

Risk score of contrast-induced nephropathy in patients after percutaneous coronary intervention



Morlim Limbong^{1*}, Yan Herry², Pipin Ardianto², Suhartono³

ABSTRACT

Background: Contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI) is still an issue in modern revascularization era. Recent risk stratification model used creatinine as biomarker which has some limitations. Increased $\geq 10\%$ of Cystatin-C after PCI has proven to be one of the earliest and accurate CIN after PCI biomarkers. The study aims to develop risk score based on predictors of contrast-induced nephropathy in patients after PCI with Cystatin-C as biomarker.

Methods: A prospective cohort study of 129 patients after PCI at Dr. Kariadi General Hospital Semarang. Predictor analysis was carried out using bivariate chi-square test and multivariate logistic regression. The independent predictors obtained were then used as risk score variables. The Hosmer and Lemeshow calibration test and AUC ROC analysis for discrimination test tested the quality of the risk score.

Results: There were 3 independent predictors used as the risk score variables: Hypotension (score 1), anemia (score 1), creatinine baseline >1.5 mg/dl (score 1). Patients with total score ≥ 1 have higher risk to have CIN after PCI. The risk score had a good quality with the Hosmer and Lemeshow calibration test > 0.05 and relative modest discrimination ROC AUC 0.700 (95% IK 0.585-0.815; $p=0.001$).

Conclusions: A risk score for risk stratification CIN after PCI has been created. The score has good calibration and modest discrimination in predicting the risk of CIN after PCI.

Keywords: cystatin-c, contrast-induced nephropathy, percutaneous coronary intervention, risk score.

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INTRODUCTION

Percutaneous coronary intervention (PCI) continues to increase. PCI is proven to decrease ischemic burden with chronic coronary syndrome especially among high-risk patients. However contrast media injections during procedure increased incidence of procedure-related contrast-induced nephropathy (CIN). CIN has become the third most common cause of hospital-acquired acute renal failure. Furthermore, the development of CIN has been associated with prolonged hospitalization, increased health care costs, especially, increased in-hospital and long-term mortality.^{1,2,3,4}

2018 ESC/EACTS Guidelines on myocardial revascularization upgraded recommendation to assess all patients for CIN's risk from IIa to 1C. Recently, there were several risk score has developed to predict risk of CIN. All of risk score models used serum creatinine (sCr) level

as the foundation for diagnosis of CIN ; however sCr level may not be determined quickly enough to reflect decreased renal function, and sCr level is affected by factors such as age, sex, and muscle mass. Cystatin C (Cys C) is a non-glycosylated protein with low molecular mass (13 kDa) has proven as one of the earliest and accurate CIN after PCI biomarkers. So, this study is going to derive simple risk score based on predictors CIN in patients after PCI with Cys C as biomarker.^{5,6,7,8}

METHODS

Subject of study

This observational prospective cohort study was performed in consecutive patients with chronic coronary syndrome who underwent elective PCI at dr.Kariadi general hospital (Semarang, Indonesia) between October-December 2019. Patients with pre-existing end-stage renal disease requiring dialysis, on glucocorticoid

medication, history of hyperthyroid, hypothyroid and malignancy were excluded.

Patients underwent PCI, according to current guidelines after written informed consent was obtained. Routine hydration was performed with 1 ml/kg/h of NaCl 0.9 % 12 hours before PCI and 24 hours after PCI (LVEF $\leq 35\%$ or heart failure NYHA III or IV 0.5 ml/kg/h). The University and Hospital Ethical Committee approved the study, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and written informed consent was obtained from all patients. Investigational procedures were in accordance with institutional guidelines.

Clinical definitions

Contrast-induced nephropathy was defined as an increase of Cys C $\geq 10\%$ from baseline, 24 hours after PCI. Anemia was defined using World Health Organization

criteria: baseline hematocrit value < 39% for men and <36% for women, or hemoglobin level < 13 g/dl for men, < 12 g/dl for women. Chronic kidney disease was baseline serum creatinine of > 1.5 mg/dl. Hypotension was systolic blood pressure < 100 mmHg before or intra-procedure or requiring inotropic/vasoconstrictor support. Left ventricular function was taken from echocardiography data at least 6 months before procedure. Proteinuria was defined as the presence of excess

proteins which determined in quality. sCr level was measured before the procedure (baseline). Cys C level was measured before procedure (baseline) and 24 hours after PCI. The contrast media in procedure was Iopamidol 370 or Iopamidol 300. Volume contrast divided into two group, >300 ml and ≤ 300 ml. Hypertension defined as history or in hypertension medication or according to ESC guidelines management for arterial hypertension 2018, systolic blood pressure ≥ 140 mmHg, diastolic

blood pressure ≥ 90 mmHg. Diabetes mellitus identified based on *American Diabetes Association* (ADA) criteria or fasting blood glucose ≥ 126 mg/dl, blood glucose post prandial ≥ 200 mg/dL and HbA1C ≥ 6.5 %.

Statistical analysis

Statistical analysis was done using software SPSS 25.0 (SPSS, Inc., Chicago, IL, USA). Predictor analysis was carried out using bivariate chi-square test and multivariate logistic regression. The independent predictors obtained were then used as risk score variables. The quality of the risk score was tested by the Hosmer and Lemeshow calibration test and AUC ROC analysis for discrimination test.

RESULTS

During October-December 2019, there were 201 patients underwent elective PCI. 72 patients were excluded. A total 129 patients completed the study. Based on Cys C, CIN occurred in 32 patients (24,80%). **Table 1** shows baseline characteristics, overall the mean age was 57,02 ± 7.75 years old and 13.96% females. There were no significant differences LVEF between CIN vs. Non-CIN, 51.93 ± 14.00 vs. 52.02 ± 11.00. (p=0.358). There

Table 1. Baseline Characteristics

Variable	CIN (n=32)	Non-CIN (n=97)
Age (year) ^a	58.87 ± 7.86	56.41 ± 7.65
Sex ^β		
Men	29 (90.62%)	82 (84.53%)
Female	3 (9.38%)	15 (15.47%)
Heart Failure NYHA III/IV ^β	3 (9.37%)	0 (0%)
Hypotension ^β	7 (21.87%)	5 (5.15%)
Anemia ^β	12 (37.50 %)	13 (13.40%)
Diabetes mellitus ^β	14 (43.75%)	31 (31.95 %)
Hypertension ^β	25 (78.12%)	65 (67.01%)
LVEF (%) ^a	51.93 ± 14.00	52.02 ± 11.00
Proteinuria ^β	8 (25%)	21 (21.64%)
Contrast Volume(cc) [∞]	252.81 ± 14.61	271.13 ± 9.14
Serum Creatinine (U/L) ^a	1.30 ± 0.33	1.19 ± 0.25
Cystatin C Pre-PCI (mg/dl) [∞]	1.09 ± 0.37	1.12 ± 0.28
Cystatin C Post-PCI (mg/dl) [∞]	1.54 ± 0.47	1.06 ± 0.29

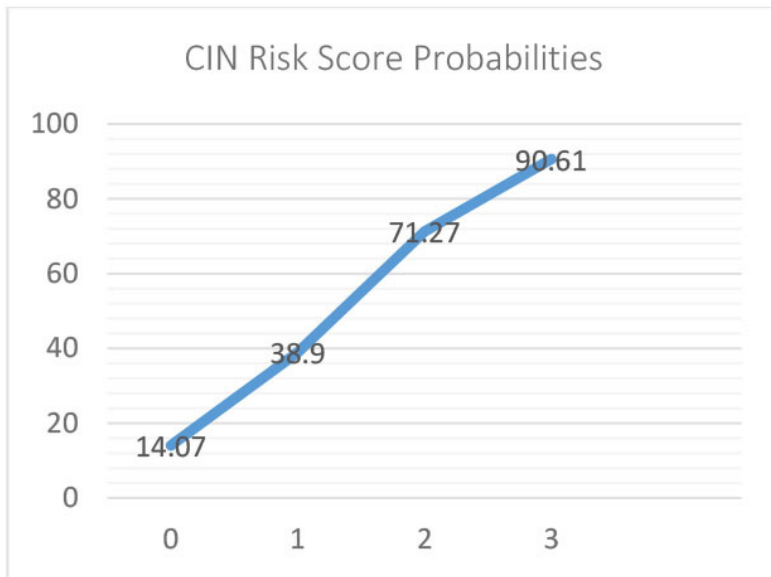
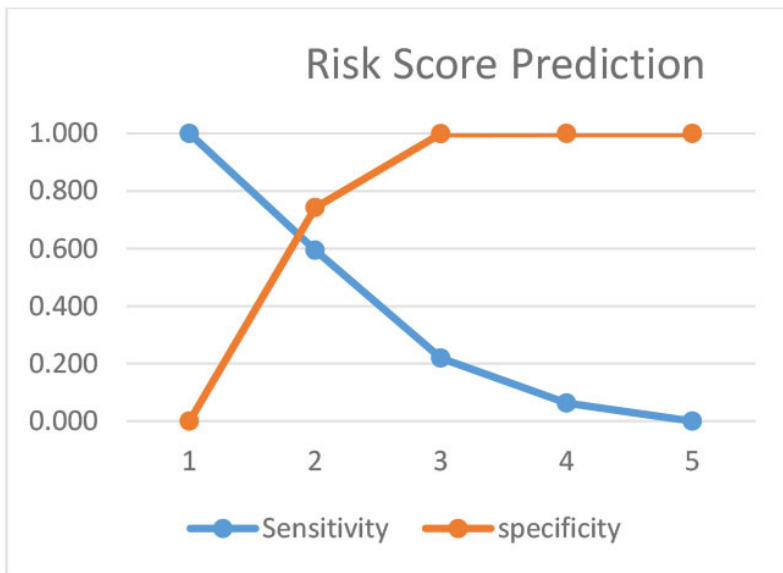
^aMean ± SD, ^βn (%), [∞]Mean ± SD; Median (min-max)

Table 2. Bivariate analysis

Variable		CIN		RR (95% IK)	P
		Yes (%)	No (%)		
Age(year)	≥ 60	15 (32.60%)	31 (67.40%)	1.592	0.189
	< 60	17 (20.48%)	66 (79.52%)		
Congestive heart failure	Yes	3 (100%)	0 (0%)	4.345	0.018
	No	29 (23.01%)	97 (76.99%)		
Hypotension	Yes	7 (58.33%)	5 (41.67%)	2.370	0.013
	No	25 (21.36%)	92 (78.64%)		
Anemia	Yes	12 (48%)	13 (52%)	2.496	0.006
	No	20 (19.23%)	84 (80.77%)		
Diabetes mellitus	Yes	14 (31.11%)	31 (68.89%)	1.452	0.317
	No	18 (21.42%)	66 (78.58%)		
Hypertension	Yes	25 (27.17%)	67 (72.83%)	1.436	0.449
	No	7 (18.91%)	30 (81.09%)		
LVEF (%)	≤ 45	11 (31.42%)	24 (68.58%)	1.407	0.405
	> 45	21 (22.34%)	73 (77.66%)		
Proteinuria	Yes	8 (27.58%)	21 (72.41%)	1.149	0.881
	No	24 (24%)	76 (76%)		
Media contrast volume (cc)	> 300	4 (15.38%)	22 (84.62%)	0.566	0.332
	≤ 300	28 (27.18%)	75 (72.82%)		
Creatinine level (U/L)	> 1.5	9 (52.94%)	8 (47.06%)	2.578	0.010
	≤ 1.5	23 (20.53%)	89 (79.47%)		
Type of media contrast	Iopamidol 370	26 (23.01%)	87 (76.99%)	0.614	0.344
	Iopamidol 300	6 (37.5%)	10 (62.5%)		

Table 3. Multivariate logistic regression and risk score in derivation cohort

Variable	OR	95 % CI	p	Score
Hypotension	5.183	1.368-19.635	0.015	1
Anemia	3.636	1.349-9.803	0.011	1
Cr > 1.5	3.598	1.141-11.349	0.029	1

**Figure 1.** CIN total risk score probabilities curve.**Figure 2.** Graphics of total score sensitivity and specificity.

were no significant differences contrast volume CIN vs. Non-CIN 252.81 ± 14.61 vs. 271.13 ± 9.14 ml ($p=0.872$). sCr levels in CIN group were significantly higher than Non-CIN (1.30 ± 0.33 vs. 1.19 ± 0.25 , $p=0.046$). Baseline Cys C in both groups was not significantly different, but 24 hours after PCI Cys C level in CIN group

higher than Non-CIN (1.54 ± 0.47 vs. 1.06 ± 0.29 mg/dl, $p=0.000$). Only 3 patients with history of heart failure NYHA III or IV and all of them experienced CIN.

Bivariate variables associated with CIN, a total of 5 variables were significantly associated with the development of CIN. The significant correlates included

demographics age ≥ 60 years and several co-morbidities (hypotension, anemia, chronic kidney disease, advanced congestive heart failure [(New York Heart Association functional class III/IV)]. Even though heart failure associated with development of CIN, it was unable to analysis in multivariate analysis (Table 2).

Table 3 shows the multivariate model of predictors of CIN. Anemia, hypotension and sCr level ≥ 1.5 U/L were indentified as independent predictors of CIN. Patients with hypotension had 5 times risk to develop CIN after PCI (OR 5.183, 95%CI 1.368-19.635, $p=0.015$)

Development of risk score based on calculation of regression coefficient divided standard error in multivariate analysis shows each variable hypotension, anemia and sCr > 1.5 got score 1 with total score was 3. We analyzed of each total score with probability of CIN with formula $p = \frac{1}{1 + \exp(-y)}$

Patients with total score 0 still have probability develop CIN 14.07 % and patients with total score 3 have probability develop CIN 90.61% (Figure 1).

The scoring system also allowed for discriminating patients with high risk for CIN, the best cut off was score ≥ 1 with sensitivity 59.4 % and specificity 74.2 % with OR 4.029 (CI 95% 1.818-9.745, $p=0.001$) (Figure 2).

The quality of the risk score was tested by the Hosmer and Lemeshow calibration test with $p > 0.05$, means scoring model had good calibration and AUC ROC analysis figure 3 for discrimination test was 0.700 (CI 95% 0.585-0.815; $p=0.001$).

DISCUSSION

Based on increased Cys C level ≥ 10 % 24 hours after PCI, the incidence of CIN in this study was 24.80 %. Hypotension, anemia and sCr > 1.5 U/L were independent predictors of CIN. Hypotension has negative impact in PCI, hypotension contributes low perfusion in renal and it was reported hypotension and use of IABP exacerbated low perfusion in renal which increased risk of CIN after PCI. The detrimental influence of prolonged hypotension on kidney function is well known. However, even relatively short periods of hypotension may be hazardous.

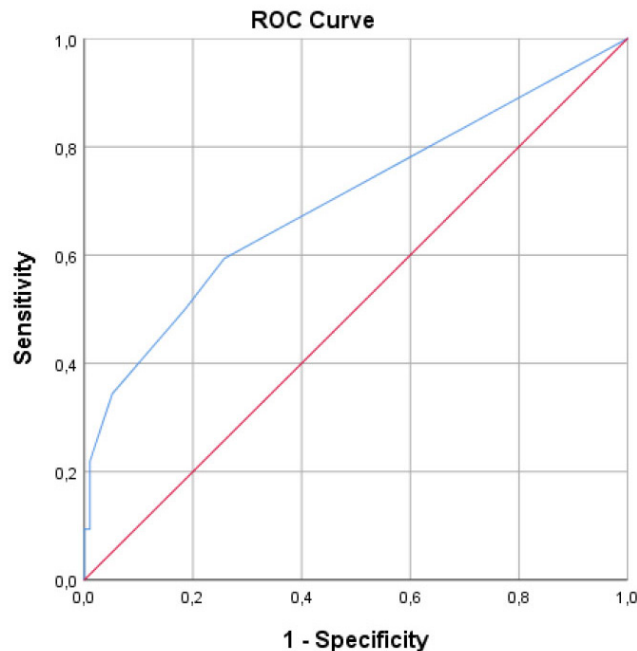


Figure 3. The area under the ROC curve for derivation score.

IABP insertion may be linked with CIN through mechanisms that may either provoke or potentiate renal impairment via atheroembolism to the renal circulation during IABP insertion, counterpulsation or removal as a partial occlusion of the renal blood flow if it is positioned too low (i.e. in the abdominal instead of the descending thoracic aorta) and as a marker of increased vascular complications and post-PCI hypotension.^{2,9,10}

Anemia might be one of the factors contributing to renal ischemia. Anemia and chronic coronary syndrome have a reciprocity correlation. Patients with chronic heart failure or chronic coronary syndrome tend to have risk of malnutrition, activation of TNF- α and declining of tissue perfusion influences red blood cell production in bone marrow. Anemia as an independent predictor of CIN in patients undergoing PCI through potentiation with contrast media. When contrast media injected, it lowering renal perfusion as a direct effect, also causes a disruption of the affinity of hemoglobin to oxygen so that there is a decrease in oxygen transport in peripheral tissue. In addition to the presence of vasoconstriction in renal capillaries accompanied by low hemoglobin levels will increase the occurrence of renal hypoxia.^{10,11}

Pre-existing renal disease with an elevated level of serum creatinine is the most crucial risk factor in the development of CIN. The incidence of CIN in patients with underlying chronic kidney disease is extremely high, ranging from 14.8 to 55%. In one study, despite pre-procedure hydration and the use of non-ionic media contrast, CIN occurred in one-third of 439 consecutive patients who underwent PCI and had baseline serum creatinine \geq 1.8 mg/dl. Cystatin-C in a normal renal state will be freely filtration through the glomerulus and almost completely reabsorbed and catabolize by the proximal tubules. In decreased renal function there is a decline in cystatin-C catabolism. So that when the contrast medium is given to patients who have high creatinine or decreased LFG, it will cause hypoxia that will decrease in cystatin-c catabolism, resulting in increased cystatin-C levels in blood.^{2,12,13 14,15,16,20,21}

In this study several traditional predictors including hypertension, diabetes mellitus, age and volume contrast were not proven as independent predictors. In previous research, long term hypertension causes atherosclerosis and decrease of renal function which causes the easy occurrence of renal ischemia during administration of contrast media.

Chao-pan et al., in study of hypertension and older patients stating gradation of hypertension (controlled or not) also affects the risk of CIN. It was evidenced in previous studies in the group of patients who experienced CIN, blood pressure higher (uncontrolled) than in patients who did not experience CIN.¹⁷ Diabetes consistently on previous research is an independent predictor of CIN after PCI. However in some other studies there was no difference between diabetic patients with good renal function and non-diabetic patients in risk of occurrence of CIN after PCI. CIN is more common in diabetic patients with clinical impairment of renal function. In this study the average sCr level of diabetic patients was 1.29 ± 0.45 or relatively good. In addition to the effect of hyperglycemia and high HbA1C can also be an independent predictor of the incidence of CIN, in a state of hyperglycemia risk of occurrence of CIN 2 times higher than in euglycemic patients.^{18,19,22,23,24}

Volume contrast > 300 ml was not proven as independent predictors in this study. In this study patients who administrated contrast media >300 ml relatively have a good baseline characteristic including renal function and hemoglobin which contributed in lowering risk of CIN after PCI.

There were several limitations of this study. Heart failure NYHA III/IV was not included in multivariate analysis due to all 3 patients with heart failure NYHA III/IV experienced CIN, so statistically it cannot be analyzed. Another limitation was LVEF data derived from echocardiographic data at least 6 months before PCI which not described the actual left ventricular function prior PCI procedure. Compared with the research of other score system, this study had small samples. This risk score has also not been conducted by the external validation test to see the strength of calibration and its discrimination in the patient population outside its score development population.

CONCLUSION

A risk score for risk stratification CIN after PCI has been created. The score has good calibration and modest discrimination in predicting the risk of CIN after PCI.

ETHICAL APPROVAL

This research has ethical approval from Health Research Ethics Committee Dr. Kariadi Hospital, Semarang with ethical clearance reference number No. 350/EC/KEPK-RSDK/2019.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Morlim Limbong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: all authors.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: Morlim Limbong.

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: Morlim Limbong, Suhartono.

Administrative, technical, or material support: Morlim Limbong.

Study supervision: Yan Herry, Pipin Ardhiyanto, Suhartono.

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