Higher Cystatin C Level Increase the Risk of Delayed Cerebral Ischemia after Endovascular Treatment of Aneurysmal Subarachnoid Hemorrhage: A Case-Control Study.

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Research Article

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Abstract

Cystatin C (CysC) has been found to be associated with hemorrhagic and ischemic stroke in many studies. However, the association between CysC level and the risk of delayed cerebral ischemia after endovascular treatment of aneurysmal subarachnoid hemorrhage has been reported rarely. Our study was proposed to explore this association. Consecutive patients from June 2015 to February 2021 in this single-center retrospective study were selected. Univariate and multivariate analyses were used to identify potential prognostic risk factors for delayed cerebral ischemia, and the stability of the association was demonstrated by several statistical methods, such as subgroup analysis, interaction testing, generalized linear models, and propensity score matching. A total of 424 patients were included in the analysis. Cystatin C was independently associated with delayed cerebral ischemia. The independent effects of CysC on delayed cerebral ischemia were shown in generalized linear models with a logit link, and the results were relatively stable in crude, partial, and full models with ORs (95% CIs) for delayed cerebral ischemia. Subgroup analysis showed no significant subgroup differences in the effect of CysC on delayed cerebral ischemia. There was also no interaction effect between CysC and other confounders. Patients in the high CysC group had a higher risk of delayed cerebral ischemia than those in the low CysC group before and after propensity score matching. CysC level could be an independent predictor for the risk of delayed cerebral ischemia after endovascular treatment of aneurysmal subarachnoid hemorrhage.

Introduction

Spontaneous subarachnoid hemorrhage (SAH) causes 1-6% of strokes [7]. Approximately 30% of SAH patients experience delayed cerebral ischemia (DCI), which usually occurs between 4 and 10 days after SAH [4, 22]. Patients who suffered from DCI are generally associated with poor functional outcome [17]. Ruptured intracranial aneurysms cause nearly 85% of SAH [25], and endovascular treatment has gradually become the preferred option for ruptured intracranial aneurysms whenever feasible [28].

Chronic kidney disease has been gradually recognized as an independent risk factor for the occurrence of cerebrovascular disease [11]. Cystatin C (CysC), as a low molecular weight inhibitor of cysteine proteases, is produced and released constantly from all nucleated cells. Compared with serum creatinine level or glomerular filtration rate, CysC is considered to be a more sensitive parameter for assessing renal function [11, 13].

CysC has been found to be associated with hemorrhagic and ischemic stroke in many studies. Research has focused on the difference of subtypes of cerebral infarction, the volume of cerebral hemorrhage, and the extent and the prognosis of cerebral infarction [3, 19, 27, 30]. Recently, a prospective and multicenter nested case-control study suggests that patients in the poor functional outcome group (mRS 3-5) present higher CysC level on admission than those in the good functional outcome group (mRS 0-2) at 90 days of follow-up after stroke onset [1]. However, the association between CysC level and risk of DCI after endovascular treatment of aneurysmal subarachnoid hemorrhage (aSAH) has been reported rarely as we

know. The purpose of this study was to explore the association between the first CysC level within 48 h after admission and the risk of DCI in patients with aSAH following endovascular treatment.

Materials And Methods

Patients

After approval from the institutional review board, informed consent was waived in this retrospective study. Consecutive patients from June 2015 to February 2021 in the First Affiliated Hospital of Shantou University Medical College were selected. The inclusion criteria for this retrospective study were as follows: (1) aSAH with available brain non-contrast computed tomography taken at admission, and confirmation of ruptured aneurysm by computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography; (2) age ≧ 18 years; (3) length of hospitalization ≧ 3 days; (4) patients had received endovascular coiling or surgical clipping during hospitalization.

Exclusion criteria were as follows: (1) history of cranial surgery; (2) history of cerebral infarction or intracerebral hemorrhage; (3) patients underwent surgical clipping treatment during hospitalization; (4) non-aneurysm-related therapeutic surgery was performed during hospitalization; (5) the time from onset to endovascular coiling exceeded 3 days; (6) patients with missing data.

Definition Of Dci

DCI was diagnosed as clinical deterioration, a new infarction on cerebral CT or MRI scanning, or both. Clinical deterioration caused by DCI was defined as: a) new focal neurological impairment (such as hemiparesis, hemianopia, aphasia, apraxia, or neglect, and b) a decrease of at least 2 points on the Glasgow Coma Scale (GCS). Clinical deterioration had to last for at least 1 hour, was not apparent immediately after accepting aneurysm occlusion, nor be attributed to other causes based on comprehensive assessment (such as relevant laboratory results, CT or MRI scanning of the brain, and clinical assessment). A new infarction on brain CT or MRI was not present on admission or between 24 and 48 hours after accepting aneurysm occlusion. Both clinical deterioration and new infarction were assessed by the same two authors independently during hospitalization [8, 26].

Data Collection

Data were recorded as follows: age, gender, and admission status at admission (World Federation of Neurosurgical Societies (WFNS) grade, Hunt-Hess grade). Baseline biological results should be obtained within the first 48 h after admission (serum CysC, albumin, white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR)). Radiological examinations should be the first within 48 h after admission (modified Fisher (mFisher) grade, intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), hydrocephalus, aneurysm size, aneurysm location). For statistical analysis of subgroups, multi-

categorical variables and continuity variables were grouped based on previous literature and clinical significance as follows: WFNS grade (grade I-III and grade IV-V), mFisher grade (grade I-II and grade III-IV), Hunt & Hess grade (grade I-III and grade IV-V), aneurysm location (group 1: posterior circulation (PC), group 2: anterior communicating artery and anterior cerebral artery (ACA+ACoA), group 3: internal carotid artery (ICA), group 4: middle cerebral artery (MCA)), age (≦ 55y, >55y), Alb (≦ 40g/L, > 40g/L), aneurysm size (≦ 5mm, > 5mm), length of hospitalization (≦ 28d, > 28d).

Statistical Analysis

Categorical variables were represented with counts (proportions) in each subgroup. After being assessed for normality in continuous variables, normally distributed variables were presented with mean ± SD. Nonparametric variables were presented with median (IQR). Statistical analysis of baseline characteristics and clinical data were compared between the non-DCI group and DCI group. The Student t-test or paired t-test was used to compare continuous normally distributed variables, and the Mann-Whitney U-test or Wilcoxon rank-sum test was used to compare nonparametric variables. The χ^2 test, McNemar's test or McNemar-Bowker's test was used to compare dichotomous and multi-categorical variables.

The multivariate logistic regression model included all variables with statistical significance (p values < 0.05) in the univariate analysis and clinically important variables. Adjusted smooth curve fitting and generalized linear models with a logit link were used to show the independent effects of CysC on DCI with crude, partial, and full models. The forest plot presented the subgroup analysis in DCI and the interaction test between CysC and other confounders.

The receiver operating characteristic (ROC) analysis was applied to investigate the effects of CysC on DCI and identify the best cutoff value for DCI. Subsequently, all included patients were dichotomized by the identified cutoff CysC value. Propensity score matching was undertaken to minimize unbalanced confounding between the high CysC and low CysC groups. Groups were matched in a 1:1 ratio and with a 0.03 caliper. Subjects were matched as follows: age, gender, WFNS grade, Hunt-Hess grade, WBC, NLR, albumin, mFisher grade, ICH, IVH, hydrocephalus, aneurysm size, aneurysm location, and length of hospitalization.

Most statistical analyses were performed using EmpowerStats software 2.0 (http://www.empowerstats.com/cn/) and R-project (version 3.4.3). Propensity score matching and normality testing were calculated by SPSS 22.0 (SPSS Institute). P-values <0.05 were considered statistically significant.

Results

In total, 671 patients satisfied the inclusion criteria. After screening strictly based on the exclusion criteria, 247 patients were excluded (history of cranial surgery, n = 17; history of cerebral infarction or intracerebral

hemorrhage, n = 10; surgical clipping, n = 36; Non-aneurysm related therapeutic surgery, n = 4; time from onset to endovascular coiling > 3 days, n =139; missing data, n = 41). Finally, 424 patients fulfilled the inclusion criteria and were not excluded by the exclusion criteria. Among included patients, 138 (32.55%) patients developed DCI. Baseline clinical characteristics of included patients are shown in Table 1. Comparison of baseline clinical characteristics between the non-DCI group and DCI group revealed no differences in gender (p = 0.726), albumin (p = 0.330), mFisher grade Ⅲ and Ⅳ (p = 0.058), IVH (p = 0.165), hydrocephalus (p = 0.263), aneurysm size (p = 0.740), and aneurysm location (p = 0.051). The following variables, however, showed significant differences: age (p = 0.022), WFNS grade Ⅲ and Ⅳ (p = 0.003), Hunt-Hess grade Ⅲ and Ⅳ (p = 0.004), WBC count(p = 0.028), CysC (p = 0.007), ICH (p = 0.008), length of hospitalization (p < 0.001).

Table 1
Baseline clinical characteristics.

Variable	Non-DCI (n=286)	DCI (n=138)	P-value
Age, median (IQR), y	58.00 (49.25-65.00)	61.00 (52.00-67.00)	0.022
Gender, male, No. (%)	117 (40.91%)	54 (39.13%)	0.726
WFNS grade Ⅳ and Ⅴ, No. (%)	85 (29.72%)	61 (44.20%)	0.003
Hunt - Hess grade Ⅳ and Ⅴ, No. (%)	144 (50.35%)	90 (65.22%)	0.004
WBC, median (IQR), 109/l	13.45 (10.54-17.01)	14.49 (11.49-17.98)	0.028
NLR, median (IQR)	9.30 (5.06-13.96)	9.13 (5.37-15.96)	0.668
CysC, median (IQR), mg/l	0.70 (0.58-0.87)	0.74 (0.64-0.97)	0.007
Albumin, mean ± SD, g/l	38.68 ± 4.10	38.23 ± 4.96	0.330
mFisher grade Ⅲ and Ⅳ, No. (%)	215 (75.17%)	115 (83.33%)	0.058
ICH, No. (%)	49 (17.13%)	39 (28.26%)	0.008
IVH, No. (%)	175 (61.19%)	94 (68.12%)	0.165
Hydrocephalus, No. (%)	81 (28.32%)	32 (23.19%)	0.263
Aneurysm size, median (IQR), mm	5.00 (3.60-6.50)	4.80 (3.60-6.88)	0.740
Aneurysm location, No. (%)			0.051
PCA	20 (6.99%)	5 (3.62%)	
ACA+ACoA	117 (40.91%)	46 (33.33%)	
ICA	79 (27.62%)	37 (26.81%)	
MCA	70 (24.48%)	50 (36.23%)	
length of hospitalization, median (IQR), d	20.00 (14.00-29.00)	28.50 (16.00-41.00)	<0.001

Notes: Continuous variables are shown as mean ± SD or median (IQR), categorical variables are shown as No. (%).

Abbreviations: DCI, delayed cerebral ischemia; IQR: interquartile range; SD, standard deviation; WFNS, World Federation of Neurosurgical Societies; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; CysC, cystatin C; mFisher scale, modified Fisher scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; PC, posterior circulation; ACoA, anterior communicating artery; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.

The multivariate logistic regression model included all variables with statistical significance (p values < 0.05) in the univariate analysis and clinically important variables, such as mFishers grade and aneurysm location. The results are presented in Table 2. CysC was independently associated with the occurrence of DCI (OR 2.3, 95% CI 1.06-5.02, p = 0.036).

Table 2
Multivariate logistic regression analysis of delayed cerebral ischemia prediction.

Variable	Odds Ratio	95% CI	P-value
Age	1.01	(0.99, 1.03)	0.464
WFNS grade and	1.2	(0.70, 2.08)	0.507
WBC	1.03	(0.98, 1.07)	0.285
Hunt - Hess grade and	1.32	(0.79, 2.20)	0.297
CysC	2.3	(1.06, 5.02)	0.036
mFisher grade and	1.46	(0.84, 2.55)	0.177
ICH	1.3	(0.75, 2.25)	0.351
Aneurysm location			
PCA	1		
ACA+ACoA	1.32	(0.46, 3.82)	0.609
ICA	2.05	(0.69, 6.05)	0.195
MCA	2.72	(0.93, 7.98)	0.068
length of hospitalization	1.01	(1.00, 1.01)	0.221

This study focuses on demonstrating the association between CysC and the occurrence of DCI. As is shown in Figure 1, the linear correlation between CysC and the probability of DCI is presented using adjusted smooth curve fitting (p = 0.033). The independent effects of CysC and DCI were shown in generalized linear models with a logit link, and the results were relatively stable in crude, partial adjustment models and full models with ORs (95% CIs) for DCI of 2.83 (1.40, 5.72), 2.56 (1.21, 5.42), and 2.42 (1.07, 5.44), respectively (Table 3). Given the small range of values and clinical applicability, the CysC.1 (CysC increase per 0.1 change) and CysC Z score (CysC increase per SD change) were used to represent the OR between CysC and DCI. After being adjusted by full models, the CysC.1 and CysC Z scores presented both significant differences with ORs (95% CIs) for DCI of 1.09 (1.01, 1.18) and 1.29 (1.02, 1.63), respectively.

Table 3
Association between CysC level and the occurrence risk of DCI.

Variable	Odds Ratio (95% CI) P-value		
	Non-adjusted	Adjust I	Adjust II
CysC	2.83 (1.40, 5.72) 0.004	2.56 (1.21, 5.42) 0.014	2.42 (1.07, 5.44) 0.033
CysC Z score*	1.35 (1.10, 1.66) 0.004	1.31 (1.06, 1.63) 0.014	1.29 (1.02, 1.63) 0.033
CysC1†	1.11 (1.03, 1.19) 0.004	1.10 (1.02, 1.18) 0.014	1.09 (1.01, 1.18) 0.033
Non-adjusted model: None;			
Adjusted model I: age, gender;			
Adjusted model II: age, gender, WFNS grade, Hunt & Hess grade, WBC count, NLR, albumin, mFisher grade, ICH, IVH, hydrocephalus, aneurysm size, aneurysm location, length of hospitalization.			
*: CysC increase per SD change.			
†: CysC increase per 0.1 change.			

The results were shown as a forest plot to better describe the subgroup differences and the interactions between CysC and other confounders on DCI (Figure 2). However, subgroup analysis indicated that there were no significant subgroup differences in DCI. There were also no interaction effects between CysC and other confounders. After ROC analysis, a CysC level of 0.595 mg/l was identified as the best cutoff threshold to discriminate the occurrence of DCI (AUC (95% CI) 0.584 (0.532-0.639), Specificity = 0.301, Sensitivity = 0.862, Youden's index = 0.163) (Figure 3).

The patients were divided into two groups based on their CysC level at the time of admission: low group(CysC ≦ 0.59 mg/l) and high group(CysC > 0.59 mg/l). Patients in the high CysC group had a higher risk of DCI in the unadjusted analysis (37.30% vs 18.10%, $p < 0.001$). Propensity score matching (PSM) was performed to minimize bias by confounding between patients with CysC level ≦ 0.59 mg/l versus > 0.59 mg/l. After PSM, two relatively balanced cohorts (n = 83 in each group, Table 4) were available to analyze the relationship between CysC and DCI. In the high CysC group, patients also presented a higher risk for DCI than those in the low CysC group (37.35% vs 19.28%, $p = 0.020$).

Table 4
Clinical characteristics of patients who were divided into the high and low level of CysC before and after propensity score matching (PSM).

	Before PSM			After PSM		
	CysC ≦0.59mg/l (n=105)	CysC > 0.59 mg/l (n=319)	P-value	CysC ≦0.59mg/l (n=83)	CysC > 0.59 mg/l (n=83)	P-value
Age, median (IQR)/ mean ± SD, y	51.00 (46.00-60.00)	61.00 (52.00-66.50)	<0.001	54.10 ± 9.22	53.81 ± 11.19	0.832
length of hospitalization, median (IQR), d	19.00 (13.00-28.00)	22.00 (16.00-35.00)	0.005	20.00 (13.00-30.00)	18.00 (12.50-27.50)	0.606
WBC, median (IQR), 10^9/l	13.48 (10.08-17.06)	14.10 (10.86-17.28)	0.379	13.67 (10.47-17.29)	13.18 (10.95-16.69)	0.863
NLR, median (IQR)	7.67 (3.13-13.53)	9.50 (5.73-14.49)	0.063	8.00 (3.50-14.50)	9.00 (6.00-12.00)	0.788
Albumin, mean ± SD, g/l	39.96 ± 4.20	38.06 ± 4.37	<0.001	39.89 ± 4.25	40.02 ± 4.04	0.816
Aneurysm size, median (IQR), mm	4.60 (3.50-6.20)	4.90 (3.60-6.65)	0.558	5.00 (3.60-6.65)	5.00 (4.00-6.35)	0.722
Gender, male, No. (%)	28 (26.67%)	143 (44.83%)	0.001	25 (30.12%)	31 (37.35%)	0.392
WFNS grade Ⅰ and Ⅱ, No. (%)	28 (26.67%)	118 (36.99%)	0.053	25 (30.12%)	26 (31.33%)	0.644
mFisher grade Ⅰ and Ⅱ, No. (%)	68 (64.76%)	262 (82.13%)	<0.001	60 (72.29%)	55 (66.27%)	0.500
ICH, No. (%)	14 (13.33%)	74 (23.20%)	0.031	14 (16.87%)	17 (20.48%)	0.690
Hydrocephalus, No. (%)	26 (24.76%)	87 (27.27%)	0.614	21 (25.30%)	18 (21.69%)	0.690
IVH, No. (%)	67 (63.81%)	202 (63.32%)	0.928	55 (66.27%)	56 (67.47%)	1.000
Hunt - Hess grade Ⅰ and Ⅱ, No. (%)	54 (51.43%)	180 (56.43%)	0.372	45 (54.22%)	45 (54.22%)	1.000
Aneurysm location, No. (%)			0.522			0.815
PCA	8 (7.62%)	17 (5.33%)		7 (8.43%)	5 (6.02%)	

	Before PSM			After PSM		
ACA+ ACoA	37 (35.24%)	126 (39.50%)		29 (34.94%)	36 (43.37%)	
ICA	33 (31.43%)	83 (26.02%)		24 (28.92%)	21 (25.30%)	
MCA	27 (25.71%)	93 (29.15%)		23 (27.71%)	21 (25.30%)	
DCI, No. (%)	19 (18.10%)	119 (37.30%)	<0.001	16 (19.28%)	31 (37.35%)	0.020

Discussion

This case-control study identified an association between CysC level and risk of DCI after endovascular treatment of aneurysmal subarachnoid hemorrhage. The incidence of DCI in our study (32.55%) is similar to previous literature [22, 24]. Several risk factors for DCI were identified in the univariate analysis, including WFNS grade, Hunt-Hess grade, WBC count, CysC, ICH, aneurysm location, and length of hospitalization. The association between DCI and other factors (such as WFNS grade, Hunt-Hess grade, WBC count, aneurysm location (MCA), ICH) have been reported [2, 6, 18, 21, 29]. In the multivariate logistic regression model, CysC showed an independent association with the occurrence of DCI. Our study demonstrates the stable association between CysC and DCI by several statistical methods. First, the test of interaction revealed no significant subgroup differences between CysC and other confounders on DCI. Secondly, the linear relationship of CysC level and the risk of DCI was confirmed after being calculated by generalized linear models with a logit link. Finally, ROC analysis was used to determine the best cutoff threshold for discriminating the occurrence of DCI; patients in the high CysC group (CysC > 0.59 mg/l) had a higher risk of DCI than those in the low CysC group both before PSM and after PSM (37.30% vs 18.10%, 37.35% vs 19.28%, respectively).

Multivariate analysis showed CysC to be independently associated with DCI. Differences in design from previous studies showed as follow. First, the occurrence of DCI is time-dependent, with DCI occurring most frequently between 4 and 10 days after SAH [4]. However, because the endpoint for DCI observation in most previous studies was at hospital discharge [12, 14, 21], outcome bias caused by different observation times could not be ignored. In our study, the DCI group had longer hospitalizations (28.50 days [IQR 16.00-41.00] vs 20.00 days [IQR 14.00-29.00]). However, few previous studies had taken the length of hospitalization into consideration, which may lead to outcome reporting bias. Therefore, the length of hospitalization was taken into account in this study. Second, this study focused on exploring the relationship between CysC and DCI after endovascular treatment of aSAH, the effect of neurosurgical clipping for DCI was ignored. Last but not least, the time of intervention was different with some reported studies. The timeliness of receiving therapeutic intervention was considered a critical factor affecting clinical deterioration by DCI [5]. Delayed hospital admission (more than 48 hours after onset of symptoms) incurred a higher risk of DCI compared to early hospital admission (within 24 hours after

onset) [9]. To reduce the impact of intervention time, this study excluded delayed intervention patients who had received endovascular coiling more than 3 days after onset.

This study identifies the independent association between CysC and DCI, and suggests that a higher level of CysC may predict a higher risk of DCI. A higher level of CysC was confirmed to be strongly associated with a higher occurrence risk of both ischemic and hemorrhagic stroke [19]. There was a study that also reported that the level of CysC in the large infarct size group (> 4 cm in diameter on MRI) was higher than those in the small infarct size group (1.100 ± 0.270 mg/l vs 0.941 ± 0.217 mg/l, p = 0.005). Similarly, the level of CysC was higher in the larger hemorrhage volume group (> 30 ml) than the small hemorrhage volume group (≦ 30 ml (1.263 ± 0.697 mg/l vs 0.957 ± 0.260 mg/l, p = 0.006) [2]. A study of 40 microsurgically clipped aSAH patients reported that cerebrospinal fluid CysC level in the delayed focal cerebral ischemia group were higher than those in the control group without delayed focal cerebral ischemia, and CysC level in the poor prognostic outcome (GOS 1-3) group had higher CysC level than those in the group with good outcome (GOS score of 4, 5) [10].

In previous experimental studies, the mechanism of CysC on cerebral ischemia remained unclear and controversial. After suffering from focal ischemia, the size of brain infarcts was larger in CysC knockout mice than in wildtype. The mechanism was probably due to weakening the inhibition of cathepsins by CysC during brain ischemia. In contrast, after suffering from global ischemia, brain damage was diminished in CysC knockout mice, suggesting that CysC aggravates global ischemia [20]. CysC has also been shown to play an important role in atherosclerosis [16]. Higher CysC level may lead to more severe vascular wall remodeling by disrupting the balance between proteolytic and antiproteolytic activities [23]. Therefore, higher CysC level may increase the risk of DCI-related cerebral infarction by affecting the pathophysiological processes of atherosclerosis. Also, another study based on SAH animals suggested that the autophagy pathway was activated in the walls of basilar arteries after SAH, and CysC may play a role in preventing SAH-induced cerebral vasospasm by inducing autophagy [15].

Although the results of the above clinical studies are not entirely consistent with our experimental studies, we prefer to consider the overall effects of CysC on DCI and need to discover more potential pathways or mechanisms by which CysC exerts an effect on DCI. Based on previous clinical and experimental studies, CysC may have a greater effect on affecting the pathophysiological processes of atherosclerosis than preventing cerebral vasospasm after suffering aSAH.

Our study has mainly two strengths compared to previous studies. First and foremost, this study reveals the association between CysC and DCI after endovascular treatment of aSAH. The stability of association was confirmed with multiple methods, such as using interaction testing, generalized linear models, propensity score matching. Last but not least, different from reported studies, the length of hospitalization was taken into consideration to minimize outcome bias.

However, there are several limitations of this study. Firstly, this is a single-center retrospective study, and the reliability of the conclusion should be demonstrated in a prospective or multicenter design study. Secondly, considering a high rate of lost-to-follow-up in this retrospective study, the association between

CysC and functional outcome (such as modified Rankin Scale and mortality) in the follow-up period was not reported in our study. Thirdly, while propensity score matching was performed to minimize unbalancing by included confounders, the effect of unmeasured confounders should not be ignored in observational studies. Lastly, the level of CysC ranges from 0.28 to 2.59 mg/l in our study, and it is unclear whether there is a saturation effect between higher CysC level and the occurrence risk of DCI.

Conclusions

CysC level could be an independent predictor for the risk of delayed cerebral ischemia after endovascular treatment of aneurysmal subarachnoid hemorrhage.

Declarations

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Conflict of interest The authors declare that they have no conflict of interest.

Availability of data and material After providing a reasonable request, all supporting data for this study are available from the corresponding author.

Code availability Not applicable.

Ethical approval This study has obtained the approval from the institutional review board (grant number: B-2021-231).

Consent to participate After approval from the institutional review board, informed consent was waived in this retrospective study.

Consent for publication The consent to publish this manuscript has been received from all participants.

Authors' contributions Conception and design: Kehua Chen. Acquisition of data: Kehua Chen, Guanghua Huang, Chengwei Cai, Chuangnan Yan, Fuguang Zhang. Statistical analysis: Kehua Chen, Min Yao. Interpretation of data: Kehua Chen, Hongwu Xu. Drafting the article: Kehua Chen. Critically revising the article: Junqiang Ma, Hongwu Xu. Reviewed and approved the submitted version of manuscript: all authors.

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Figures

Figure 1

Association between CysC and the probability of DCI .

Figure 2

Subgroup analysis in DCI and the interaction test between CysC and other confounders.

Figure 3

Receiver operating characteristic analysis for predicting DCI by CysC level.

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