Role of serum cystatin C in the prediction of contrast-induced nephropathy after intra-arterial interventions

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Abstract

Background: The diagnosis of contrast-induced nephropathy (CIN) is usually based on changes in serum creatinine (sCr). However, sCr has poor sensitivity as a biomarker of kidney injury. The aim of this study was to investigate the usefulness of serum cystatin C (sCysC) to predict CIN after intra-arterial interventions.

Methods: A total of 360 consecutive patients underwent intra-arterial procedures using digital subtraction angiography. SCr, sCysC, and estimated glomerular filtration rate were measured at 1 to 2 days before and at 48, 72 h, and 7 days after the procedure.

Results: Thirty-one patients (8.61%) developed CIN. Receiver operating characteristic (ROC) curve analysis showed that preoperative sCysC levels had good discriminatory power (area under the curve [AUC] = 0.634; 95% confidence interval [CI] = 0.526–0.743) for evaluating the risk of CIN after an endovascular procedure, with a sensitivity of 53.33% and specificity of 73.70%. ROC analysis showed that sCysC at 48 h after contrast medium administration was predictive of CIN after an endovascular procedure (AUC = 0.735; 95% CI = 0.647–0.822) with satisfactory sensitivity of 74.20% and specificity of 63.90%. Diabetes mellitus was an independent risk factor for CIN (odds ratio = 2.778; 95% CI = 1.045–7.382; $P = 0.040$).

Conclusions: SCysC is an appropriate biomarker to predict the occurrence of CIN. Baseline sCysC before an intervention is useful to obtain a preliminary estimate of the risk of CIN. A 48-h cut-off value of sCysC of 0.99 mg/L after an endovascular procedure may help to rule out patients at lower risk of CIN.

Keywords: Contrast-induced nephropathy; Intra-arterial intervention; Serum cystatin C; Serum creatinine

Introduction

With the development of image-guided interventional diagnoses and therapies, the use of iodine-based contrast medium (CM) has recently increased dramatically in patients undergoing interventional angiographic procedures, which can lead to contrast-induced nephropathy (CIN). Iatrogenic contrast-induced acute kidney injury (AKI) is characterized by impairment of renal function following CM administration in the absence of an alternative cause and is associated with increased morbidity and mortality, prolonged hospital stays, and increased costs.[1] CIN is generally defined as an increase in serum creatinine (sCr) of 0.5 mg/dL or 25%, as assessed within 3 days after the intravascular administration of CM, in the absence of an alternative etiology.[2,3] However, sCr is influenced by factors that affect body composition including age, sex, lean body mass (muscle mass), and others. For most patients, sCr levels may be normal, despite the presence of a certain degree of kidney dysfunction and the risk of CIN after exposure to CM, as sCr has poor sensitivity as a biomarker of kidney damage.[4] Therefore, it is essential to identify a biomarker to predict CIN to reduce the risk of significant kidney injury and even failure by using preventive strategies. Serum cystatin C (sCysC), also known as γ-trace and post-γ-globulin, is a cysteine-proteinase inhibitor with widespread distribution in biological fluids. SCysC is a cysteine protease with a low molecular mass (13 kDa) consisting of 120 amino acid residues that is produced at a constant rate by all human nucleated cells.[5,6] SCysC levels are influenced by the glomerular filtration rate (GFR), but not some external factors, such as inflammation, fever, sex, age, diet, and body composition.[7] A meta-analysis showed that sCysC is more sensitive than sCr for the diagnosis of AKI.[8] SCysC levels change earlier than sCr and reach a steady state faster in patients with CIN.[9] Because of wide application of advanced operation

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techniques and risk assessment tools,[10,11] most studies for CIN diagnosis were limited in patients undergoing coronary angiography and/or intervention. So, in the present study, sCysC was used to diagnose mild renal damage and to evaluate the utility of sCysC for the prediction of CIN in patients with peripheral blood vessel disease, cerebrovascular lesions, or malignant tumors who undergo endovascular procedures.

Methods

Ethical approval

All procedures performed in this study were approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University, and in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent for participation was obtained from all patients before the study was commenced.

Patient selection

The cohort of this prospective observational study included 360 consecutive patients (241 males, 119 females; age range, 31.0–92.0 years; mean age, 61.0 ± 13.2 years) who underwent intra-arterial interventions from October 2014 to May 2017, while those who received nephrotoxic drugs before or during the study period, had renal failure, dehydration or who had undergone emergency interventional procedures or recent surgery were excluded.

Study design

All patients underwent endovascular procedures via the femoral artery using digital subtraction angiography (Siemens AXIOM Artis dTA DSA system; Siemens AG, Munich, Bayern, Germany) by experienced physicians in the Endovascular Department of our hospital. The baseline characteristics of all patients were recorded. All patients received 0.9% sodium chloride at a rate of 1 mL/kg/h through an angiographic catheter during the procedure. Patients with an estimated GFR (eGFR) <60 mL/min/1.73 m^2 received a continuous intravenous hydration with 0.9% sodium chloride at a rate of 1.5 mL/kg/h from 6 h before to 12 h after an endovascular procedure. SCr and sCysC levels were measured at 1 to 2 days before and at 48, 72 h, and 7 days after endovascular procedures. SCr level was quantified by the sarcosine oxidase method using a commercially available creatinine (enzymatic) test kit (Olympus Diagnostica GmbH, Lismeehan, O'Callaghan's Mills, Co. Clare, Ireland). ScysC level was measured with a latex-enhanced turbidimetric immunoassay using a commercially available CysC test kit (Beijing Leadman Biochemistry Co., Ltd., Beijing, China). Computation of the eGFR for this study was conducted using the simplified modification of diet in renal disease study formula for a Chinese population: $eGFR = 175 \times (sCr\ [in\ \mu mol/L]/88.4)^{-1.234} \times (age\ [in\ years])^{-0.179}$ [if female, × 0.79].[12] Patients received a low-osmolar CM, (iohexol; 300 mg of iodine per mL; 680 mOsm per kg of water; GE Healthcare, Princeton, NJ, USA) or an iso-osmolar CM (iodixanol; 320 mg of iodine per mL; 290 mOsm per kg of water; Hengrui Health, Nanjing, Jiangsu, China) during endovascular procedures. CIN was defined as an increase of more than 25% from the baseline sCr value or an absolute increase of at least 0.5 mg/dL (44.2 μmol/L) within 3 days after the administration of the CM, in the absence of an alternative etiology.[2,3] Arterial hypertension was assumed when the arterial blood pressure exceeded 140 (systolic) and/or 90 mmHg (diastolic) on at least two different occasions, or if the patient was receiving an antihypertensive medication. Diabetes mellitus (DM) was defined as a fasting blood sugar level >120 mg/dL or a hemoglobin A1c level >6%.

Statistical analysis

All analyses were performed with IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean ± standard deviation when normally distributed. The difference between CIN– and CIN+ patients was analyzed using the independent-samples *t*-test. Variables without normal distribution are expressed as the median and interquartile range. The Mann-Whitney *U* test was used to compare continuous variables between patients with and without CIN. The Wilcoxon signed-rank test was used to compare variables before and after an endovascular procedure. Differences in categorical data between groups were identified using the Chi-square test. Univariate and multiple logistic regression analyses were conducted to identify independent risk factors for the onset of CIN. A receiver operator characteristic (ROC) curve was used to evaluate the cut-off value, as well as the sensitivity and specificity of sCysC for the prediction of CIN after an intervention. The cut-off value was determined with the Youden index, the maximum difference between sensitivity (true positive) and 1- specificity (false positive). The two-tailed test was used for all statistical analyses. A probability (*P*) value < 0.05 was considered statistically significant.

Results

All 360 consecutive patients underwent fluoroscopically guided endovascular procedures. Baseline characteristics of the study population are presented in Table 1. The

Table 1: Baseline characteristics of the study patients (*n* = 360).

Characteristics	Values
Sex	
Male	241 (66.94)
Female	119 (33.06)
Age (years)	61.0 ± 13.2
Pre-operative renal insufficiency	18 (5.00)
Hypertension	113 (31.39)
DM	33 (9.17)
Type of CM	
Iohexol	282 (78.33)
Iodixanol	78 (21.67)
Malignant tumor	139 (38.61)
Administration of chemotherapy drugs	135 (37.50)

Data are presented as *n* (%) or mean ± SD. DM: Diabetes mellitus; CM: Contrast medium.

Table 2: Changes in sCr at different time points (μmol/L).

Groups	Before procedure	48 h	72 h	7 days
No-CIN	67.0 (57.7–77.6)	65.7 (57.8–77.0)	65.4 (57.0–75.2)*	64.0 (56.0–74.0)*
CIN	62.0 (50.4–81.0)	76.0 (62.0–105.3)*	81.7 (64.0–109.0)*	69.9 (59.5–91.1)*
Z	–0.686	–3.047	–4.015	–2.441
P	0.493	0.002	<0.001	0.015

Values are presented as median (interquartile range). *$P < 0.05$ compared with pre-operative sCr levels; sCr: Serum creatinine; CIN: Contrast-induced nephropathy.

Table 3: Changes in eGFR at different time points (mL/min/1.73 m^2).

Groups	Before procedure	48 h	72 h	7 days
No-CIN	111.00 (93.99–131.88)	114.42 (94.55–133.41)	115.05 (96.53–134.89)*	116.69 (98.46–138.86)*
CIN	111.41 (88.78–155.49)	96.70 (61.79–113.24)*	92.55 (59.24–115.35)*	97.66 (64.58–139.29)*
Z	–0.687	–3.449	–4.215	–2.733
P	0.492	0.001	<0.001	0.006

Values are presented as median (interquartile range). *$P < 0.05$ compared with pre-operative eGFR levels. eGFR: Estimated glomerular filtration rate; CIN: Contrast-induced nephropathy.

Table 4: Changes in sCysC at different time points (mg/L).

Groups	Before procedure	48 h	72 h	7 days
No-CIN	0.92 (0.78–1.08)	0.93 (0.80–1.09)*	0.92 (0.79–1.09)	0.90 (0.79–1.05)
CIN	1.08 (0.83–1.21)	1.17 (0.92–1.53)*	1.21 (0.92–1.62)*	1.15 (0.88–1.44)
Z	–2.435	–4.327	–3.968	–3.618
P	0.015	<0.001	<0.001	<0.001

Values are presented as median (interquartile range). *$P < 0.05$ compared with pre-operative sCysC levels. sCysC: Serum cystatin C; CIN: Contrast-induced nephropathy.

endovascular procedures were performed in the bronchial artery in 64 patients, the cerebral artery in 126 patients, the celiac artery in 120 patients, and the lower-limb artery in 50 patients. Several patients had hypertension, diabetes, a malignant tumor, or renal insufficiency [Table 1]. Chemotherapy drugs, which included oxaliplatin, epirubicin, pirarubicin, or hydroxycamptothecin, were administered via arterial perfusion to patients with malignant tumors.

Thirty-one patients (8.61%) developed CIN within 72 h. All thirty-one patients had an increase in sCr level of ≥25%, which included three with an increase ≥0.5 mg/dL (44.2 μmol/L). The results of the Mann-Whitney *U* test showed that there was no statistically significant difference in pre-operative sCr levels between patients with and without CIN ($Z = -0.686$, $P = 0.493$), but there were statistically significant differences in sCr levels at 48 h, 72 h, and 7 days after an endovascular procedure ($Z = -3.047$, –4.015, and –2.441, $P = 0.002$, <0.001, and 0.015, respectively) [Table 2]. The Wilcoxon signed-rank test revealed that sCr levels were decreased at 48 h after an endovascular procedure, with statistically significant differences at 72 h and 7 days post-procedure in patients without CIN, while sCr levels were significantly increased at 48 and 72 h after an endovascular procedure and established a new baseline within 7 days after exposure to CM in patients with CIN [Table 2].

Meanwhile, the results of the Mann-Whitney *U* test revealed that there was no statistically significant difference in pre-operative eGFR values between patients with and without CIN ($Z = -0.687$, $P = 0.492$), while there were statistically significant differences in eGFR values at 48, 72 h, and 7 days after an endovascular procedure between patients with and without CIN ($Z = -3.449$, −4.215, and −2.733; $P = 0.001$, <0.001, and 0.006, respectively) [Table 3]. The results of the Wilcoxon signed-rank test showed that eGFR was increased at 48 h after an endovascular procedure, with significant difference at 72 h and 7 days post-procedure in patients without CIN. The eGFR values at 48 and 72 h after an endovascular procedure were significantly decreased, as compared with the baseline values, and established new baseline values within 7 days in patients with CIN [Table 3].

The results of the Mann-Whitney *U* test showed that there were statistically significant differences in sCysC levels from before an endovascular procedure to 48, 72 h, and 7 days after exposure to CM between patients with and without CIN ($Z = -2.435$, –4.327, –3.968, and –3.618; $P = 0.015$, <0.001, <0.001, and <0.001, respectively) [Table 4]. The Wilcoxon signed-rank test revealed that sCysC levels were statistically increased at 48 h after an endovascular procedure and returned to baseline values within 7 days in patients without CIN. In addition, sCysC

Table 5: Predictive ability of sCysC at different time points.

Time	AUC	*P*	95% CI	Cut-off (mg/L)	Sensitivity (%)	Specificity (%)	Youden index	PPV (%)	NPV (%)
Baseline	0.634	0.015	0.526–0.743	1.07	53.33	73.70	0.270	16.04	94.37
48 h	0.735	<0.001	0.647–0.822	0.99	74.20	63.90	0.381	16.22	96.34
72 h	0.714	<0.001	0.610–0.818	1.32	48.40	90.20	0.386	31.36	94.89

sCysC: Serum cystatin C; AUC: Area under the curve; 95% CI: 95% Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

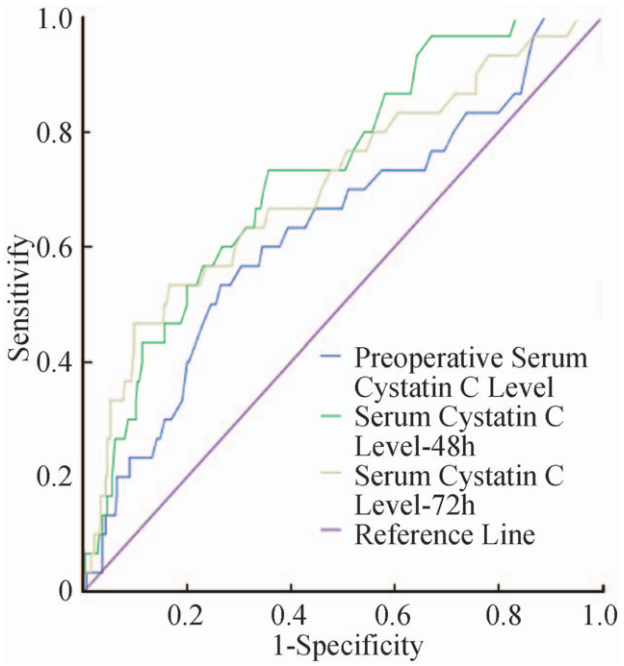

Figure 1: Accuracy of sCysC for the diagnosis of CIN. CIN: Contrast-induced nephropathy; sCysC: Serum cystatin C.

levels were significantly increased at 48 and 72 h after an endovascular procedure, as compared with the baseline values, and established new baseline values within 7 days in patients with CIN [Table 4]. The results of ROC curve analysis showed that pre-operative sCysC levels had good discriminatory power (area under the curve [AUC] = 0.634; 95% confidence interval [CI] = 0.526–0.743) for evaluation of the risk of CIN after an endovascular procedure, with a sensitivity of 53.33% and specificity of 73.70% [Table 5 and Figure 1]. A cut-off value of 1.07 mg/L for baseline sCysC before an endovascular procedure was established as a reference threshold to rule out CIN (Youden index = 0.270) with a negative predictive value (NPV) of 94.37% [Table 5]. Overall, the incidence of CIN is low in patients with a pre-operative sCysC value of <1.07 mg/L. ROC analysis showed that CysC at 48 h after exposure to CM could predict the risk of CIN after an endovascular procedure (AUC = 0.735; 95% CI = 0.647–0.822) with satisfactory sensitivity of 74.20% and specificity of 63.90% [Table 5]. We believe that a cut-off value of 0.99 mg/L for sCysC at 48 h after an endovascular procedure is the best threshold to rule out CIN (Youden index = 0.381) with satisfactory positive predictive value of 16.22% and NPV of 96.34% [Table 5]. Overall, the incidence of CIN is low in patients with a 48-h sCysC level of <0.99 mg/L after an endovascular procedure.

Results of univariate analysis showed that there were no statistically significant differences in sex, age, pre-operative renal insufficiency, type of CM used, DM, dosage of CM, malignancy, administration of chemotherapy drugs, and hypertension between patients with and without CIN [Table 6]. Multivariate logistic regression analysis was performed to identify independent factors influencing the occurrence of CIN with a *P* value of <0.200, which included age, DM, type of contrast agent, and administration of chemotherapy drugs as the independent variable, and the occurrence of CIN as a dependent variable in univariate analysis. The results of multiple logistic regression analysis indicated that baseline DM was an independent risk factor for CIN (odds ratio = 2.778, 95% CI = 1.045–7.382, *B* value = 1.022; *P* = 0.040). The risk of AKI from CM in patients with DM was increased by 2.778-fold, as compared to those without DM.

Discussion

In recent years, CIN has become the third most common cause of hospital-acquired AKI after surgery and hypotension.[13] The occurrence of renal injury is transient within 1 to 3 days of an endovascular procedure, usually peaking at 3 to 5 days after CM administration and returning to baseline (or a new baseline) within 7 days.[14-16] However, CIN may result in clinically severe adverse outcomes, such as longer hospitalizations, chronic kidney disease, renal failure or death. Therefore, a sensitive marker of renal injury after CM administration for patients undergoing interventional procedures is required for the early assessment of the risk of CIN to avoid serious or permanent renal impairment by using effective prevention and treatment strategies.

Several promising biomarkers exist for the early detection of renal injury and prediction of CIN development, such as sCysC, kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, and interleukins 18.[17-19] However, no validated cut-off points for these biomarkers have yet been established for the prediction of CIN development. In this study, changes in sCr, eGFR, and sCysC were observed at 48, 72 h, and 7 days after exposure to CM. For CIN patients, sCysC levels were significantly elevated at 48 h after an endovascular procedure and almost always returned to a new baseline value within 1 week, which is similar to the trend in the variation of eGFR or sCr. However, for patients without CIN, post-operative sCr was decreased, while eGFR was increased, and no renal

Table 6: Univariate analysis of risk factors for the onset of CIN.

Confounding factor	No-CIN $n = 329$	CIN $n = 31$	$\chi^2/t/Z$	P
Sex			0.010	0.929
Male	220 (91.29)	21 (8.71)		
Female	109 (91.60)	10 (8.40)		
Age (years)	60.6 ± 13.0	64.6 ± 14.6	–1.620	0.106
Pre-operative renal insufficiency	15 (83.33)	3 (16.67)	0.671	0.413
Hypertension	101 (89.38)	12 (10.62)	0.844	0.358
DM	27 (81.82)	6 (18.18)	2.996	0.083
Type of CM			2.242	0.134
Iohexol	261 (92.55)	21 (7.45)		
Iodixanol	68 (87.18)	10 (12.82)		
CM dose (mL)	140 (120–210)	160 (130–210)	–0.937	0.349
Malignant tumor	124 (89.21)	15 (10.79)	1.368	0.242
Administration of chemotherapy drugs	120 (88.9)	15 (11.1)	1.715	0.150

Data are presented as *n* (%), mean ± standard deviation or median (range). CIN: Contrast-induced nephropathy; CM: Contrast medium; DM: Diabetes mellitus.

damage was observed. Meanwhile, sCysC was increased transiently, which suggests some injury to renal function after an endovascular procedure. Our data demonstrate that sCysC is a sensitive marker for the identification of renal injury in the absence of a diagnostic increase in sCr. CysC is freely filtered by the glomeruli and reabsorbed and almost completely catabolized in the proximal renal tubules. The plasma concentration of CysC is determined by the GFR, but not significantly affected by any external factors, such as sex, age, diet, and weight.[5,20-22] Therefore, CysC is a suitable endogenous marker for the early identification of deviations in GFR and injury to the renal tubular epithelial cells.[4] Tubular cells undergo swelling, blebbing, and apoptosis in patients exposed to CM.[23] Tubular damage often results in GFR decreases. So, measurement of sCysC levels has the potential to be a useful method for the early detection of tubular injury and to evaluate the degree of renal impairment after an endovascular procedure. In this study, among patients without CIN, sCysC levels were significantly elevated at 48 h after the endovascular procedure and returned to baseline values within 1 week, but sCr levels were not elevated. The incidence of CIN was only 8.61% (31/360 patients), while sCr measurements indicated no deterioration in kidney function in other patients after exposure to CM. However, sCysC levels indicated slight renal injury and predicted a risk of developing CIN in those patients with no increase in sCr of ≥25% or ≥0.5 mg/dL (44.2 μmol/L) within 3 days. So, sCysC is a sensitive biomarker for early prediction of CIN.[24] In this study, sCysC before endovascular procedures was predictive of the risk of CIN in patients following exposure to CM. Our results demonstrated that the risk of CIN is low when the sCysC value is less than 1.07 mg/L before an endovascular procedure. So, preventative strategies are not necessary for patients with sCysC levels <1.07 mg/L before an interventional procedure. However, this value may not be the best threshold for ruling out CIN and post-operative sCysC values should be observed because the NPV was only 94.37%. We believe that preventative strategies are necessary for patients with pre-operative sCysC levels >1.07 mg/L to reduce the risk of CIN. In this study, we determined the cut-off value of sCysC for prediction of CIN after an interventional procedure. We believe that the sCysC at 48 h after an endovascular procedure is predictive of the risk of CIN after CM administration. Our analysis demonstrated that a sCysC cut-off value of 0.99 mg/L at 48 h after an endovascular procedure is the best threshold for ruling out CIN, with a high NPV of 96.34%, sensitivity of 74.20%, and specificity of 63.90%. Patients with sCysC levels <0.99 mg/L 48 h after an endovascular procedure can be discharged early with no need to continue to observe changes in kidney function.

In this study, DM was a risk factor for the development of CIN, but not other comorbidities of hypotension, type of CM, sex, age, pre-operative renal insufficiency, malignant tumor, administration of chemotherapy drugs and contrast volume. Hydration with 0.9% sodium chloride and the use of an iso-osmolar CM may reduce the risk of CIN in patients with renal insufficiency. Therefore, pre-operative renal dysfunction is not a risk factor of CIN. There was no statistically significant difference in contrast dosage in patients with and without CIN, although the contrast dosage was higher in patients with CIN in this study, which may be associated with the control of CM dosage during an interventional procedure. Higher contrast volume was also reported to increase risk of cerebrovascular events and cause bleeding events in patients undergoing cardiac catheterization.[25] Hence, we recommend reducing the CM dosage to decrease risk of adverse events. The use of an iso-osmolar CM was associated with a slightly lower risk of CIN than low-osmolar CM, but the lower risk had only borderline statistical significance and was not clinically important.[26] We found no statistically significant difference in the risk of CIN in patients given iso-osmolar CM (iodixanol) *vs*. low-osmolar CM (iohexol) in this study. Intra-arterial perfusion and embolization with chemotherapy drugs in patients with malignant tumors have a small impact on the body because the chemotherapy drugs used in this study had lower nephrotoxicity. Therefore, only one risk factor for CIN suggests that continuous perfusion of 0.9% sodium chloride through an angiographic catheter during

the procedure may also reduce the risk of CIN. As compared to those without DM, patients with DM are at a greater risk of CM-induced renal injury, although eGFR is increased in patients with incipient DM.[8,27,28] The results of this study indicate that DM is an independent risk factor of CIN. So, preventive strategies should be implemented to mitigate CIN in high-risk patients with DM, and the CM volume should also be reduced as far as possible during endovascular interventional therapy.

The limitations of this study included its single-center design, with no observation of renal pathology or long-term follow-up. Patients with renal injury after intra-arterial interventions will be followed up to evaluate the long-term effects on renal function of CM. Further studies with animal models of CIN are needed to monitor kidney function and renal pathological changes. The advantage of this study was the use of sCysC to predict CIN after intra-arterial interventional therapy before changes in sCr levels were detectable and especially pre-operative sCysC to get a preliminary estimate of the occurrence of CIN. The measurement of sCysC is a popular non-invasive method to clinically assess tubular function, which is convenient for the prediction of CIN after intra-arterial interventions.

Conclusions

The results of this study demonstrated that sCysC is a useful marker for the identification of renal injury after intra-arterial interventions. SCysC is an appropriate biomarker for the early prediction of CIN with acceptable sensitivity and specificity in the absence of a diagnostic increase in sCr. Baseline sCysC before an intervention could be used to obtain a preliminary estimate of the risk of CIN. SCysC at 48 h after an endovascular procedure with a cut-off value of 0.99 mg/L may help to rule out patients at lower risk of CIN for early hospital discharge. A larger study cohort with a long-term follow-up is required to confirm these findings and to optimize the clinical use of sCysC.

Data sharing statement

The individual de-identified participant data (including original data) in this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

None.

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