Elevation of preoperative cystatin C as an early predictor of contrast-induced nephropathy in patients receiving percutaneous coronary intervention

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Abstract

Introduction: Contrast-induced nephropathy (CIN) is a serious complication of percutaneous coronary intervention (PCI). The most important predictor of CIN is renal function before PCI. Serum creatinine (SCr) is a commonly used biomarker of renal function, but an elevation in SCr lags behind the onset of kidney injury and is not viable for early detection of CIN after PCI. Our primary objective was to investigate whether preoperative cystatin C (CysC) before PCI was an early predictor of postoperative CIN. The secondary objective was to evaluate associations between preoperative CysC and renal biomarkers.

Methods: From December 2014 to December 2015, 341 patients with normal renal function were enrolled into the study at our medical centre. All patients were apportioned to normal CysC (≤1.03 mg/L) or high CysC (>1.03 mg/L) groups before PCI and were hydrated from four hours prior to PCI to 24 hours after it. Renal function was monitored at 48 hours after PCI. Clinical parameters were recorded before and after PCI.

Results: There was no significant difference in preoperative SCr between the CIN and non-CIN groups. However, preoperative CysC demonstrated significant difference between the two groups (p <0.01). Logistic regression analysis showed that elevated CysC before PCI was a risk factor for CIN (p = 0.013). Furthermore, the linear regression models identified an association between CysC before PCI and renal function after PCI.

Conclusion: CysC before PCI was viable as a biomarker of renal function after PCI and high preoperative CysC was able to predict CIN earlier than SCr.

Keywords: Contrast-induced nephropathy, creatinine, cystatin C, percutaneous coronary intervention

INTRODUCTION

Contrast-induced nephropathy (CIN) is an acute iatrogenic kidney injury caused by the contrast agent used for medical imaging procedures. CIN is indicated by an increase in serum creatinine (SCr) of 44.2 μmol/L (or 0.5 mg/dL) above baseline or SCr ≥ 125% of baseline within 48 hours of contrast use,[1,2] barring other explanations for renal impairment (e.g., acute heart failure, malignant arrhythmia or other disorders). CIN can lead to a poor prognosis, both in the short and long terms, and its management increases the cost of medical care. Prevention and early diagnosis of CIN is an important focus in cardiology and nephrology research.

Although SCr is considered a biomarker of renal injury, its specificity and sensitivity are relatively low. SCr levels are also influenced by other factors, and its elevation, as a response to kidney injury, usually lags behind the onset of renal injury.

Recent studies have indicated that cystatin C (CysC) may be a viable biomarker of renal function.[3,4] CysC is an extracellular subtype of cystatin that is abundant in the bodily fluids,

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and is synthesised and released at a constant rate. CysC is freely filtered at the glomerulus, reabsorbed and metabolised completely. However, CysC is not secreted by kidney tubules. CysC levels are not associated with age, ethnicity, gender or muscle mass.[5] In addition, the half-life of CysC is only about one-third that of SCr. Thus, the blood levels of CysC stabilise more quickly when renal injury occur as compared to SCr levels. Previous research has shown that when compared with SCr, using CysC as a predictor of acute kidney injury allows earlier diagnosis (by one or two days), and both the sensitivity and specificity of CysC are higher than those of SCr.[6] Many studies have reported similar findings.[7-9] Moreover, various other studies have also shown that preprocedural CysC levels were an early useful biomarker for contrasted scanning of peripheral vascular disease and computed tomography coronary angiography.[10-13] A study found that CysC was an early marker of CIN in patients with sepsis in the intensive care unit.[14] Moreover, CysC and CysC-to-creatinine ratio could independently predict renal impairment after contrast administration, whereas blood urea nitrogen and creatinine were not predictive.[15] Altogether, CysC has been reported specifically as a potential biomarker for the early diagnosis of CIN.[4,16]

As was known, besides the renal marker, cardiac markers are also important in the process of CIN. For instance, the prevalence of CIN was about 1%–2% in the general population, but patients with coronary artery disease, congestive heart failure and chronic kidney disease have a dramatically higher prevalence of CIN at 20%–30%.[17] Left ventricular end-diastolic pressure (LVEDP) was a cardiac marker that presented the pressure at the end diastole produced by blood reflux from pulmonary circulation to the left ventricle and accurately reflected the haemodynamic changes. A recent study showed that LVEDP correlated inversely with CIN in patients undergoing percutaneous coronary intervention (PCI).[18]

PCI, used to treat acute coronary syndrome, involves the use of radiography to visualise blood vessels. The incidence of CIN has increased significantly since the application of PCI has become common. Therefore, the primary objective of the present study was to evaluate whether preoperative high CysC before PCI was associated with increased risk of CIN. A secondary objective was to identify the relationship between preoperative CysC and renal biomarkers.

METHODS

The institutional review board at The Second Hospital of Hebei Medical University, Shijiazhuang, China, approved this prospective study. All patients and their families provided written informed consent.

In total, 341 patients with normal renal function who underwent PCI at our medical centre from December 2014 to December 2015 (men, n = 245; women, n = 96; age

range 31–78 years) were enrolled. For the study's analysis, patients were apportioned to two groups based on their baseline CysC levels: normal (CysC ≤1.03 mg/L; n = 192); or high (CysC >1.03 mg/L; n = 149).

Only patients who conformed to the following criteria were included in the study: patients had received PCI; were in the age range 18–78 years; and both patient and family had provided informed consent.

Patients satisfying any of the following criteria were excluded: those who had undergone emergency PCI; were on renal replacement therapy; had received contrast medium during the two-day period before enrolment; were allergic to contrast medium; had received aortic valve replacement, renal transplantation or heart transplantation; had acute heart failure, severe valvular disease or left ventricular (LV) thrombus; or had other contraindications for PCI.

Postoperative CIN was diagnosed as an elevation of SCr of 44.2 μmol/L (or 0.5 mg/dL) above baseline or SCr ≥125% of baseline within 48 hours after PCI,[1,2] when other factors that could lead to kidney impairment were excluded (e.g. acute heart failure, malignant arrhythmia).

Hyperlipidaemia is a disorder of lipid metabolism in the body that leads to increased blood lipid levels and causes a series of clinical and pathological symptoms. Hyperlipidaemia is diagnosed when cholesterol >5.20 mmol/L or triglyceride >1.70 mmol/L, and low-density lipoprotein cholesterol >3.37 mmol/L or high-density lipoprotein cholesterol <0.91 mmol/L, according to medical reference ranges.

Renal biomarkers included SCr, creatinine clearance (CCr) and glomerular filtration rate (GFR).

The following clinical data was collected: demographics (including bodyweight, height, age and gender); medical history; physical examination findings; laboratory test results (including routine blood test, renal functioning and blood glucose); and cardiac ultrasonography.

Hydration was performed with normal saline (dose 1 mL/kg/hour) from four hours before PCI to 24 hours after PCI. All patients were administered furosemide (dose 20 mg) after PCI. Venous blood samples were collected before PCI. CysC and SCr were tested using particle-enhanced turbidimetric immunoassay and automatic biochemical analyser, respectively, and these two biomarkers were retested 48 hours after PCI.

The CKD-EPI (Chronic Kidney Disease-Epidemiology Collaborative Group) creatinine-cystatin C equation (2012) can be expressed as a single equation:

$135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{age}$ [× 0.969, if female] [× 1.08, if black]

where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for women and 0.9 for men, α is −0.248 for women and −0.207 for men, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.[19,20]

The Cockcroft-Gault equation was used to calculate 24-hour CCr:[21]

CCr, mL/min = [(140 − age, y) × (bodyweight, kg) × (0.85, women only)]/(72 × SCr, mmol/L)

where CCr is creatinine clearance and SCr is serum creatinine.

Statistical analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA). The baseline characteristics of demographics and clinical indicators were analysed between the normal CysC and high CysC groups. Continuous variables were presented as the mean ± standard deviation for normally distributed values, or as median and interquartile range for variables that were not normally distributed. Comparisons between the two groups were conducted using independent sample *t*-tests, when the data were normally distributed. Otherwise, a non-parametric test was used for data analysis. Categorical variables were presented as number and percentage and compared using Chi-square test. The univariate factor analysis between CIN and non-CIN groups were conducted in the same manner. The incidence of CIN in different CysC groups was assessed using Chi-square test. Demographic characteristics (e.g. gender and age) and clinical characteristics (e.g. contrast media, whether patients had hypertension and diabetes mellitus) were adjusted during univariate logistic regression analysis.

Following adjustment for demographics and clinical characteristics as well as other confounding factors, the factors that exhibited significant difference during univariate logistic regression analysis included the following: preoperative CysC, contrast agent type; LV ejection fraction (LVEF); LVEDP; LV diameter; B-type natriuretic peptide (BNP); C-reactive protein (CRP); and the presence or absence of heart failure, acute myocardial infarction and hyperlipidaemia. Multivariate logistic regression analysis was conducted for the above factors as independent variables, and CIN as the dependent variable, to analyse risk factors of CIN. The multivariate logistic regression was performed with backward stepwise regression. Linear regression model analysis was applied to identify the relationship between CysC before PCI and renal function after PCI. A *P* value <0.05 was considered to be statistically significant.

RESULTS

Overall, 341 patients were enrolled –245 (71.85%) men and 96 (28.15%) women. All patients were aged 31–78 years, with a median age of 58 years. Of all patients, 145 (42.52%) were diagnosed with acute myocardial infarction and 196 (57.48%) patients were diagnosed with unstable angina [Table 1].

To evaluate whether preoperative high CysC was associated with increased risk of CIN, multivariate logistic regression analysis was conducted, which revealed that higher CysC levels before PCI was a risk factor of CIN (odds ratio [OR] 3.876, 95% confidence interval [CI] 1.332–11.278; *P* = 0.013) [Tables 2 and 3].

The probability formula of CIN:

$$= \frac{\exp(-11.510 + 1.355\text{High} - \text{CysC} + 0.132\text{LV} - 0.134\text{LVEDP})}{1 + \exp(-11.510 + 1.355\text{High} - \text{CysC} + 0.132\text{LV} - 0.134\text{LVEDP})}$$

Before PCI, there was no significant difference in preoperative SCr, CCr and GFR between the CIN and non-CIN groups. However, preoperative CysC, which was seen earlier than SCr, demonstrated significant difference between these groups. The incidence of CIN in patients with high preoperative CysC was higher than among those with low preoperative CysC [Table 2].

Linear regression analyses of CysC before PCI and renal function after PCI found that there was an inverse relationship between CysC before PCI and GFR after PCI (r = 0.662, *P* <0.001) [Table 4].

Logistic regression analysis also demonstrated that an enlarged LV was a risk factor for CIN (OR 1.141 [95% CI 1.045–1.245]; *P* = 0.003), while LVEDP was a protective factor of CIN (OR 0.875 [95% CI 0.797–0.960]; *P* = 0.005) [Tables 2 and 3].

DISCUSSION

This study investigated the predictive role of preoperative CysC level for renal function and its potential application in the clinical settings. We enrolled patients undergoing PCI with renal function within the normal range (measured using SCr), and divided them into two groups according to their CysC levels. Our findings suggested that preoperative CysC levels positively correlated with SCr levels but negatively correlated with GFR and CCr. This indicates that preoperative CysC level may be regarded as a biomarker of renal function. The SCr levels before PCI were similar in the CIN and non-CIN groups, while preoperative CysC in the CIN group was significantly higher than that in the non-CIN group. Logistic regression analysis also found that higher preoperative CysC level was a risk factor for CIN. Thus, aside from acting as a biomarker of renal function, preoperative CysC might also predict the development of CIN early. Furthermore, while high LVEDP was a protective factor for CIN, an enlarged LV was a risk factor for it.

Previous studies found that renal insufficiency at baseline was a risk factor of CIN, which was confirmed by our results.[22,23] CysC was more sensitive to renal injury than SCr. Some studies have reported that SCr lags behind a decrease in

Table 1. Preoperative demographic and clinical characteristics.

Variable	No. (%)			P
	Total (*n*=341)	Normal CysC (*n*=192)	High CysC (*n*=149)	
Male gender	245 (71.85)	132 (53.88)	113 (46.12)	0.149
Age (yr)*	58.00 (52.00-64.00)	57.00 (51.00-63.00)	60.00 (53.00-66.00)	0.001†
Smoking	144 (42.23)	82 (56.94)	62 (43.06)	0.839
Hypertension	190 (55.72)	108 (56.84)	82 (43.16)	0.823
Heart failure	37 (10.85)	18 (48.64)	19 (51.35)	0.320
Acute myocardial infarction	145 (42.52)	78 (53.79)	67 (46.21)	0.421
Hyperlipidaemia	154 (45.16)	89 (57.79)	65 (42.21)	0.615
Multivessel disease	204 (59.82)	115 (56.37)	89 (43.63)	0.976
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	157 (46.04)	91 (57.96)	66 (42.04)	0.569
Statins	321 (94.13)	178 (55.45)	143 (44.55)	0.203
Lopromide injection	315 (92.38)	176 (55.87)	139 (44.13)	0.576
CIN	21 (6.16)	7 (33.33)	14 (66.67)	0.028‡
Left ventricular ejection fraction (%)*	62.03 (60.17-63.56)	62.00 (60.09-63.54)	62.12 (60.37-63.56)	0.921
Haemoglobin (g/L)§	138.00±13.59	136.93±13.57	139.38±13.55	0.099
Bodyweight (kg)*	72.00 (65.00-80.00)	71.50 (65.00-80.00)	72.00 (65.00-78.00)	0.579
Height (cm)*	170.00 (160.00-173.00)	170.00 (160.00-173.00)	170.00 (163.00-173.00)	0.449
Left ventricular diameter (mm)*	48.00 (45.00-51.00)	48.00 (45.00-51.00)	48.00 (45.00-51.00)	0.239
Left ventricular end-diastolic pressure (mmHg)*	18.00 (14.00-22.00)	18.00 (14.00-22.00)	18.00 (14.00-22.00)	0.615
B-type natriuretic peptide (pg/mL)*	36.60 (15.00-94.10)	33.45 (13.05-89.60)	40.30 (17.40-94.30)	0.215
C-reactive protein (mg/L)*	3.60 (2.00-6.20)	3.80 (1.70-6.25)	3.60 (2.10-6.20)	0.753
Contrast media (mL)*	100.00 (100.00-160.00)	100.00 (100.00-160.00)	100.00 (100.00-160.00)	0.245
CysC (mg/L)*	1.00 (0.88-1.18)	0.89 (0.81-0.96)	1.20 (1.12-1.33)	<0.001†
Serum creatinine (μmol/L)§	69.84±12.44	68.70±12.42	71.31±12.34	0.055

*Data presented as median (range) and §mean±standard deviation. †*P*<0.01 was considered statistically significant. ‡*P*<0.05 was considered statistically significant. CIN=contrast-induced nephropathy, CysC=cystatin C.

Table 2. Demographic and clinical characteristics of the CIN and non-CIN groups.

Variable	No. (%)		P
	CIN group (*n*=21)	Non-CIN group (*n*=320)	
Male gender	18.00 (85.71)	227.00 (70.94)	0.145
Age (yr)*	59.19±8.42	57.51±9.14	0.412
Smoking	12.00 (57.14)	132.00 (41.25)	0.153
Hypertension	8.00 (38.10)	182.00 (56.88)	0.093
Diabetes mellitus	6.00 (28.57)	92.00 (28.75)	0.986
Heart failure	7.00 (33.33)	30.00 (9.38)	0.002†
Acute myocardial infarction	17.00 (80.95)	128.00 (40.00)	0.000†
Hyperlipidaemia	5.00 (23.81)	149.00 (46.56)	0.042‡
Multivessel disease	14.00 (66.67)	190.00 (59.38)	0.509
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	7.00 (33.33)	150.00 (46.88)	0.228
Statins	20.00 (95.24)	301.00 (94.06)	1.000
Lopromide injection	16.00 (76.19)	299.00 (93.44)	0.014‡
Left ventricular ejection fraction (%)*	54.14±12.16	61.14±6.78	0.016‡
Haemoglobin (g/L)*	75.00±11.22	72.00±10.03	0.390
Bodyweight (kg)*	75.00±11.22	72.00±10.03	0.245
Height (cm)§	172.00 (166.00-174.50)	170.00 (160.00-173.00)	0.192
Left ventricular diameter (mm)§	52.00 (48.50-56.00)	48.00 (45.00-51.00)	0.000†
Left ventricular end-diastolic pressure (mmHg)§	14.00 (10.00-19.00)	18.00 (14.00-22.00)	0.010‡
B-type natriuretic peptide (pg/mL)§	117.00 (51.00-403.00)	35.45 (14.55-83.55)	0.000†

Contd...

Table 2. Contd...

Variable	No. (%)		P
	CIN group (*n*=21)	Non-CIN group (*n*=320)	
C-reactive protein (mg/L)[§]	7.40 (2.45-23.15)	3.60 (1.90-5.90)	0.005[†]
Contrast media (mL)[§]	100.00 (100.00-160.00)	100.00 (100.00-160.00)	0.832
Before PCI			
Low CysC	7.00 (33.33)	185.00 (57.81)	0.028[‡]
High CysC	14.00 (66.67)	135.00 (42.19)	
Serum creatinine (μmol/L)[§]	69.30 (63.60-73.50)	70.75 (60.53-78.75)	0.313
Creatinine clearance ml/min[§]	105.20 (93.87-133.85)	98.68 (85.86-114.29)	0.094
Glomerular filtration rate ml·min^{-1}·1.73 m^{-2}[*]	83.59±15.19	86.12±15.21	0.467
After PCI			
Low CysC	6 (28.57)	193 (60.31)	0.004[†]
High CysC	15 (71.43)	127 (39.69)	
Serum creatinine (μmol/L)[§]	91.60 (82.50-100.25)	70.15 (59.95-78.85)	<0.001[†]
Creatinine clearance (ml/min)[*]	85.04±28.19	103.72±26.50	0.002[†]
Glomerular filtration rate ml·min^{-1}·1.73 m^{-2}[*]	72.19±15.78	87.90±16.06	<0.001[†]

[*]Data presented as mean±standard deviation and [§]median (range). [†]P<0.01 was considered statistically significant. [‡]P<0.05 was considered statistically significant. CIN=contrast-induced nephropathy, CysC=cystatin C, PCI=percutaneous coronary intervention.

Table 3. Multivariate logistic regression analysis of factors related to CIN.

Variable	Odds ratio	95% CI for Exp (B)	P
Preoperative CysC (mg/L)			
Normal CysC	1 (reference)		
High CysC	3.876	1.332-11.278	0.013[*]
Left ventricular diameter (mm)	1.141	1.045-1.245	0.003[*]
Left ventricular end-diastolic pressure (mmHg)	0.875	0.797-0.960	0.005[*]

[*]P<0.01 was considered statistically significant. CI=confidence interval, CIN=contrast-induced nephropathy, CysC=cystatin C.

Table 4. Linear regression analysis of preoperative CysC (before PCI) and postoperative renal function (after PCI).

Y[*]	X[*]	Intercept	Slope	P
Postoperative glomerular filtration rate	Preoperative CysC	133.12	−44.54	<0.01[†]
Postoperative creatinine clearance	Preoperative CysC	137.69	−33.87	<0.01[†]
Postoperative serum creatinine	Preoperative CysC	54.27	15.88	<0.01[†]

[*]Y indicated the dependent variable and X indicated the independent variable. [†]P<0.01 was considered statistically significant. CysC=cystatin C, PCI=percutaneous coronary intervention.

GFR, so that SCr could not reflect the patient's renal function precisely.[5,24] However, CysC was sensitive to early renal injury – its sensitivity and specificity were 89.6% and 63.6%, respectively.[23] When renal injury occurred, the CysC level rose before the SCr level.[23]

LVEDP represents the preload of LV. Our study suggested that higher LVEDP was protective against CIN.

Logistic regression analysis suggested that higher preoperative CysC level was a risk factor of CIN. We also found that elevated preoperative CysC was associated with older age. Odden *et al.*[25] found that there was a strong relationship of age with kidney function based on CysC, even for healthy individuals. Many other studies have also reported that elevated CysC was not only associated with age but also gender, ethnicity, uric acid level, blood urea nitrogen, renal function, body mass index and blood pressure among others.[26-29] However, most studies considered CysC as a new and stable parameter that could reflect renal function independent of age, gender, height and other parameters.[5,30,31] In our study, patients with elevated preoperative CysC were older; older age may have been a reason for the higher CysC levels found in them. The possible reasons for elevated preoperative CysC will be further elucidated in future polycentric randomised controlled trials.

This study had its strengths and limitations. Renal function was tested 48 hours after PCI, but there was no other follow-up. Therefore, we were unable to demonstrate changes in renal function over time after PCI. The fluctuation of clinical parameters was also not monitored continuously. Again, CysC assessments remain more expensive and are not yet widely available for it to be considered a viable option for routine investigations prior to invasive procedures.

In conclusion, CysC before PCI may have a higher potential to function as a biomarker for renal function that predicts CIN after PCI when compared with SCr. To improve the prognosis of patients undergoing PCI, it is recommended that caregivers monitor patients with high CysC levels more intensively.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Morcos SK, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: A consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). Eur Radiol 1999;9:1602-13.
2. Mehran R, Nikolsky E. Contrast-induced nephropathy: Definition, epidemiology, and patients at risk. Kidney Int Suppl 2006;S11-5. doi: 10.1038/sj.ki.5000368.
3. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. Am J Kidney Dis 2002;40:221-6.
4. Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R, *et al*. Cystatin C and contrast-induced acute kidney injury. Circulation 2010;121:2117-22.
5. Herget-Rosenthal S, Metzger J, Albalat A, Bitsika V, Mischak H. Proteomic biomarkers for the early detection of acute kidney injury. Prilozi 2012;33:27-48.
6. Herget-Rosenthal S, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, *et al*. Early detection of acute renal failure by serum cystatin C. Kidney Int 2004;66:1115-22.
7. Kim BJ, Sung KC, Kim BS, Kang JO, Lee KB, Kim H, *et al*. Effect of N-acetylcysteine on cystatin C-based renal function after elective coronary angiography (ENABLE Study): A prospective, randomized trial. Int J Cardiol 2010;138:239-45.
8. Alharazy SM, Kong N, Saidin R, Gafor AHA, Maskon O, Mohd M, *et al*. Serum neutrophil gelatinase-associated lipocalin and cystatin C are early biomarkers of contrast-induced nephropathy after coronary angiography in patients with chronic kidney disease. Angiology 2014;65:436-42.
9. Wang M, Zhang L, Yue R, You G, Zeng R. Significance of cystatin C for early diagnosis of contrast-induced nephropathy in patients undergoing coronary angiography. Med Sci Monit 2016;22:2956-61.
10. Takeuchi T, Isobe S, Sato K, Kato MI, Kasai NN, Ohyama H, *et al*. Cystatin C: A possible sensitive marker for detecting potential kidney injury after computed tomography coronary angiography. J Comput Assist Tomogr 2011;35:240-5.
11. Li S, Zheng Z, Tang X, Peng L, Luo Y, Dong R, *et al*. Preprocedure and postprocedure predictive values of serum β2-microglobulin for contrast-induced nephropathy in patients undergoing coronary computed tomography angiography: A comparison with creatinine-based parameters and cystatin C. J Comput Assist Tomogr 2015;39:969-74.
12. Otaki Y, Takahashi H, Watanabe T, Yamaura G, Funayama A, Arimoto T, *et al*. Cystatin C-based eGFR is a superior prognostic parameter to creatinine-based eGFR in post-endovascular therapy peripheral artery disease patients. Circ J 2015;79:2480-6.
13. Yang Y, Zhao X, Tang X, Lu J, Zhou M, Wang W, *et al*. Comparison of serum cystatin C and creatinine level changes for prognosis of patients after peripheral arterial angiography. Angiology 2015;66:766-73.
14. Al-Beladi FI. Cystatin C is an early marker of contrast-induced nephropathy in patients with sepsis in the intensive care unit. Saudi J Kidney Dis Transpl 2015;26:718-24.
15. Wacker-Gußmann A, Bühren K, Schultheiss C, Braun SL, Page S, Saugel B, *et al*. Prediction of contrast-induced nephropathy in patients with serum creatinine levels in the upper normal range by cystatin C: A prospective study in 374 patients. AJR Am J Roentgenol 2014;202:452-8.
16. Rickli H, Benou K, Ammann P, Fehr T, Brunner-La Rocca HP, Petridis H, *et al*. Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media. Clin Nephrol 2004;61:98-102.
17. Jorgensen AL. Contrast-induced nephropathy: Pathophysiology and preventive strategies. Crit Care Nurse 2013;33:37-46.
18. Gu G, Xing H, Zhou Y, Cui W. Inverse correlation between left ventricular end-diastolic pressure and contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. Clin Exp Nephrol 2018;22:808-14.
19. Inker LA, Eckfeldt J, Levey AS, Leiendecker-Foster C, Rynders G, Manzi J, *et al*. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. Am J Kidney Dis 2011;58:682-4.
20. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, *et al*; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20-9.
21. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
22. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, *et al*. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. J Am Coll Cardiol 2004;44:1393-9.
23. Omar M, Abdel-Razek W, Abo-Raia G, Assem M, El-Azab G. Evaluation of serum cystatin C as a marker of early renal impairment in patients with liver cirrhosis. Int J Hepatol 2015;2015:309042.
24. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: Physiological principles. Intensive Care Med 2004;30:33-7.
25. Odden MC, Tager IB, Gansevoort RT, Bakker SJ, Katz R, Fried LF, *et al*. Age and cystatin C in healthy adults: A collaborative study. Nephrol Dial Transplant 2010;25:463-9.
26. Ziegelasch N, Vogel M, Müller E, Tremel N, Jurkutat A, Löffler M, *et al*. Cystatin C serum levels in healthy children are related to age, gender, and pubertal stage. Pediatr Nephrol 2019;34:449-57.
27. Marmarinos A, Garoufi A, Panagoulia A, Dimou S, Drakatos A, Paraskakis I, *et al*. Cystatin-C levels in healthy children and adolescents: Influence of age, gender, body mass index and blood pressure. Clin Biochem 2016;49:150-3.
28. Huang JB, Huang ZG, Deng ZY, Wang L, Jia CY. Association of sex, age, renal function, metabolic index and types of diseases with serum cystatin-C in patients. Sichuan Da Xue Xue Bao Yi Xue Ban 2012;43:888-92.
29. Groesbeck D, Köttgen A, Parekh R, Selvin E, Schwartz GJ, Coresh J, *et al*. Age, gender, and race effects on cystatin C levels in US adolescents. Clin J Am Soc Nephrol 2008;3:1777-85.
30. Takuwa S, Ito Y, Ushijima K, Uchida K. Serum cystatin-C values in children by age and their fluctuation during dehydration. Pediatr Int 2002;44:28-31.
31. Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C--A new marker of glomerular filtration rate in children independent of age and height. Pediatrics 1998;101:875-81.