Singapore Med J 2012; 53(3) : 164

Risk scoring system for prediction of contrast-induced nephropathy in patients with pre-existing renal impairment undergoing percutaneous coronary intervention

Chong E[1,2,3], MRCP, FAMS, *Shen L*[2], PhD, *Poh KK*[2,3], MRCP, FAMS, *Tan HC*[3], FRCP, FAMS

INTRODUCTION Baseline renal impairment is the most recognised risk factor for development of contrast-induced nephropathy (CIN) post percutaneous coronary intervention (PCI). We examined the additional risk factors in this high-risk group and aimed to develop a risk model for prediction of CIN.

METHODS A cohort of 770 consecutive patients with existing impaired renal function (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2), who received routine prophylactic saline hydration and oral N-acetylcysteine treatment while undergoing PCI between May 2005 to October 2008 in our centre, were enrolled. The study endpoint, CIN, was defined as > 25% increase from baseline creatinine within 48 hours post PCI.

RESULTS Despite routine prophylaxis, CIN occurred in 11.4% of the patients. Important clinical predictors for CIN were age (odds ratio [OR] 1.59, 95% confidence level [CI] 1.0–2.52, p = 0.049), anaemia with haemoglobin < 11 mg/dL (OR 2.26, 95% CI 1.41–3.61, p = 0.001), post-procedure creatinine kinase rise (OR 1.12, 95% CI 1.07–1.16 for every 500 u/L increase, p < 0.001), systolic hypotension with blood pressure < 100 mmHg (OR 2.53, 95% CI 1.16 –5.52, p = 0.016) and higher contrast volume. The incidence of CIN was significantly higher in patients with more severe renal failure (6.3%, 17.4% and 40.8% when eGFR was 40–60, 20–40 and < 20 ml/min/1.73m^2 respectively, p < 0.001). A prediction model was developed based on these findings. The incidence of CIN could vary from 2% to > 50% depending on these additional risk profiles.

CONCLUSION Patients with impaired renal function undergoing PCI are at high risk of developing CIN despite traditional prophylaxis. A model of risk prediction could be used to predict its occurrence.

Keywords: contrast-induced nephropathy, renal impairment, risk score
Singapore Med J 2012; 53(3): 164–169

INTRODUCTION

Contrast-induced nephropathy (CIN) is an important and common complication post percutaneous coronary intervention (PCI).[1] The most recognised risk factor for development of CIN is baseline renal impairment.[2] Despite prophylaxis with saline hydration and oral N-acetylcysteine (NAC) at our institution, the risk of developing CIN in renal-impaired patients undergoing PCI can still be high. Additional risk factors play a part in the causation of CIN and hence, more aggressive prophylactic treatment pre-PCI and monitoring post-PCI may be required. Our study examined the additional CIN risk factors in renal-impaired patients and aimed to develop a simple risk model for prediction of CIN by elucidating the more important risk factors. By such means, a subgroup of patients with the highest risk could be idenfified so that they could receive additional prophylactic therapy and attention.

METHODS

This was a retrospective cohort study using the cardiac database from a university hospital cardiac centre. A cohort of 770 consecutive patients with existing renal impairment (defined using estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 prior to PCI), who received prophylactic saline hydration and oral NAC treatment and underwent non-emergency PCI between May 2005 to October 2008 in our centre, were enrolled. Patients with end-stage renal failure who were undergoing renal dialysis were excluded. Patient who had a recent contrast-related procedure, such as coronary angiogram and computed tomography (CT) with contrast within two weeks prior to the index PCI, were also excluded from the study, as recent contrast load may have potential confounding and additive effect on the development of CIN. In addition, all patients who were included in the study had only one PCI procedure, and there was no repeat recruitment of the same patient during the study period. The study was approved by the ethics committee of our institution. The study endpoint, CIN, was defined as > 25% or 0.5 mg/dL increase from baseline creatinine (Cr) within 48 hours post PCI.

Patients with significant baseline renal impairment, defined as eGFR < 60 ml/min/1.73m^2 using the abbreviated Modification of Diet in Renal Disease (MDRD) formula, would receive normally 6–12 hours of 0.9% normal saline pre-hydration and oral NAC at 1.2 g bid dosage for two days. For elective PCI, patients with renal impairment would be admitted one day prior to the procedure and pre-hydration would start at 10 pm. In acute coronary syndrome

[1]Alexandra Hospital, Singapore, [2]Yong Loo Lin School of Medicine, [3]Cardiac Department, National University Heart Centre, National University of Singapore, Singapore
Correspondence: Dr Eric Chong, Cardiologist, Alexandra Hospital, Jurong General Health, 378 Alexandra Road, Singapore 159964. ericchong80@hotmail.com

cases, where more urgent coronary angioplasty procedure was planned on the same day, pre-hydration would start as soon as the decision for invasive strategy was made. Saline hydration would continue to about 12 hours post-PCI, unless the patient developed pulmonary congestion or signs of significant fluid overload.

The eGFR was calculated by using the abbreviated MDRD formula, in which the patient's age, race, gender and serum Cr were used.[3] The racial distribution of our cohort consisted mainly of Asians. We examined the occurrence of CIN and identified the incidence and risk predictors in this group. In addition, we performed subgroup analysis by dividing the patients into three subgroups according to the eGFR range (40–60, 20–40 and < 20 ml/min/1.73 m^2) These subgroup ranges were chosen based on Dr Mehran's CIN risk score system, where the same subclassifications were used for the eGFR groups.[4] Prior to PCI, metformin was routinely withheld. The use of angiotensin-converting enzyme inhibitors, platelet glycoprotein IIb/IIIa inhibitors and diuretics, as well as indications for intra-aortic balloon pump (IABP) or inotropic drugs support, was left to the discretion of the interventional cardiologists in accordance with guidelines.[5,6]

A total of 770 patients were enrolled. Patients' data was extracted from the institution's cardiac database, which was designed and maintained by a dedicated group of doctors and database technologists. It was prospectively designed and included the patient's baseline clinical data and procedural details. The interventional cardiologists entered the data into pre-designed data templates. Blood parameters at baseline and after PCI were entered by independent research nurses who were not aware of the purpose of the study. Echocardiogram evaluation was performed for patients during hospitalisation or within a few weeks before or after discharge.

It was our cardiology unit's policy that all patients undergoing PCI would have full blood count and renal panel tested within two weeks prior to PCI. The patients would be kept overnight as inpatients, and post-PCI renal panel and cardiac enzymes were routinely measured for patients with baseline renal impairment. Patients who developed further elevation of Cr would be kept in hospital for a longer time, with daily Cr measured until renal dysfunction had resolved or improved. For more urgent PCI cases, baseline serum Cr would be taken at the Emergency Department. Complications and mortality that occurred during hospitalisation were documented by the cardiologists in charge. Morbidity and mortality at one month and six months post discharge were assessed by independent research nurses via clinical appointments and telephone calls.

PCI was performed according to standard clinical guidelines.[7] Our cardiology unit offered 24-hour PCI service. A low osmolality, low ionic contrast agent Iohexol (Omnipaque®, GE Healthcare Inc, San Diego, CA, USA) was used. Angioplasty technique and the use of adjunctive pharmacologic therapies were left to the discretion of the interventional cardiologists. All patients received loading and maintenance doses of dual antiplatelets according to concurrent guidelines.[7] The rationale for excluding patients who had only diagnostic coronary angiogram was that the contrast volume used (average of 30–40 ml) during the procedure alone was too low for meaningful correlation to development of CIN. Based on the published data, CIN is likely to occur at higher contrast volumes of > 100 ml. When > 5 ml/kg body weight contrast is used, the incidence of CIN could be significantly increased.[8] A ratio of contrast volume to eGFR > 3.7 has also been shown to increase CIN significantly, and hence, could be used for contrast volume limit calculation prior to PCI.[9]

CIN was defined as > 25% or 0.5 mg/dL increase from baseline Cr within 48 hours after PCI.[10] If more than one post-PCI Cr were measured, the highest value was used for the calculation. Anaemia was defined as serum haemoglobin (Hb) < 11 g/dL. Renal impairment was defined as baseline eGFR < 60 ml/min/1.73 m^2. Hypotension was defined as systolic blood pressure < 100 mmHg by aortic opening pressure during angiogram and PCI. Pre-specified clinical, laboratory and procedural information was obtained from the case notes by the independent research nurses who were unaware of the objectives of the study. Data was entered prospectively into the database.

Continuous data was reported as mean value ± standard deviation (SD), unless otherwise specified. Categorical data was presented as absolute values and percentages. Comparison of continuous variables was performed by student's *t*-test. Chi-square and Fisher's exact tests were performed for comparison of categorical variables as appropriate. Multivariate analysis was performed with an enter model, including variables of age, gender, myocardial infarction (MI), renal impairment, diabetes mellitus, cardiac enzymes level, contrast volume and left ventricular ejection fraction (LVEF). A p-value < 0.05 was considered statistically significant. Analysis was conducted using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA). The risk score development dataset was initially used for identifying univariate associations between baseline clinical and PCI characteristics and development of CIN. Multivariate logistic regression analysis was then performed to identify independent predictors of CIN and to estimate odds ratios (ORs). All 770 patients screened were included into the validation dataset.

Risk factors that were significant in the univariate analysis were available for selection in the final model; a bootstrap method was used to select the best subset of risk factors to avoid overfitting the data. A total of 50 bootstrap samples were selected from the development dataset, including all patients with available Cr pre- and post-PCI and documented record for clinical follow-up. For each sample, a stepwise selection procedure was used to select the independent predictors of CIN. Variables that were selected in at least 90% of the bootstrap models were included in the final multivariate models. The regression models created account for the eGFR. The variables in each of the final models with p < 0.001 were assigned a weighted integer coefficient value. For this purpose, the estimated ORs from the logistic model were used, giving an integer of 1 to each 0.5 value of OR; the integer of 1 was

Table I. Baseline characteristics (n = 770).

Baseline characteristic	% patients
Median age; range (yrs)	65; 25–90
> 70 yrs	28.6
Male gender	65.8
Smoker	42.8
Hypertension	77.0
Diabetes mellitus	45.9
Hyperlipidaemia	71.7
Anaemia (Hb < 11 g/dL)	22.9
Hypotension with aortic systolic BP < 100 mmHg	6.1
Acute coronary syndrome	27.1
Median CK; range (U/L)	118; 40–2,070
LVEF ± SD (%)	48 ± 14.6
Contrast volume ± SD (ml)	192 ± 84

Hb: haemoglobin; BP: blood pressure; CK: creatinine kinase; LVEF: left ventricular ejection fraction; SD: standard deviation

Table II. Clinical predictors of contrast-induced nephropathy.

Predictor	OR; 95% CI	p-value
Age > 70 yrs	2.65; 1.37–5.13	0.004
Baseline renal impairment (ml/min/1.73 m^2)		
40–60	1	< 0.0005
20–40	3.79; 1.68–8.54	
< 20	37.25; 16.46–84.26	
Post-PCI CK rise (for every 500 U/L increase)	1.23; 1.15–1.32	< 0.0005
Contrast volume (for every 50 ml use)	1.34; 1.14–1.62	0.002

OR: odds ratio; CI: confidence interval; PCI: percutaneous coronary intervention; CK: creatinine kinase

given for each 100 ml increment in contrast media administered during the procedure. The final risk score represented the sum of integer coefficients. The risk score was tested in the validation dataset.

RESULTS

The racial distribution in our cohort consisted of mainly Asians, with 61.8% Chinese, 21.8% Malay, 10.1% Indians and 6.3% other races. Baseline clinical characteristics of the renal-impaired group are listed in Table I. 65% were male, and this cohort had a high prevalence of diabetes mellitus (46%). 23% of patients were anaemic with Hb < 11g/dL. 27% presented with acute coronary syndrome, and the mean contrast volume used was approximately 200 ml. 66.2% of the patients had their highest Cr ascertained on Day 2 (i.e. at approximately 24 hours post-PCI), while 33.8% of patients had their highest Cr ascertained on Day 3 (i.e. at approximately 48 hours post-PCI). 50.4% of all PCIs were elective and planned, while 49.6% were ad hoc cases. 87.1% and 75.5% of the patients had their vital status ascertained at one and six months post-PCI, respectively, via clinical follow-up and case notes documentations.

Despite routine saline and NAC prophylaxis, CIN occurred in 11.4% of the patients. Multivariate tests were performed using a number of important risk predictors based on Mehran's risk

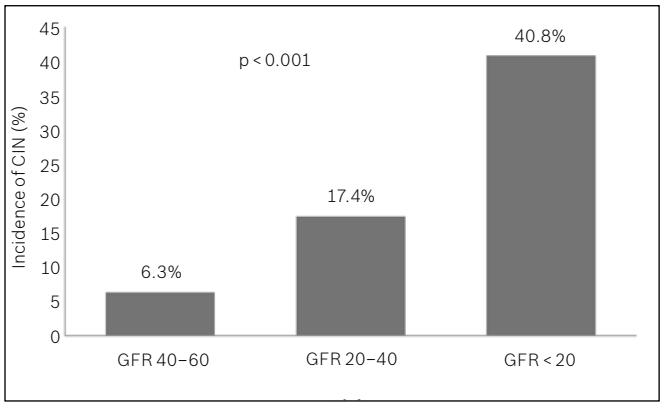

Fig. 1. Graph shows the incidence of contrast-induced nephropathy (CIN) in each of the three eGFR groups. CIN increased with worsening of renal function.

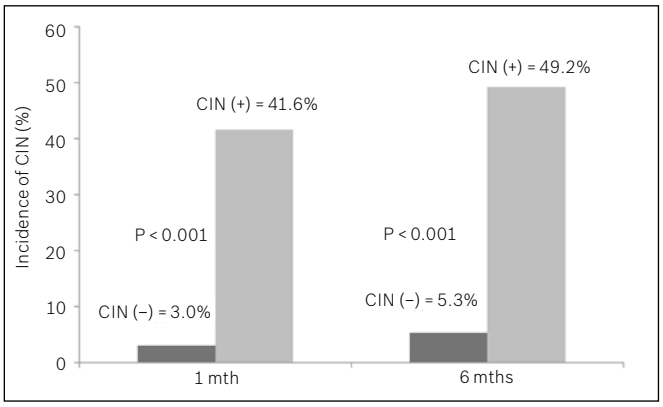

Fig. 2. Correlation between contrast-induced nephropathy (CIN) and mortality at one and six months. This suggested that the development of CIN in renal-impaired patients leads to higher mortality in the short term.

prediction scoring system. The significant predictors in Merhan's risk score system were the degree of renal impairment based on the three eGFR ranges, old age, hypotension, diabetes mellitus, contrast volume and anaemia. We did not include IABP use, as the number of patients on IABP in our study was low.

Univariate tests showed that the clinical predictors for CIN were old age (OR 1.59, 95% confidence interval [CI] 1.0–2.52, p = 0.049), anaemia with Hb < 11 mg/dL (OR 2.26, 95% CI 1.41–3.61, p = 0.001), post-procedure creatinine kinase (CK) rise (OR 1.12, 95% CI 1.07–1.16 for every 500 u/L increase, p < 0.001), systolic hypotension with blood pressure < 100 mmHg (OR 2.53, 95% CI 1.16–5.52, p = 0.016) and higher contrast volume use (200 ml in CIN[+] patients vs. 170 ml in CIN[–] patients, p = 0.032). The incidence of CIN was significantly higher in patients with existing severe renal failure (6.3%, 17.4% and 40.8% in groups with eGFR of 40–60, 20–40 and < 20 ml/min/1.73 m^2, respectively, p < 0.001). Diabetes mellitus was, however, not significantly correlated with the incidence of CIN in our renal-impaired cohort.

Table II showed the various risk predictors for CIN after multivariate analysis, adjusting for potential confounding factors, including age, gender, LVEF, diabetes mellitus, hypertension, cardiac enzymes, anaemia, hypotension, baseline renal function, contrast volume and indications for PCI. The four most important risk factors were old age (> 70 years), rise in CK level

post-PCI, higher contrast load and greater severity of baseline renal impairment.

Fig. 1 shows the incidence of CIN in each of the three eGFR groups. CIN is found to increase with worsening renal function. Fig. 2 shows the correlation between CIN and mortality at short term of one and six months. This suggests that the development of CIN in renal-impaired patient leads to higher mortality at a short-term. Table III shows the risk prediction score for occurrence of CIN. Each of the significant risk factors was given a numerical score from 1 to 8. Predicted incidence of CIN was stratified according to the risk of occurrence from low to extremely high (2%–57%).

Table III. Risk scoring for CIN after saline and N-acetylcysteine prophylaxis.

Predictor	Assigned score
Age > 70 yrs	2
eGFR (ml/min/1.73 m^2)	
40–60	2
20–40	4
< 20	6
Post-PCI CK (for every 500 U/L increase)	1
Contrast volume (for every 100 ml increase)	1

Score 1–3: low risk; 2% incidence of CIN
Score 4–6: moderate risk; 12.4% incidence of CIN
Score 7–8: high risk; 35.0% incidence of CIN
Score ≥ 9: extremely high risk; 57.4% incidence of CIN
CIN: contrast-induced nephropathy; eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention; CK: creatinine kinase

DISCUSSION

CIN is a common and important risk during PCI, and is a cause for concern among interventionists.[11] Patients with renal impairment (commonly an eGFR of 60 ml/min/1.73 m^2 was used as a cut-off point) are subject to this risk, and routine counselling on worsening renal function and potential dialysis would be given to these patients prior to consent for PCI. Most institutions would suggest a prophylactic protocol, including saline hydration, oral NAC and minimisation of contrast use. Despite these routine/standard strategies, CIN still occurs frequently in patients with baseline renal impairment. Many of these patients develop CIN and progress to renal deterioration rapidly post-PCI. Hence, it would be useful to further stratify the renal-impaired cohort into subgroups with different CIN risks and consider offering an even more aggressive preventive strategy in the subgroup with higher or multiple CIN risks. A risk prediction model using a simple scoring system would be helpful and objective.

Our study examined the incidence of CIN among consecutive renal-impaired patients undergoing PCI in a non-emergency setting. These patients had fairly adequate time to receive pre-hydration and oral NAC as standard prophylaxis in our institution. The corresponding mortality rates in these patients were also documented at one and six months. The overall incidence of CIN was 11.4%, and this was consistent with other published data involving renal-impaired patients.[12] Statistical analysis showed that the four most predictive risk factors for CIN in our cohort were old age, low eGFR (especially when eGFR drops below 20 ml/min/1.73 m^2), post-PCI rise in CK and contrast volume use. The mean contrast volume used was 200 ml in the CIN (+) group compared to 170 ml in the CIN (–) group ($p < 0.001$). The CIN (+) group showed a contrast volume/eGFR ratio of 4.0 vs. that of 3.3 in the CIN (–) group. This finding corresponds to the reference cut-off ratio of 3.7.[9] Hence, it would be prudent to keep a close surveillance on the usage of contrast and try to minimise the contrast volume. The calculated contrast volume cut-off using the contrast volume/eGFR ratio of 3.7 would be useful. The radiographer in charge could warn the interventional cardiologist to stop once the contrast limit is being approached.

In our institution, several strategies have been employed to reduce contrast usage. Firstly, a biplane fluoroscopy system is used instead of a single plane system. This potentially reduces contrast volume by nearly half, as each injection could produce two cine images instead of one. The injected contrast is diluted with saline (half contrast and half saline); this could further reduce the total contrast by half. Fluoroscopy images are saved instead of using repeated cine images; hence, repeat contrast injection for cine documentation is avoided. Route mapping should be used prior to coronary wiring; minimal contrast would be needed during wiring of the target vessel when route mapping is followed. In patients with multi-vessel disease, a staged PCI approach should be adopted. The most significant lesion is treated first, and the remaining lesions are treated as a staged procedure at least four weeks later and when Cr has returned to baseline. A contrast limit to call stop the PCI procedure would benefit the patients. More experienced operators should preferably perform PCI in renal-impaired patients, as PCI could be performed more speedily and complications minimised in experienced hands.

PCI-induced MI and CK rise could negatively affect renal function. This has been suggested in a previous study.[13] A combination of factors during MI could impair renal blood flow and renal tubule oxygenation. These include systolic hypotension, renal hypoperfusion and renal ischaemia. A cascade of events could be generated, leading to free oxygen radical production, renal vasoconstriction and endothelial activation, ultimately causing further damage to the kidney.[14] Hence, careful patient selection and prior planning would be important in this cohort in order to prevent post-procedural MI resulting from complications such as jailing of side branches and no-flow phenomenon. In addition, prolonged procedure time should best be avoided. It may be circular to say that our model could be used to predict CIN when pre-PCI CK is also elevated. This is because pre-PCI CK can be correlated with post-PCI CK, particularly in MI patients when the CK level has been elevated even prior to PCI.

Our study predicted a high CIN risk of over 35% when the score was 7. An elderly patient over 70 years of age with eGFR < 20 ml/min/1.73 m^2 automatically reaches a score of 8. Alternately, a patient with eGFR < 20 ml/min/1.73 m^2 who receives a contrast volume of more than 100 ml would have a score of

more than 7. Hence, the risk of CIN in such patients would be high despite standard prophylaxis. With the aging population in our society and the increasing prevalence of diabetes mellitus patients with co existing nephropathy, patients with a high CIN score undergoing PCI would become more common. We suggest a more comprehensive CIN prophylaxis regime in these high-risk patients. Studies have shown that diluted sodium bicarbonate infusion was safe and beneficial in high-risk patients.[15] Other studies had shown evidence that using high-dose oral vitamin C and intravenous infusion of NAC instead of oral NAC can further prevent CIN.[16,17] These therapies carry very few side effects and are less costly, and hence, worth consideration. In patients with high risk scores, prophylactic renal haemo-filtration could also be beneficial.[18]

Our study has shown that the development of CIN increased mortality in the short term (Fig. 2). This correlation has already been shown in previous studies.[19] The difference in mortality between CIN (+) and CIN (–) patients with known underlying chronic renal impairment was striking. In studies involving patients without baseline renal impairment, the development of CIN had marginal impact on mortality,[20] whereas in patients with known chronic renal impairment, it was strongly correlated with mortality.[21] Hence, it is of utmost importance to prevent the occurrence of CIN in this high-risk cohort.

Lastly, we would like to point out that other CIN risk predictors from studies involving 'all-comer' patients had demonstrated that female gender, diabetes mellitus, presence of anaemia, hypotension, cardiogenic shock, use of IABP and depressed LVEF could adversely affect renal function and increase the risk of CIN, morbidity and mortality.[22,23] These studies include large cohorts of patients with both normal and impaired baseline renal functions. However, in our cohort, which comprised only renal-impaired patients, we found four most significant risk factors for developing CIN. This simple risk score model could be used to further stratify patients with renal impairment and alert the interventional cardiologist prior to PCI. In addition, the high-risk predictability model could also be used to ration healthcare, thus avoiding PCI in patients with extremely high risk of CIN. One example would be an elderly patient with very low eGFR.

The major limitation of the study is the retrospective nature of the cohort analysis. There was no record of peri-procedural hydration volume, presence of proteinuria and urine output. The data collection and analysis would be ideal in a randomised controlled setting. However, our study consisted of a reasonably large number of patients, and thus, a randomised study of this scale would be time-consuming and costly. Although the analysis was retrospective, the data were collected prospectively by independent observers. Diabetes mellitus and low LVEF were not found to be risk factors for CIN in this cohort possibly due to a lower number of such patients studied. In other studies involving 'all-comer' patients, regardless of baseline renal function, both diabetes mellitus and heart failure have been proven to be risk factors for CIN.[24,25] The mean LVEF in our cohort was 48%, which was not considered very low. This suggests that patients with very low LVEF could be underrepresented in our cohort, and hence could explain why low LVEF did not stand out as a significant scoring predictor in our study.

In conclusion, patients with impaired renal function undergoing PCI are at high risk of developing CIN despite traditional prophylaxis. A model of risk prediction could be used to predict its occurrence. Saline and oral NAC prophylaxis in our cohort were less effective in preventing CIN among renal-impaired patients with a risk score > 4, resulting in a 12%– 57% risk of developing CIN depending on concomitant risk factors. Additional CIN prophylactic therapy may prove useful in patients at higher risk. Old age, post PCI MI and eGFR < 40 ml/min/1.73 m^2 were the most significant high-risk features in our cohort. Patients who developed CIN had a higher mortality rate at one and six months. A lower contrast volume threshold should be used during PCI.

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