol/L, the survival rate of postoperative dialysis patients is higher than that of nondialysis patients (Fig. 2). Neither of the two stratified curves is nonlinear (Supplementary Table 3, http://links.lww.com/JCMA/A47).

4. DISCUSSION

The SCr test is a popular assessment performed to evaluate renal function. Creatinine, which is mainly filtered by glomerular filtration, is the metabolic product of creatine that is produced by muscle (Fig. 3). SCr is not affected by extra-renal factors such as diet and high catabolism and is homeostatically regulated through glomerular filtration.[9] The eGFR is also a commonly used indicator of renal function to evaluate the outcomes of cardiac surgery. However, there are numerous methods by which eGFR can be calculated, which have not been popularized uniformed in clinical practice.[10] Type A aortic dissection (AD) is a severe condition with a high early mortality and requires emergency surgery. Therefore, to facilitate the use of preoperative indicators to quantitatively predict the risk of operative mortality in a wide range of clinical practice, we choose SCr instead of eGFR.

Whether patients with aortic-related disease have differences in renal function compared with normal people is worth exploring. Previous study found that chronic renal insufficiency is prevalent in patients with thoracic and abdominal aortic aneurysm.[11] The elderly are particularly vulnerable to such conditions, probably because the risks of impaired renal function appear to increase with age.[12] However, in our study, no significant differences in age were found between the subgroups of different creatinine levels (*p* = 0.549). This suggests that the effect of type A AD on SCr is acute and exceeds the effect of age differences on baseline SCr levels. Also, the stratified analysis did not reveal any evidence that age influences the effect of preoperative creatinine on postoperative 30-day mortality. It is worth noting that the Bentall surgery and degree of aortic insufficiency affect the relationship between preoperative SCr and mortality in subgroup analysis (*p* for interaction = 0.0256, 0.0234, respectively) (Supplementary Table 2, http://links.lww.com/JCMA/A47). It is well known that surgeons prefer Bentall surgery to reconstruct the aortic root if the dissection

Table 3

Multivariate regression for 30-day mortality

	Unadjusted	Mildly adjusted[a]	Fully adjusted[b]
SCr, 1 μmol/dL increment	1.118 (1.079, 1.159)	1.123 (1.079, 1.169)	1.085 (1.027, 1.146)
SCr group[c], (μmol/L)			
<71.0	Ref	ref	ref
71.0-93.7	2.750 (0.955, 7.914)	2.846 (0.938, 8.636)	2.035 (0.456, 9.072)
93.7-127.5	4.749 (1.741, 12.955)	4.878 (1.688, 14.095)	4.339 (1.029, 18.297)
>127.5	9.970 (3.808, 26.104)	12.269 (4.290, 35.086)	5.785 (1.352, 24.747)
SCr quartile group[d]	2.044 (1.591, 2.625)	2.209 (1.662, 2.938)	1.744 (1.172, 2.595)
p per quartile trend	*<0.001*	*<0.001*	*0.006*

Presented as OR (95% CI).

The italics were statistically significant ($p < 0.05$).

CI = confidence interval; CPB = cardiopulmonary bypass; CRRT =, continuous renal replacement therapy; OR = odds ratio; SCr = serum creatinine; TARSET = total arch replacement combined with stented elephant trunk implant procedure.

[a]Adjusted for age, gender, height, and weight.

[b]Adjusted for age, gender, height, weight, operation in acute phase, circulatory arrest, CPB time, TARSET procedure, previous aortic surgery, aortic insufficiency, and CRRT.

[c]According to quartile division.

[d]SCr quartile group is treated as a continuous variable.

involves the aortic root and causes severe aortic regurgitation. Our results demonstrate that higher preoperative SCr was more harmful in patients whose aortic root was more severely involved by dissection. This interaction between SCr and early mortality was discovered first by our study and its mechanism needs further study.

In terms of surgical methods, more patients who had high preoperative creatinine underwent a TARSET procedure. In fact, the difference between using this surgical procedure or not suggests there is a difference in the extent of dissection. In our center, TARSET procedure is a mature and routine method of total arch replacement. It is generally accepted that patients with a DeBakey type I or complex dissection (aneurysm formation in the aortic arch or distal end thereof (diameter >5.0 cm), complicated with Marfan syndrome) should undergo a total arch replacement in order to prevent recurrence and progression of the AD. In addition, the DeBakey type I dissection is more likely to expand further, which will affect the branches of peritoneal organs such as the mesenteric artery and renal arteries, which leads to malperfusion, causing organ ischemia and SCr elevation.[13] Although visceral hypoperfusion has a very poor prognosis and is more lethal than renal malperfusion, malperfusion of these two adjacent abdominal organs always occurs simultaneously.[14] Therefore, the cause of elevated baseline SCr in dissection patients is different from other aortic diseases and can mostly be attributed to an abnormal hemodynamic state, such as false lumen blood supply, double-lumen blood supply, or false lumen thrombus compression.[15] Therefore, SCr as an indicator of poor organ perfusion can reflect the severity of the disease.

We also found that patients with higher preoperative SCr tend to have a longer CPB time. This perhaps is because patients with higher SCr have a greater proportion of aortic arch or more

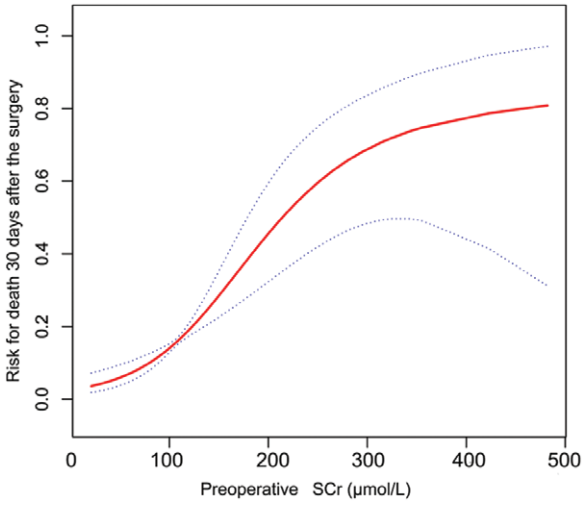

Fig. 1 Relationship between preoperative SCr level and 30-day mortality. Adjusted for age, gender, height, weight, operation in acute phase, circulatory arrest, CPB time, preoperative critical state, Bentall procedure, TARSET procedure, previous aortic surgery, aortic insufficiency, pericardial effusion, EF, and CRRT. The blue line represents the fitted curve, and the red line represents the 95% confidence interval. CPB = cardiopulmonary bypass; CRRT = continuous renal replacement therapy; EF = eject fraction; SCr = serum creatinine; TARSET = total arch replacement combined with stented elephant trunk implant procedure.

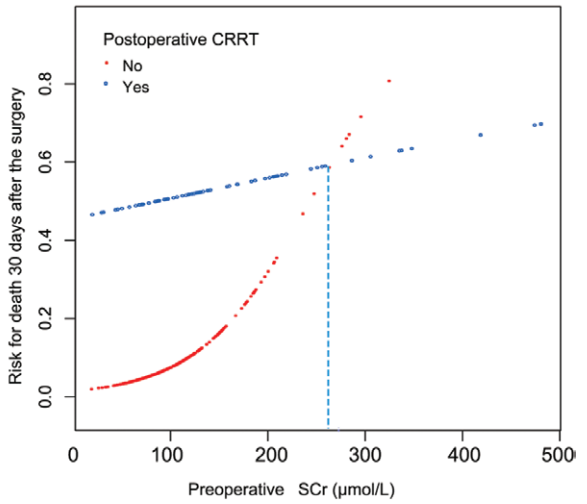

Fig. 2. Relationship between preoperative SCr level and 30-day mortality after stratified by whether postoperative CRRT was performed. A nonlinear relationship between preoperative SCr level and 30-day mortality was observed in not perform postoperative CRRT subgroup after adjusted for age, gender, height, weight, operation in acute phase, circulatory arrest, CPB time, preoperative critical state, Bentall procedure, TARSET procedure, previous aortic surgery, aortic insufficiency, pericardial effusion, and EF. CPB = cardiopulmonary bypass; CRRT = continuous renal replacement therapy; SCr = serum creatinine.

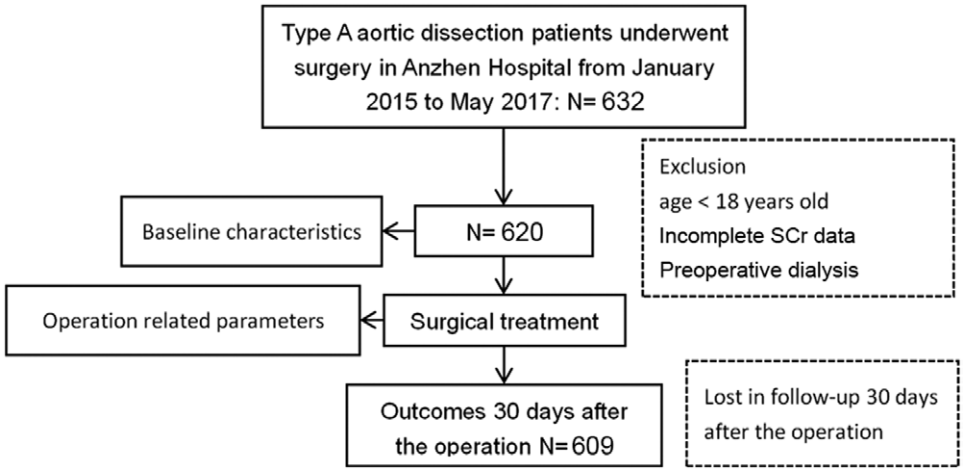

Fig. 3 Flow chart of the study. SCr, serum creatinine.

extensive aorta involvement, requiring more complicated surgery. Evidence from previous literature on whether longer CPB time is more likely to causes postoperative ARF is still contradictory.[16,17] In our study, univariate analysis showed that longer CPB time were risk factors for 30-day mortality, but there was no interaction between CPB parameters and SCr 30-day mortality relationship. This suggests that CPB parameters affect early postoperative prognosis through other mechanisms.

Among postoperative complications, most death patients experienced postoperative ARF (58.97%), followed by nervous system complications (56.41%) and cardiovascular adverse events (43.59%); the proportion of postoperative dialysis was 55.13%. Of the 197 patients who developed postoperative ARF, 108 did not undergo dialysis treatment. Even after taking into account that some patients could not withstand dialysis treatment, we wonder whether the indication of dialysis treatment for AD is too strict in clinical practice.

In our center, the use of postoperative dialysis treatment complies with the following indications: SCr level 3 times higher than the upper limit of the reference value, serum K+ higher than 6.5 mmol/L, and anuria. But in clinical practice after AAAD surgery, the stability of the patient's hemodynamics and the risks associated with dialysis treatment would also be taken into account.

Although in univariate analysis we found that postoperative dialysis was a risk factor for 30-day mortality, but in a stratification analysis, postoperative dialysis treatment reduced the risk of elevated SCr on 30-day mortality (OR = 1.04 versus OR = 1.18). Postoperative continuous dialysis treatment can ameliorate electrolyte imbalances effectively and reduce SCr levels. In addition, preoperative SCr reflects not only renal function but also the severity of disease in patients with AAAD. Therefore, postoperative dialysis cannot completely reverse the risk of preoperative hyper creatinine.

In fact, whether or not and when to perform renal replacement therapy in the early stages of elevated SCr are both important and difficult decision to make. Some studies have shown that early prophylactic dialysis improves prognosis before creatinine levels rise.[18,19] Other studies have shown that prophylactic dialysis should be performed before surgery for cardiac surgery patients with moderate renal insufficiency (SCr exceeding 2-2.5 mg/dL); postoperative renal replacement therapy can reduce overall morbidity and mortality.[20,21] We do not recommend the use of preoperative prophylactic dialysis in patients with AAAD because of the delay of surgery. But our study suggests that applying postoperative dialysis in AAAD patients should be pursued more radical and the indications of dialysis should be assessed in combination with preoperative and postoperative SCr levels.

This study is based on a large AAAD patient sample of single center in China. Whether the results can be applied to other races requires further research. In addition, this study involved many different surgical procedures that would be underwent in AAAD patients and baseline variables such as age and gender of patients varied among groups. To compensate for these differences, we did a stratified analysis and explained the results in different subgroups.

In conclusion, preoperative creatinine is an independent risk factor for early postoperative death in AAAD patients. Thirty-day mortality increased by 8.5% for per 10 μmol/L creatinine increase, and the fourth-quarter creatinine population increased by 4.79 times 30-day mortality compared with the first quartile.

Postoperative CRRT treatment was correlated with a trend toward lower risk of 30-day mortality in patients with preoperative creatinine above 260 μmol/L.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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