Original Article

Serum cystatin C is a potential predictor of short-term mortality and acute kidney injury in acute aortic dissection patients: a retrospective cohort study

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Background: Serum cystatin C concentration is associated with cardiovascular disease. However, the relationship between cystatin C and acute aortic dissection (AAD) remains unclear. In the current study, we aim to evaluate the predictive value of cystatin C in the occurrence of acute kidney injury (AKI) and the prognosis of AAD patients.

Methods: The patients with AAD admitted to our hospital from November 2019 through January 2022 were consecutively included in the retrospective cohort study. A complete blood cell count, serum biochemistry tests, including cystatin C and creatinine, in-hospital mortality and the incidence of AKI were recorded. All the patients were categorized into four groups according to the quartile of their serum cystatin C levels. Multivariate logistic and Cox regression analyses were conducted to determine the independent risk factors for the incidence of AKI and the prognosis of AAD patients, respectively. Kaplan-Meier analyses and log-rank tests were used to evaluate differences in survival. Receiver operating characteristic (ROC) curves were used to assess the predictive value of cystatin C for short-term mortality and the incidence of AKI in AAD patients.

Results: A total of 357 patients were included in this study. The results showed that the higher the concentration of cystatin C, the higher the level of serum creatinine and the higher the incidence of AKI. Mortality was significantly higher in the group with serum cystatin C levels >1.18 mg/L. Type A AAD, white blood cell count >10×10^9/L, platelet count <100×10^9/L, and serum cystatin C concentration >1.18 mg/L [adjusted hazards ratio (HR) =2.405, 95% confidence interval (CI), 1.029–4.063, P=0.041] were independent risk factors for in-hospital mortality. Cystatin C levels >1.18 mg/L remained an independent predictor of AKI in AAD after adjusting for the confounding [odds ratio (OR) 76.489, 95% CI, 25.586–228.660]. The areas under the ROC curves of cystatin C in predicting the mortality and incidence of AKI in AAD patients were 0.655 (95% CI, 0.551–0.760) and 0.807 (95% CI, 0.758–0.856), respectively.

Conclusions: In sum, serum cystatin C concentration is a potential predictor of short-term mortality and the incidence of AKI in AAD patients.

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Keywords: Acute aortic dissection (AAD); cystatin C; mortality; acute kidney injury (AKI); prognosis

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Introduction

Acute aortic dissection (AAD) is a life-threatening aortic syndrome with high mortality (1,2). In a large autopsy series, the prevalence of aortic dissection ranged from 0.2–0.8% (3). Population-based study estimated the incidence of AAD to be between 2.5 and 7.2 cases per 100,000 per year (4). It is reported that the mortality rate of AAD ranged from 10.8–74.5% in the last 30 years (4). Despite the gradual standardization of AAD management, the mortality rate remains high. It has been reported that if untreated with swift open surgical repair, acute type A aortic dissection has a mortality rate as high as 90% (5). Due to its poor prognosis, early rapid assessment of prognosis, as well as organ functional damage, and timely and appropriate treatment interventions are crucial.

Currently, the diagnostic gold standard for AAD still relies on imaging, such as computed tomography CT scan, echocardiography or magnetic resonance angiography (6). AAD is featured with the rapid development of an intimal flap that separates the true lumen from the false lumen (7). The formation of the false lumen causes multi-organ dysfunction and even death. Thus, some indicators for early post-diagnosis assessment need to be identified.

In recent decades, some studies have shown that some biomarkers, such as D-dimer, monocytes/high-density lipoprotein ratio, and a triglyceride/high-density lipoprotein cholesterol ratio, have certain value in the prognosis assessment of AAD patients (8-10). However, we still need to explore some simple and readily available indicators for organ function and the prognosis assessment of AAD patients.

Cystatin C is a potent cysteine protease inhibitor that plays a pleiotropic role in human vascular pathophysiology, particularly in regulating cathepsins S and K (11,12). Cystatin C levels increase earlier than urea and creatinine when renal is injured (13). A previous study showed that cystatin C is strongly associated with cardiovascular disease risk in a dose-dependent manner (14). However, to date, the role of cystatin C in the renal function and prognosis assessment of AAD patients has not been closely examined. In the present study, we aim to evaluate the relationship between serum cystatin C levels and the renal function and prognosis of AAD patients. We present the following article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-937/rc).

Methods

Study design and population

We conducted a retrospective observational study of AAD patients admitted to the Department of Cardiovascular Surgery at The First Affiliated Hospital of Soochow University from November 2019 through January 2022. The diagnostic criteria was based on guidelines proposed by European Society of Cardiology (ESC) 2014 on the treatment and diagnosis of aortic diseases (15). The Stanford classification system was used to categorize AAD type (16). Only patients admitted to hospital within 14 days of AAD onset were included in our study. Patients with intramural hematoma, chronic kidney disease, and missing cystatin C data were excluded from the study. The flow chart of patient inclusion is shown in *Figure 1*.

This study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (IRB No. 2022–212). As a retrospective study, the requirement of informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection

Data on patients' demographic information, chronic comorbidities (including hypertension, diabetes, and hyperlipemia), clinic symptoms, Stanford classification type, previous treatments, laboratory tests, complications, the time from symptom onset to admission, and patients' survival at 60 days were collected. All the data were obtained from the electronic medical records system using data collection forms.

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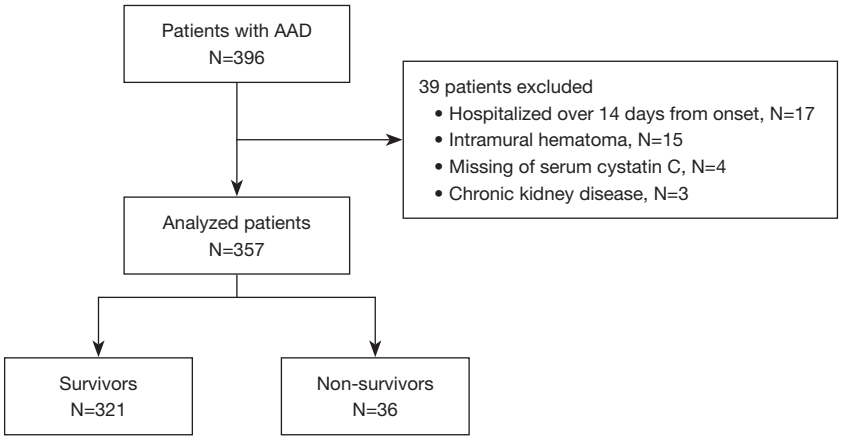

Figure 1 Flow chart of patient inclusion. AAD, acute aortic dissection.

The definition of hypertension was systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DPB) ≥90 mmHg. Accelerated hypertension was defined as SBP ≥180 mmHg and/or DPB ≥110 mmHg (17). Shock was defined as SBP <90 mmHg. Patients were diagnosed with diabetes if they had a fasting plasma glucose level >7.0 mmol/L, a random blood glucose level >11.1 mmol/L, or used any hypoglycemic drugs. Patients were diagnosed with heart failure if they had an ejection fraction <50% according to echocardiography. Patients were diagnosed with liver injury if they had elevated bilirubin and aminotransferase serum levels. Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes (KIDGO) clinical practice guidelines (18). Patients who met the criteria for AKI during hospitalization were diagnosed. All the data were collected from electronic medical record system and cross-checked independently by 3 physicians. Missing data were excluded from the analysis.

Laboratory tests

A complete blood cell count, a high-sensitivity C-reactive protein (hs-CRP) test, serum biochemistry tests, including tests to determine the level of serum cystatin C, creatinine, and total cholesterol, routine blood coagulation tests, including tests for D-dimer were conducted. All the tests were performed in the Clinical Testing Center at The First Affiliated Hospital of Soochow University.

Statistical analysis

The continuous variables are expressed as the mean ± standard deviation of the mean (normal distribution) or median with interquartile range (Q1, Q3) (skewed distribution), while the categorical variables are expressed as frequencies or percentages. Kruskal-Wallis H (skewed distribution) and One-Way ANOVA analysis of variance tests (normal distribution) or χ^2 tests (categorical variables) were performed to compare the different groups.

Univariate and multivariate Cox proportional-hazards regression analyses were conducted to identify the independent risk factors for mortality, and the adjusted hazard ratios (HRs) of mortality are presented in a forest plot. Given the total number of deaths in our study and to avoid overfitting in the model, all variables with P<0.1 in univariate analysis except for creatinine were chosen for the multivariate analysis based on previous findings and the clinical constraints. Kaplan-Meier analyses were conducted to compare the survival rates among the patients with different levels of serum cystatin C using the log-rank test.

The association between cystatin C and AKI was evaluated in different multivariate logistic regression models. In Model I, covariates including sex, age, and BMI were incorporated for adjustment. In Model II, the covariates in Model I and comorbidities were adjusted. In Model III, the covariates in Model II and other covariates (white blood cell counts, platelet counts, hs-CRP, total bilirubin and D-dimer) were adjusted. Area under the receiver operating characteristic curves (AUROCs) were conducted to evaluate the predictive value of cystatin C in terms of the mortality of and the incidence of AKI in AAD patients.

A 2-sided α value of <0.05 was considered statistically significant. All statistics were analyzed using SPSS statistical

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Table 1 Baseline characteristics of patients according to the quartile distribution of serum cystatin C concentration

Characteristics	Cystatin C, mg/L				P
	Q1 (n=91)	Q2 (n=87)	Q3 (n=91)	Q4 (n=88)	
Age, years	50.09±12.64	53.01±13.75	55.43±13.84	53.10±13.56	0.068
Male, n (%)	64 (70.3%)	74 (85.1%)	87 (95.6%)	78 (88.6%)	<0.001
BMI, kg/m^2	24.50 (21.48, 26.57)	26.06 (23.66, 29.06)	25.65 (23.51, 28.73)	25.868 (23.55, 29.06)	0.001
AAD type A, n (%)	53 (58.2%)	46 (52.9%)	47 (51.6%)	54 (61.4%)	0.521
Hypertension, n (%)	48 (52.7%)	58 (66.7%)	73 (80.2%)	71 (80.7%)	<0.001
DM, n (%)	4 (4.4%)	5 (5.7%)	4 (4.4%)	3 (3.4%)	0.904
Hyperlipemia, n (%)	22 (24.2%)	17 (19.5%)	17 (18.7%)	21 (23.9%)	0.729
Smoker, n (%)	20 (22%)	16 (18.6%)	29 (31.9%)	27 (30.7%)	0.119
Heart rate, bpm	77 (73, 89)	80 (70, 92)	80 (72, 92)	80 (72, 94)	0.766
SBP, mmHg	140 (126, 153)	140 (127, 157)	147 (126, 162)	145 (120, 165)	0.546
DBP, mmHg	75 (65, 87)	75 (61, 88)	76 (63, 93)	76 (64, 88)	0.854
WBC, ×10^9/L	10.93 (8.42, 14.01)	11.51 (8.46, 13.92)	11.22 (8.90, 13.63)	12.50 (9.93, 14.86)	0.099
PLT, ×10^9/L	162.00 (137.00, 204.00)	169.50 (132.25, 217.50)	172.00 (128.00, 210.00)	159.50 (127.25, 203.75)	0.835
TBIL, μmol/L	16.40 (12.90, 22.10)	17.75 (12.13, 27.98)	18.20 (13.20, 25.40)	17.55 (11.90, 23.175)	0.608
TCHOL, mmol/L	4.27 (3.70, 4.87)	4.34 (3.47, 4.99)	4.03 (3.59, 4.62)	3.79 (3.21, 4.58)	0.013
sCr, μmol/L	59.00 (50.40, 68.10)	72.20 (63.80, 79.48)	88.40 (74.90, 101.00)	131.05 (105.15, 186.52)	<0.001
hs-CRP, mg/L	7.14 (2.45, 27.07)	11.20 (2.70, 37.76)	7.83 (3.69, 25.71)	8.59 (2.71, 42.55)	0.557
D-Dimer, μg/mL	4.07 (1.61, 12.16)	5.43 (1.81, 16.76)	4.76 (1.93, 11.83)	9.88 (2.51, 20.00)	0.016
IVST, mm	10.00 (10.00, 11.00)	11.00 (10.00, 12.00)	11.00 (10.00, 13.00)	12.00 (10.00, 13.00)	<0.001
AKI, n (%)	8 (8.8%)	21 (24.1%)	25 (27.5%)	70 (79.5%)	<0.001
Death, n (%)	6 (6.6%)	6 (6.9%)	6 (6.6%)	18 (20.5%)	0.003

The data are shown as mean ± standard or median (Q1, Q3). Q1: <0.81 mg/L; Q2: 0.81–0.98 mg/L; Q3: 0.98–1.18 mg/L; Q4: >1.18 mg/L. BMI, body mass index; AAD, acute aortic dissection; DM, diabetes mellitus; SBP, systolic pressure; DBP, diastolic pressure; WBC, white blood cell count; PLT, platelet counts; TBIL, total bilirubin; TCHOL, total cholesterol; sCr, serum creatinine; CRP, C-reactive protein; IVST, interventricular septum thickness; AKI, acute kidney injury.

software program package (SPSS version 26.0 for Windows, IBM), and graphs were collated and created with GraphPad Prism 9.0 software (GraphPad Software).

Results

Study participants and baseline characteristics

A total of 396 patients were diagnosed with AAD and hospitalized in the Department of Cardiovascular Surgery at The First Affiliated Hospital of Soochow University from November 2019 to January 2022. Among them, 17 patients were admitted to hospital >14 days from onset, 15 patients were diagnosed with intramural hematoma, 4 patients had missing serum cystatin C data, and 3 patients with CKD were excluded. Ultimately, 357 patients met the inclusion criteria for the study. The flow chart of patients selection is shown in *Figure 1*.

All the participants were categorized into four groups according to quartiles of serum cystatin C concentration (Q1 <0.81 mg/L; Q2 =0.81–0.98 mg/L; Q3 =0.98–1.18 mg/L; and Q4 >1.18 mg/L). Base line characteristics are presented in *Table 1*. Notably, the proportion of males and the frequency of hypertension were higher in the high serum cystatin C concentration group (P<0.001). The higher the

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concentration of cystatin C, the higher the level of serum creatinine and the higher the incidence of AKI (P<0.001). Mortality was significantly higher in the Q4 group (P=0.003).

The relationship between cystatin C and in-hospital mortality

In the univariate Cox regression analysis for in-hospital mortality, patients in the Q4 group had an increased risk of death [HR =3.184, 95% confidence interval (CI), 1.656–6.121, P=0.001]. Subsequently, in the multivariate Cox regression analysis, type A AAD, a white blood cell (WBC) count >10×10^9/L, a platelet (PLT) count <100×10^9/L, and a serum cystatin C concentration level >1.18 mg/L (adjusted HR =2.405, 95% CI, 1.029–4.063, P=0.041) were independent risk factors for in-hospital mortality (see *Table 2*). The adjusted HRs of each independent risk factor for in-hospital mortality are presented in a forest plot (see *Figure 2*). All the patients were categorized into two groups (Q1–3 and Q4) according to the lower quartile, and the Kaplan-Meier analysis indicated that the Q4 group had a significantly higher cumulative death rate than the Q1–3 group (log-rank test, χ^2=13.62, P<0.001; see *Figure 3*). A ROC curve was used to further investigate the predictive power of serum cystatin C in evaluating in-hospital mortality in AAD patients, and the area under the curve (AUC) was 0.655 (95% CI, 0.551–0.760), which shows that cystatin C can act as a prognostic predictor for AAD patients (see *Figure 4*).

The association between cystatin C and AKI in AAD patients

Serum cystatin C concentration was significantly higher in AAD patients with AKI than AAD patients without AKI (1.245, IQR 0.985–1.777 *vs.* 0.880, IQR 0.770–1.045; P<0.001; see *Figure 5*). Subsequently, we established 3 logistic regression models to examine the independent effects of cystatin C on the incidence of AKI after adjusting for confounding factors (see *Table 3*). In the fully adjusted model, the results indicated that serum cystatin C remains an important and independent predictor of AKI. Further, the higher the concentration of serum cystatin C, the higher the incidence of AKI (P for trend <0.001; see *Table 3*). A ROC curve was used to evaluate the predictive power of cystatin C in determining the incidence of AKI, and the AUC was 0.807 (95% CI, 0.758–0.856; see *Figure 6*). The results indicated that cystatin C is an appropriate predictor of AKI in AAD patients.

Discussion

As is well known, the mortality of AAD patients is high. Further, AAD is often complicated by multi-organ dysfunction, of which AKI is one of the most common organ injuries. As some researches showed that the incidence of AKI following surgery in patients with type A AAD varies from 20% to 67% (19-21). The development of AKI affects the quality of life and prognosis of AAD patients, even those that have partially or completely recovered from the disease (20). Some studies have shown that the occurrence of AKI postoperatively results in prolonged intensive care unit stay and total hospital stay, and the 28-day mortality of patients increases to 53.84% and is as high as 67.5% in those requiring CRRT (21,22). Thus, the early detection of AKI is crucial to the prognosis of AAD patients.

Cystatin C is a non-glycosylated protein produced by nucleated cells at a constant rate. It has been reported that it is a better biomarker than serum creatinine for renal dysfunction (23). Cystatin C is considered an early marker for the diagnosis of AKI, and can predict AKI 1–2 days earlier than serum creatinine (24). In the current study, we also found that the levels of serum cystatin C were associated with AKI in AAD patients. Further, the higher the level of cystatin C, the higher the incidence of AKI. Cystatin C remained an independent risk factor for AKI in AAD patients after adjusting for numerous covariates. In our study, we were surprised to find that when serum cystatin C acting as a predictor of AKI in AAD patients, the AUC was 0.807, which indicates that cystatin C is an appropriate predictor of AKI in AAD patients.

In the present study, cystatin C was also found to be associated with the prognosis of AAD patients. The results of the multivariate Cox regression analysis indicated that cystatin C was an independent risk factor of in-hospital mortality and that a serum concentration >1.18 mg/L was associated with higher mortality. Further, the short-term mortality of AAD patients is well predicted by cystatin C. A previous research indicated that cystatin C is associated with inflammation (25). Recently, it was reported that serum cystatin C concentration is well correlated with hs-CRP levels (26). However, inflammation and oxidative stress were found to play key roles in the pathogenesis and progression of AAD (27,28). This may explain why cystatin C is a good prognostic predictive factor for AAD patients.

We identified a novel predictor of AKI and short-term mortality in AAD patients. However, our research had some limitations. First, it was a single-center retrospective study

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Table 2 Univariate and multivariate Cox regression analysis of short-term mortality in AAD patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, years	0.999 (0.976–1.023)	0.927	–	–
Male	0.773 (0.340–1.757)	0.539	–	–
BMI, kg/m^2	1.021 (0.947–1.100)	0.588	–	–
AAD				
Type B	1 (Ref)	–	1 (Ref)	–
Type A	9.174 (2.818–29.870)	<0.001	10.631 (2.521–44.829)	0.001
Hypertension	1.212 (0.589–2.496)	0.602	–	–
DM	1.238 (0.298–5.145)	0.769	–	–
Hyperlipemia	0.934 (0.428–1.279)	0.865	–	–
Smoke	0.535 (0.224–1.270)	0.159	–	–
Heart rate per 10 bpm	1.136 (0.931–1.387)	0.210	–	–
SBP, mmHg				
<90	2.549 (0.759–8.565)	0.130	–	–
≥90 to ≤140	1 (Ref)	–	–	–
>140	0.567 (0.288–1.115)	0.100	–	–
WBC, ×10^9/L				
<10	1 (Ref)	–	1 (Ref)	–
≥10	3.630 (1.409–9.348)	0.008	4.138 (1.508–11.355)	0.006
PLT, ×10^9/L				
≥100	1 (Ref)	–	1 (Ref)	–
<100	2.608 (1.139–5.971)	0.023	2.909 (1.160–7.297)	0.023
TBIL, μmol/L				
≤23	1 (Ref)	–	–	–
>23	0.893 (0.407–1.960)	0.779	–	–
TCHOL, mmol/L				
≤5.2	1 (Ref)	–	–	–
>5.2	1.344 (0.520–3.475)	0.542	–	–
sCr per 10 μmol/L	1.078 (1.039–1.119)	<0.001	–	–
CRP, mg/L	0.998 (0.990–1.006)	0.639	–	–
D-Dimer				
<20	1 (Ref)	–	1 (Ref)	–
≥20	2.815 (1.441–5.501)	0.002	1.457 (0.713–2.978)	0.302

Table 2 (*continued*)

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Table 2 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
IVST, μg/mL				
≤10	1 (Ref)	–	–	–
>10	1.326 (0.675–2.604)	0.413	–	–
Cystatin C, mg/L				
Q1–Q3	1 (Ref)	–	1 (Ref)	–
Q4	3.184 (1.656–6.121)	0.001	2.405 (1.029–4.063)	0.041

Q1: <0.81 mg/L; Q2: 0.81–0.98 mg/L; Q3: 0.98–1.18 mg/L; Q4: >1.18 mg/L. AAD, acute aortic dissection; HR, hazards ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; SBP, systolic pressure; WBC, white blood cell counts; PLT, platelet counts; TBIL, total bilirubin; TCHOL, total cholesterol; sCr, serum creatinine; CRP, C-reactive protein; IVST, interventricular septum thickness.

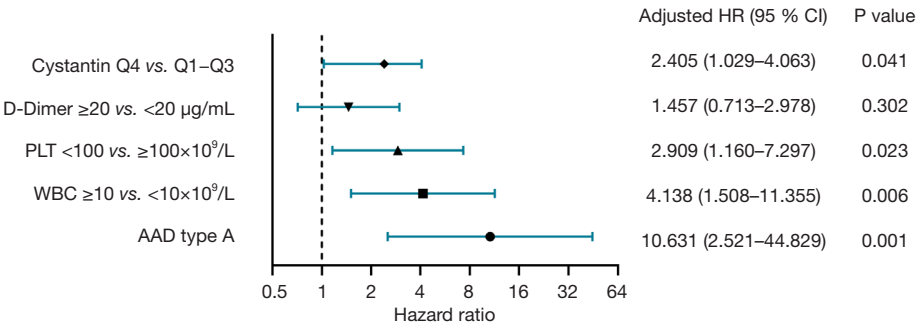

Figure 2 Forest plot of multivariate Cox regression analysis. Q1: <0.81 mg/L; Q2: 0.81–0.98 mg/L; Q3: 0.98–1.18 mg/L; Q4: >1.18 mg/L. PLT, platelet counts; WBC, white blood cell count; AAD, acute aortic dissection; HR, hazards ratio; CI, confidence interval.

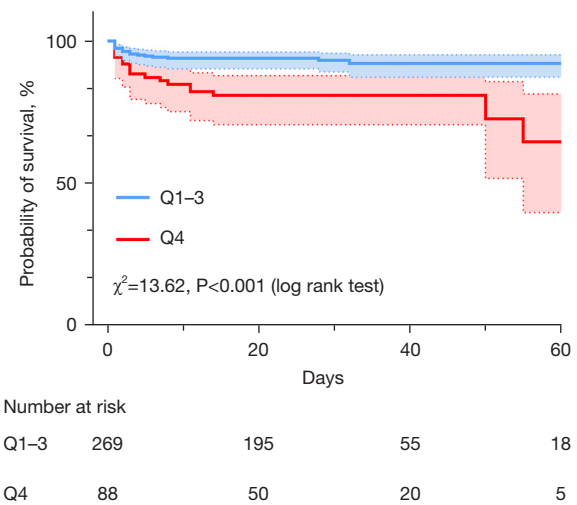

Figure 3 Kaplan-Meier analysis of survival according to cystatin C (lower quartile) in AAD patients. Q1–3, patients with cystatin C concentration ≤1.18 mg/L; Q4, patients with cystatin C concentration >1.18 mg/L. AAD, acute aortic dissection.

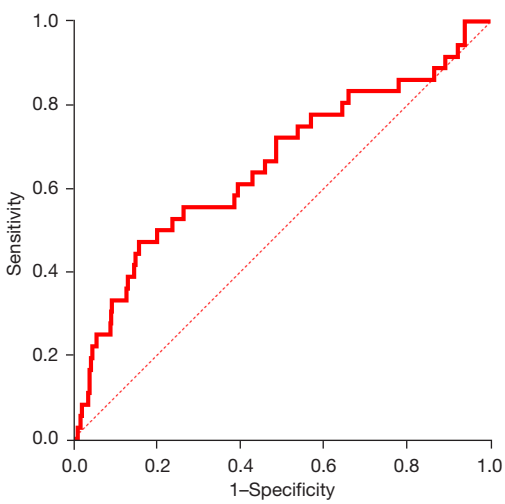

Figure 4 ROC curve for predictive value of cystatin C for short-term mortality in AAD patients. AUC =0.655 (95% CI, 0.551–0.760). ROC, receiver operating characteristic; AAD, acute aortic dissection; AUC, area under the curve; CI, confidence interval.

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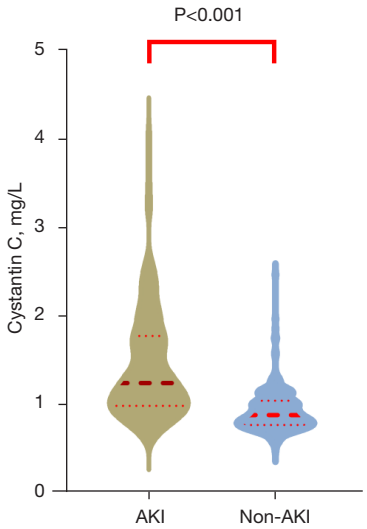

Figure 5 Comparison of serum cystatin C concentration levels between AKI and non-AKI patients. AKI, acute kidney injury.

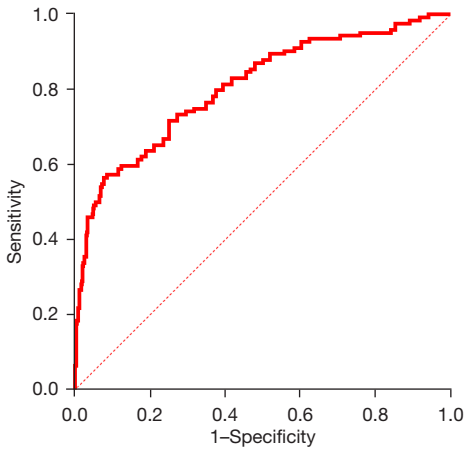

Figure 6 ROC curve for predictive value of cystatin C for the incidence of AKI in AAD patients. AUC =0.807 (95% CI, 0.758–0.856). ROC, receiver operating characteristic; AKI, acute kidney injury; AAD, acute aortic dissection; AUC, area under the curve; CI, confidence interval.

Table 3 Correlation between cystatin C and the incidence of AKI in AAD patients

Models	Cystatin C, mg/L				P for trend
	Q1	Q2	Q3	Q4	
AKI, n (%)	8 (8.8%)	21 (24.1%)	25 (27.5%)	70 (79.5%)	–
Unadjusted OR (95% CI)	1	3.301 (1.375–7.928)	3.930 (1.664–9.280)	40.347 (16.544–98.397)	<0.001
Adjusted OR (95% CI)					
Model I	1	3.865 (1.518–9.842)	4.882 (1.889–12.618)	54.694 (20.499–145.933)	<0.001
Model II	1	4.276 (1.646–11.108)	5.408 (2.055–14.229)	60.359 (21.992–165.661)	<0.001
Model III	1	3.707 (1.371–10.021)	5.351 (1.968–14.522)	76.489 (25.586–228.660)	<0.001

Model I: adjusted for sex, age and BMI; Model II: adjusted for sex, age, BMI, AAD type, hypertension, DM, hyperlipemia and smoke; Model III: adjusted for sex, age, BMI, AAD type, hypertension, DM, hyperlipemia, smoke, WBC, PLT, CRP, TBIL and D-Dimer. Q1: <0.81 mg/L; Q2: 0.81–0.98 mg/L; Q3: 0.98–1.18 mg/L; Q4: >1.18 mg/L. AKI, acute kidney injury; AAD, acute aortic dissection; OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; WBC, white blood cell counts; PLT, platelet counts; CRP, C-reactive protein; TBIL, total bilirubin.

with a small number of patients. Further, as all the patients included in the study originated from southeast China, the conclusions may not be appropriate for all AAD patients. Second, we only focused on the short-term prognosis of patients and the incidence of AKI and did not consider their long-term prognosis and renal recovery. Thus, a long-term follow-up study needs to be conducted. Third, as a prognostic marker, we only assessed the relationship between static values at admission and prognosis and did not examine dynamic alterations in cystatin C.

Conclusions

In sum, serum cystatin C concentration is a potential predictor of short-term mortality and the incidence of AKI in AAD patients. As a result, it has good clinical applicability and promotion potential.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-937/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-937/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (IRB No. 2022–212). As a retrospective study, the requirement of informed consent was waived.

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