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Impact of Contrast-Induced Nephropathy and Cardiovascular Events by Serum Cystatin C in Renal Insufficiency Patients Undergoing Cardiac Catheterization

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Abstract

We assessed the usefulness of serum cystatin C for predicting contrast-induced nephropathy (CIN) in patients (n = 100) undergoing coronary catheterization. After a 12-month follow-up, the incidence of CIN was 8.3% (n = 5) in patients with mild renal insufficiency (estimated glomerular filtration rate [eGFR] 60-89 mL/min per 1.73 m^2), 34.4% (n = 10) in those with moderate renal insufficiency (eGFR 30-59 mL/min per 1.73 m^2), and 100% (n = 3) in those with severe renal insufficiency (eGFR 15-29 mL/min per 1.73 m^2). The sensitivity was 81.8% and specificity was 90.9% at the cutoff level of serum cystatin C >1.18 mg/L. Serum cystatin C levels were significantly ($P < .001$) higher in the patients with moderate renal insufficiency in the CIN group than those in the non-CIN group. Multivariate logistic regression analysis demonstrated that baseline serum cystatin C independently predicted short-term mortality (odds ratio [OR], 0.311; 95% confidence interval [CI] 0.058-0.538; $P = .026$). Baseline serum cystatin C significantly predicted the occurrence of CIN in the patients with moderate renal insufficiency.

Keywords

contrast-induced nephropathy, cystatin C, coronary catheterization, estimated glomerular filtration rate

Introduction

Iodinated contrast medium used for coronary angiography and percutaneous coronary intervention (PCI) may cause acute kidney injury (AKI) and contrast-induced nephropathy (CIN).[1] Contrast-induced nephropathy is often a reversible dysfunction, but it can lead to irreversible renal insufficiency in some cases.[2] Contrast-induced nephropathy is one of the adverse effects associated with investigation and treatment of coronary artery disease, which accounts for approximately 10% of renal dysfunction during hospitalization.[1]

McCullough et al investigated the epidemiology of CIN; the incidence of AKI was 14.5%, with 0.7% requiring dialysis; creatinine clearance, diabetes mellitus, and the volume of contrast medium were significant risk factors.[3] One study reported the incidence of CIN ranged from 11% to 44% in patients with moderate chronic kidney disease (CKD).[4] Another study reported the incidence of CIN was 25% in patients with risk factors, such as diabetes mellitus, congestive heart failure, and aging.[5] The pathogenesis of CIN has not been fully elucidated.[6-8]

Renal dysfunction increases the risks of death, requires longer hospital stay, and affects long-term survival and prognosis after PCI.[9,10] Therefore, it is important to prevent CIN. Once CIN occurs, it is highly recommended to provide treatment as early as possible. Therefore, identifying a biomarker to predict the occurrence of CIN will provide early diagnosis and help monitor treatment. Many investigators have reported the usefulness of new markers, such as blood/urinary neutrophil gelatinase-associated lipocalin, blood/urinary cystatin C, urinary liver type fatty acid-binding protein (L-FABP), and urinary kidney injury molecule 1.[11,12] A multicenter clinical trial in patients with CKD demonstrated that the sensitivity of urinary L-FABP was superior to that of other markers.[13]

Serum cystatin C is a nonglycosylated protein with low-molecular mass (13 kDa), which belongs to the cysteine protease inhibitors.[14] Cystatin C is produced in all nucleated cells at constant rate and removed from blood plasma by glomerular filtration. Cystatin C is considered a reliable marker for renal function and glomerular filtration rate (GFR). There is

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a linear relationship between serum cystatin C concentration and GFR; when GFR decreases to 51 to 70 mL/min per 1.73 m^2, serum cystatin C concentration increases.[15] Serum cystatin C is also useful for detecting the early stages of diabetic mellitus and hypertensive nephropathy.[16,17]

We conducted a retrospective study to assess the usefulness of serum cystatin C for predicting the occurrence and early diagnosis of CIN in patients who underwent elective coronary cardiac catheterization. We also investigated the association between baseline serum cystatin C, the severity of renal insufficiency, and prognosis after discharge.

Methods

Participants

This study included 100 consecutive patients who underwent coronary angiography for suspected coronary artery disease at the St Marianna University School of Medicine Hospital between April 2006 and September 2007. The following patients were excluded from this study: patients who did not undergo left ventriculography, underwent bypass radiography or aortography, received Swan-Ganz catheterization, had another examination using contrast medium within the last 7 days before enrollment, those with estimated GFR (eGFR) < 15 mL/min per 1.73 m^2, those who received maintenance dialysis, or those who were infused a large volume of solution before or after examination. Patients with systolic blood pressure (SBP) $\geq$140 mm Hg and/or diastolic blood pressure (DBP) $\geq$85 mm Hg or those treated with antihypertensives were defined as having hypertension. Patients with fasting blood glucose $\geq$126 mg/dL or those under diabetic treatment were defined as having abnormal glucose tolerance. Estimated GFR was calculated according to the modification of diet in renal disease equation for Japanese males: eGFR = 0.741 $\times$ 175 $\times$ age in years$^{-0.203}$ $\times$ serum creatinine$^{-1.154}$; and Japanese females: eGFR female = eGFR $\times$ 0.742.[18] All patients were categorized as follows based on eGFR, according to the CKD Clinical Guide 2009 edited by the Japanese Society of Nephrology[19]: normal, eGFR $\geq$90 mL/min per 1.73 m^2; mild renal insufficiency, 60 $\leq$ eGFR $\leq$ 89 mL/min per 1.73 m^2; moderate renal insufficiency, 30 $\leq$ eGFR $\leq$ 59 mL/min per 1.73 m^2; or severe renal insufficiency, 15 $\leq$eGFR $\leq$ 29 mL/min per 1.73 m^2. The levels of serum cystatin C were compared in each category.

Serum Cystatin C Measurement

Serum cystatin C was measured according to the latex condensation method (Mitsubishi Chemical Medience Co Ltd, Tokyo, Japan). The measurement was performed immediately after blood collection using anti-human cystatin C polyclonal antibodies developed in rabbit and turbidity analysis which was an optical measurement with scattered light. The stabilizing agent was added to the collected blood sample (3.0 μL) which was kept at 37°C for 5minutes; antihuman cystatin C polyclonal antibodies were added. Afterward, the blood sample kept at 37°C was measured after 1 and 5 minutes, respectively, using absorbance at dominant wavelength of 570 nm and subwavelength of 800 nm. In all study participants, interfering substances, such as the serum hemoglobin and bilirubin concentration and turbidity, had no influence on measuring serum cystatin C.

Cardiac Catheterization

Cardiac catheterization was performed at the St Marianna University School of Medicine Yokohama-city Seibu Hospital using a single plane imaging system (Toshiba AREX-NB 300A/DFP-2000A). Extracellular fluid solution was infused at a dose of 1 mL/kg per h at least 4 hours before examination. The Seldinger method was adopted to insert a catheter from the right upper arm; heparin of 3000 units was injected. All patients underwent coronary angiography using a Judkins catheter (Unite, St Jude Medical, Tokyo, Japan) and left ventriculography using a pigtail catheter (Carry, Tokyo, Japan) supported by ACIST power injection system (ACIST Medical systems, Eden Prairie, Minnesota) which consisted of a software-controlled syringe injector, a disposable automated manifold, a disposable hand controller, and a touch screen panel. During left coronary angiography, the flow rate was set at 3 mL/s with the total volume of 6 mL, the rise time of 0.5 seconds, and the pressure limit of 500 psi. During right coronary angiography, the flow rate was set at 2 mL/s with the total volume of 5 mL, the rise time of 0.5 seconds, and the pressure limit of 500 psi. The infusion dose was changed if necessary. During left ventriculography, the flow rate was set at 10 mL/s, with the total volume of 30 mL, the rise time of 0.5 seconds, and the pressure limit of 950 psi. Iopamiron 370 (Nihon Schering, Osaka, Japan) kept at 37°C was used as the contrast medium.

Contrast-Induced Nephropathy

Blood samples were collected before and after cardiac catheterization. Contrast-induced nephropathy was defined as a rise in serum creatinine of 0.5 mg/dL (29.7 μmol/L) or a 25% increase from the baseline values, assessed at 48 hours after the procedure.[9,20,21] All patients were divided into CIN or non-CIN groups. The risk factors for CIN included renal dysfunction, diabetes mellitus, aging, cardiac insufficiency, anemia, excessive volumes of contrast medium, and dehydration, which was assessed before catheterization and at 48 hours, 3 months, 6 months, and 1 year after catheterization. The short-term morbidity and mortality was defined as cardiac death, repeated revascularization, and acute stroke within 1 year after catheterization.

Statistical Analysis

Statview 5.0 software program (SAS Institute Inc, Cary, North Carolina) was used for analysis. All values are expressed as mean $\pm$ SD. The unpaired *t* test was used to compare the mean values of parameters between the 2 groups. Differences

Table 1. Baseline Characteristics of All Patients

	CIN Group n = 18	Non-CIN Group n = 82	*P* Value
Age (years)	68.8 ± 10	65.9 ± 9	.189
Male/Female	18/5	42/35	.107
BMI (kg/m^2)	23.7 ± 2.3	23.2 ± 3.1	.510
Previous history	–	–	■
Hypertension, n (%)	57.9%	49.1%	.144
Diabetes,n (%)	31.5%	32.7%	.214
Old myocardial infarction	47.3%	40.9%	.180
Contrast volume (mL)	114.4 ± 14.1	111.9 ± 19.3	.104
Hb (mg/dL)	13.2 ± 1.7	13.4 ± 1.3	.402
Baseline SCr (mg/dL)	1.08 ± 0.48	0.77 ± 0.15	<.001
Cystatin C (mg/L)	1.18 ± 0.42	0.74 ± 0.11	<.001
eGFR (ml/min per 1.73 m^2)	63.1 ± 18.5	81.7 ± 20.2	.004
LVEF (%)	57.3 ± 17.4	65.9 ± 10.0	.003
BNP (pg/mL)	170.8 ± 238.1	62.8 ± 127.2	.005

Abbreviations: CIN, contrast induced nephropathy; BMI, body mass index; Hb, hemoglobin; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide.

between groups were determined by analysis of variance (ANOVA); Bonferroni correction was used for multiple comparisons. *P* value of less than 5% was considered significant. To set a cutoff level of serum cystatin C at the occurrence of CIN, a receiver operating characteristic (ROC) curve, the sensitivity, and specificity were calculated. Multivariate logistic regression analysis was used to assess the short-term mortality and morbidity.

Results

The baseline clinical characteristics in the CIN and non-CIN groups are shown in Table 1. We found no significant differences in age, gender, underlying diseases, contrast medium volumes, statin medication, or anemia between the 2 groups. Serum creatinine, serum cystatin C, and brain natriuretic peptide (BNP) were significantly higher, whereas eGFR and left ventricular ejection fraction (LVEF) were significantly lower significantly in the CIN group.

The incidence of CIN was 0% in the patients with normal renal function, 8.3% (n = 5) in those with mild renal insufficiency, 34.4% (n = 10) in those with moderate renal insufficiency, and 100% (n = 3) in those with severe renal insufficiency. As eGFR decreased, the incidence of CIN increased (Figure 1).

Figure 2 shows the cutoff level of serum cystatin C. The vertical axis represents sensitivity and the horizontal axis represents specificity. When the cutoff level of serum cystatin C was set at >1.18 mg/L, the sensitivity was 81.8% (95% confidence interval [CI], 0.810-1.064) and the specificity was 90.9% (95%CI, 0.810 – 1.064).

The clinical characteristics of the patients with moderate renal insufficiency in the CIN and non-CIN groups are summarized in Table 2. We found no significant differences in age, underlying diseases, contrast medium volumes, serum creatinine, or prescribed medications before coronary angiography between the 2 groups; however, serum cystatin C was significantly greater in the CIN group.

Table 3 shows the short-term mortality and morbidity. The incidence of repeated revascularization was 7 patients, those of acute stroke was 3 patients, and those of cardiac death was 3 patients. No significant differences were observed in the risk factors for CIN except serum cystatin C.

Discussion

The Occurrence of CIN

The incidence of CIN was 18% according to the definition adopted in this study. Solomon et al[22,23] defined the incidence of CIN when serum creatinine increased by 0.5 mg/dL and more, within 48 hours after contrast medium infusion. They reported the incidence of CIN was 11% in the patients treated with normal saline to prevent CIN. When Solomon's definition was applied to the current study, the incidence of CIN was 12%, which was similar to the result of Solomon et al.[22,23] The risk factors for CIN include renal dysfunction, diabetes mellitus, aging, cardiac insufficiency, anemia, excessive volumes of contrast medium, and dehydration.[24] When renal dysfunction is not included as one of the risk factors for CIN, the incidence of CIN accounts for 1% to 2%; meanwhile, when patients have one of the above risk factors, the incidence of CIN becomes 4% to 12%.[13] One study reported that of the 7586 patients undergoing coronary angiography, 254 (3.3%) developed CIN.[25] The incident of CIN in this study was greater than that in the large population study. In the current study, CIN occurred in 34.4% of the patients with moderate renal insufficiency and 18.0% of all study patients. When patients have eGFR <60 mL/min per 1.73 m^2, kidney toxicity may be reduced using contrast medium <100 mL; thus the minimum volume of contrast medium should be required.[26-29] In this study, patients with eGFR 30 to 59 mL/min per 1.73 m^2 were categorized as having moderate renal insufficiency. These patients probably had a strong expression of kidney toxicity, although, contrast medium ≥100 mL might be injected to some of those who developed CIN (the mean volume of contrast medium was 119.2 ± 12.4 mL). These findings suggest that GFR is an important factor for the development of CIN. Furthermore, in the current study, the patients with moderate renal insufficiency were relatively old (mean age of 74.2 ± 7.4 years); thus, aging along with contrast medium volumes might contribute to the occurrence of CIN.

Usefulness of Cystatin C for Detecting CIN in CKD

Shimizu et al[30] investigated the correlation between serum cystatin C or serum creatinine and creatinine clearance. Serum creatinine significantly increased when creatinine clearance was ≤50 mL/min, which was less than half of normal renal function. Meanwhile, serum cystatin C revealed no significant

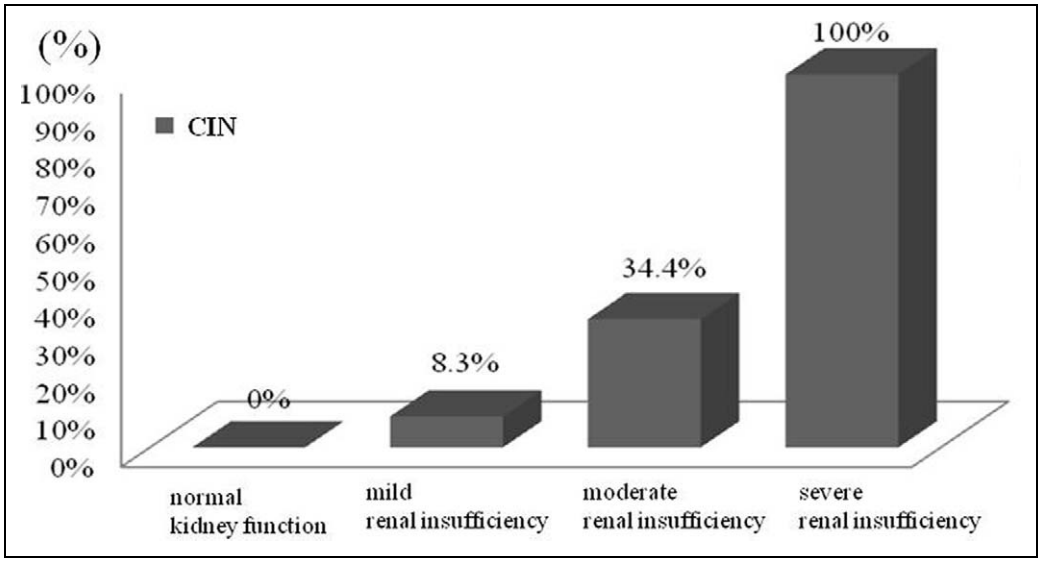

Figure 1. Incidence of contrast-induced nephropathy (CIN). The incidence of CIN was compared in the patients categorized as follows based on estimated glomerular filtration rate (eGFR): normal, eGFR $\geq$90 mL/min per 1.73 m^2; mild renal insufficiency, 60 $\leq$ eGFR $\leq$ 89 mL/min per 1.73 m^2; moderate renal insufficiency, 30 $\leq$ eGFR $\leq$ 59 mL/min per 1.73 m^2; or severe renal insufficiency, 15 $\leq$ eGFR $\leq$ 29 mL/min per 1.73 m^2. The incidence of CIN was 0% in the patients with normal renal function, 3.3% (n = 5) in those with mild renal insufficiency, 34.4% (n = 10) in those with moderate renal insufficiency, and 100% (n = 3) in those with severe renal insufficiency. As eGFR decreased, the incidence of CIN increased.

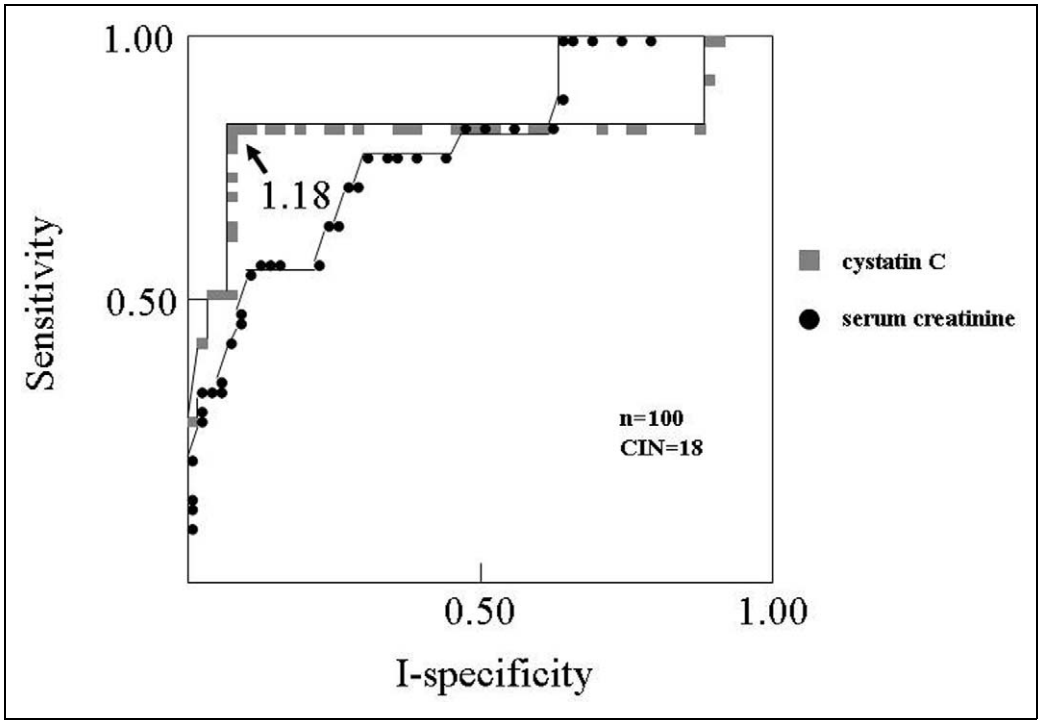

Figure 2. The cutoff level of cystatin C. The vertical axis represents sensitivity and the horizontal axis represents specificity. When the cutoff level of serum cystatin C was set at >1.18 mg/L, the sensitivity was 81.8% (95% confidence interval, 0.810 - 1.064) and the specificity was 90.9%.

changes when creatinine clearance ranged from 71 to 90 mL/min; serum cystatin C significantly increased when creatinine clearance was $\leq$70 mL/min. This is why serum cystatin C has difficulty in detecting early renal impairment. Serum cystatin C is more sensitive in detecting decreased renal function in the early stage than serum creatinine. Macisaac et al[31] conducted a study on 251 diabetic patients and found the accuracy of cystatin C $\geq$1.10 mg/L for detecting CKD (eGFR <60 mL/min

Table 2. Baseline Characteristics of the Patients With Moderate Renal insufficiency

	CIN Group n = 10	Non-CIN Group n = 19	*P* Value
Age (years)	74.2 ± 7.4	72.9 ± 6.7	.635
Male/female	7/3	5/14	.079
BMI (kg/m^2)	24.3 ± 2.5	22.5 ± 3.0	.116
Previous history	–	–	–
Hypertension, n (%)	57.9%	49.1%	.144
Diabetes, n (%)	31.5%	32.7%	.214
Old myocardial infarction	47.3%	40.9%	.180
CHF hospitalization	7.1%	2.6%	.269
Contrast volume (mL)	119.2 ± 12.4	113.9 + 11.4	.372
Hb (mg/dL)	13.3 ± 1.0	12.9± 1.1	.142
Baseline SCr (mg/dL)	1.12 ± 0.19	0.98 ± 0.28	.074
Cystatin C (mg/L)	1.26 ± 0.18	0.78 ± 0.12	<.001
LVEF (%)	66.0 ± 10.8	66.5 ± 11.7	.907
Previous therapy	–	–	–
ACEI, n (%)	30.0%	26.3%	.455
Angiotensin-receptor blocker, n (%)	30.0%	31.5%	.724
β-blocker, n (%)	20.0%	21.1%	.811
Calcium-channel blocker, n (%)	40.0%	42.1%	.787
Diuretics, n (%)	40.0%	10.5%	.121
Statin, n (%)	50.0%	31.5%	.298

Abbreviations: CIN, contrast induced nephropathy; BMI, body mass index; Hb, hemoglobin; SCr, serum creatinine; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; ACEI, angiotensin-converting enzyme inhibitor.

per 1.73 m^2). In the current study, the sensitivity and the specificity increased when the cutoff level of cystatin C was set at ≥1.18 mg/L, which could possibly predict the occurrence of CIN. The mean baseline serum cystatin C was 1.26 mg/L in the patients with moderate renal insufficiency in the CIN group, which was relatively high. Baseline serum cystatin C, rather than eGFR or serum creatinine, strongly predicted the occurrence of CIN in the patients with moderate renal insufficiency. It has been reported that patients with normal serum cystatin C account for 0% and those with normal serum creatinine account for 17% in the CKD stage 3, according to the definition described by the Japanese Society of Nephrology.[32,33] Accordingly, serum cystatin C probably indicates an expression of kidney toxicity caused by contrast medium and predicts early renal impairment.

Predictors of Cardiovascular Events

Multivariate logistic regression analysis showed that only serum cystatin C could predict short-term mortality and morbidity, in the patients who developed CIN. Renal dysfunction is associated with an increase in the mortality and longer hospital stay.[33] Some studies reported the influence of renal dysfunction on the survival rate and long-term prognosis after PCI.[22,34,35] Other studies investigated the association between serum cystatin C and total death, cardiovascular death, or the onset of cardiovascular events in elderly patients >65 years and demonstrated the subsequent overall mortality increased as the levels of serum cystatin C increased.[36,37] Death from myocardial infarction or cerebral accidents and the risks of cardiovascular death significantly increased in patients with serum cystatin C ≥1.29 mg/L compared with those with serum cystatin C ≤0.99 mg/L, whereas no association was found between serum creatinine and mortality in these patients.[22,38,39] Therefore, we conclude that baseline serum cystatin C could be a predictor of cardiovascular events in patients developing CIN.

Table 3. Variables Related to Short-Term Mortality Based on the Multivariate Logistic Regression Analysis[a]

	Odds Ratio	95% CI	*P* Value
Age (years)	0.902	0.265-1.763	.087
Gender (male)	2.175	0.344-8.763	.409
Previous history	–	–	–
Hypertension, n (%)	0.804	0.103-6.003	.832
Diabetes, n (%)	0.279	0.024 - 3.240	.308
Old myocardial infarction	2.722	0.844-7.676	.370
Contrast volume (mL)	0.754	0.589-1.403	.081
Hb (mg/dL)	2.304	1.272-9.003	.882
Baseline SCr (mg/dL)	0.604	0.243-1.412	.078
Cystatin C (mg/L)	0.311	0.058-0.538	.026
LVEF (%)	0.781	0.480-4.879	.219

Abbreviations: CI, confidence interval; Hb, hemoglobin; LVEF, left ventricular ejection fraction; SCr, serum creatinine.
[a] Mortality: cardiac death, repeated revascularization, and acute stroke for 12 months after cardiac catheterization.

Study Limitations

The number of patients was small and they were relatively old. Therefore, the outcome was applicable to a limited group of patients. The follow-up period of this study was 1 year. Further studies with a large population and a longer follow-up period should be required to assess the values of cystatin C in predicting CIN.

Conclusions

Baseline serum cystatin C significantly predicted the occurrence of CIN in the moderate renal insufficiency patients undergoing coronary angiography. Baseline serum cystatin C was also a predictor for cardiac events after the occurrence of CIN.

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Declaration of Conflicting Interests

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References

1. Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation*. 2006;113(14): 1799-1806.
2. Cronin RE. Contrast-induced nephropathy: pathogenesis and prevention. *Pediatr Nephrol*. 2010;25(2):191-204.
3. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med*. 2003;4(suppl 5):S3-S9.
4. Briguori C, Airoldi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115(10):1211-1217.
5. Ghani AA, Tohamy KY. Risk score for contrast induced nephropathy following percutaneous coronary intervention. *Saudi J Kidney Dis Transpl*. 2009;20(2):240-245.
6. McCullough PA, Adam A, Becker CR, et al. Risk prediction of contrast-induced nephropathy. *Am J Cardiol*. 2006;98(6A): 27K-36K.
7. Finn WF. The clinical and renal consequences of contrast-induced nephropathy. *Nephrol Dial Transplant*. 2006;21(6):i2-i10.
8. Nikolsky E, Mehran R, Lasic Z, et al. Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. *Kidney Int*. 2005;67(2):706-713.
9. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol*. 2008;51(15):1419-1428.
10. Mueller-Lenke N, Buerkle G, Klima T, et al. Incidence of contrast-induced nephropathy with volume supplementation–insights from a large cohort. *Med Princ Pract*. 2008;17(5):409-414.
11. Kato K, Sato N, Yamamoto T, Iwasaki YK, Tanaka K, Mizuno K. Valuable markers for contrast-induced nephropathy in patients undergoing cardiac catheterization. *Circ J*. 2008;72(9):1499-1505.
12. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, et al. NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C: are they good predictors of contrast nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine? *Int J Cardiol*. 2008; 127(2):290-291.
13. Mehran R, Aymong ED, Nikolsky E, 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(7):1393-1399.
14. Shlipak MG, Ix JH, Bibbins-Domingo K, et al. Biomarkers to predict recurrent cardiovascular disease: the Heart and Soul Study. *Am J Med*. 2008;121(1):50-57.
15. Benohr P, Grenz A, Hartmann JT, Müller GA, Blaschke S. Cystatin C–a marker for assessment of the glomerular filtration rate in patients with cisplatin chemotherapy. *Kidney Blood Press Res*. 2006;29(1):32-35.
16. Fehr T, Rickli H. Reply to Sjostrom et al. Cystatin C and creatinine for assessment of kidney function: differences in pharmacokinetics–and more. *Clin Nephrol*. 2004;62(4):327-328.
17. Rickli H, Benou K, Ammann P, et al. Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media. *Clin Nephrol*. 2004;61(12):98-102.
18. Imai E. [Equation for estimating GFR from creatinine in Japan]. *Nippon Rinsho*. 2008;66(9):1725-1729.
19. Matsuo S. CKD (chronic kidney disease) [in Japanese]. *Nippon Jinzo Gakkai Shi*. 2007;suppl 50th Ann:67-72.
20. Toprak O. What is the best definition of contrast-induced nephropathy? *Ren Fail*. 2007;29(3):387-388.
21. Jabara R, Gadesam RR, Pendyala LK, et al. Impact of the definition utilized on the rate of contrast-induced nephropathy in percutaneous coronary intervention. *Am J Cardiol*. 2009; 103(12):1657-1662.
22. Solomon RJ, Mehran R, Natarajan MK, et al. Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol*. 2009;4(7):1162-1169.
23. Solomon RJ, Natarajan MK, Doucet S, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation*. 2007;115(25):3189-3196.
24. Senoo T, Motohiro M, Kamihata H, et al. Contrast-induced nephropathy in patients undergoing emergency percutaneous coronary intervention for acute coronary syndrome. *Am J Cardiol*. 2010;105(5):624-628.
25. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105(19):2259-2264.
26. McCullough PA, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol*. 2006;48(4):692-699.
27. Dangas G, Iakovou I, Nikolsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol*. 2005;95(1):13-19.
28. Iakovou I, Dangas G, Mehran R, et al. Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. *J Invasive Cardiol*. 2003; 15(1):18-22.
29. Marenzi G. Can contrast-induced nephropathy after percutaneous coronary intervention be accurately predicted with a risk score? *Nat Clin Pract Cardiovasc Med*. 2005;2(2):80-81.
30. Shimizu A, Horikoshi S, Rinnno H, Kobata M, Saito K, Tomino Y, et al. Serum cystatin C may predict the early prognostic stages of patients with type 2 diabetic nephropathy. *J Clin Lab Anal*. 2003;17(5):164-167.
31. Macisaac RJ, Tsalamandris C, Thomas MC, et al. The accuracy of cystatin C and commonly used creatinine-based methods for detecting moderate and mild chronic kidney disease in diabetes. *Diabet Med*. 2007;24(4):443-448.
32. Sato H, Kazama JJ, Kuroda T, Narita I, Nakano M, Gejyo F. Serum cystatin C measured by a sol particle homogeneous immunoassay can accurately detect early impairment of renal function. *Clin Exp Nephrol*. 2008;12(4):270-276.
33. Toso A, Maioli M, Leoncini M, et al. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. *Am J Cardiol*. 2010;105(3):288-292.

34. Tamba K, Kusano E, Ando Y, Asano Y. [Prospective evaluation of renal function by serum cystatin-C: comparison with three other parameters of glomerular filtration rate]. *Nippon Jinzo Gakkai Shi*. 2001;43(8):646-650.
35. Niccoli G, Conte M, Della Bona R, et al. Cystatin C is associated with an increased coronary atherosclerotic burden and a stable plaque phenotype in patients with ischemic heart disease and normal glomerular filtration rate. *Atherosclerosis*. 2008;198(2):373-380.
36. Larsson A, Helmersson J, Hansson LO, Basu S. Serum cystatin C is associated with other cardiovascular risk markers and cardiovascular disease in elderly men. *Int J Cardiol*. 2008; 125(2):263-264.
37. Shlipak MG, Katz R, Cushman M, et al. Cystatin-C and inflammatory markers in the ambulatory elderly. *Am J Med*. 2005; 118(12):1416.
38. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, et al. Could neutrophil-gelatinase-associated lipocalin and cystatin C predict the development of contrast-induced nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine values? *Kidney Blood Press Res*. 2007;30(6):408-415.
39. Gambaro G, Graziani MS, Ribichini F. Cystatin C and contrast-induced nephropathy. *Nephrol Dial Transplant*. 2008;23(12): 4079-4080.