

Predictive value of baseline C-reactive protein for periprocedural myocardial infarction of higher risk stratifications: A retrospective cohort clinical study

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ABSTRACT

Objective: It is controversial whether preprocedural elevated high sensitivity C-reactive protein (CRP) could increase the incidence of periprocedural myocardial infarction (PMI) of higher risk stratifications. The primary aim of this study was to evaluate whether preoperative elevated CRP level was related to the incidence of PMI in patients who underwent percutaneous coronary intervention (PCI).

Methods: A total of 4,426 patients [66 y (59, 75); 72.3% males] with normal preprocedural cardiac enzymes were prospectively divided into two groups; the elevated CRP group was defined as CRP >3 mg/L, which was approximately 30.4% of the patients. The relationship between CRP and the incidence of PMI was established by multivariate logistic regression analysis, and multivariate linear regression analysis was used to assess the correlation between CRP and the severity of myocardial injury.

Results: The incidence rates were similar between the two groups with periprocedural myocardial minor necrosis (34.23% versus 32.74%, $p=0.607$), but significantly differed based on the 2007 (defined as cardiac enzymes >3-fold elevations), 31.25% in high CRP group versus 26.25% in low group [odds ratio (OR) 1.19; $p=0.046$] and the 2012 universal PMI (defined as cardiac enzymes >5-fold elevations with at least one clinical evidence, such as chest pain, ECG changes or imaging diagnosis of heart ischemia), 19.79% versus 15.35% (OR 1.26, $p=0.023$); besides, the PMI ratios increased in line with the elevation of CRP ($p=0.006$ for the 2007 and $p=0.011$ for the 2012 universal PMI). However, no significant linear relationship was found between CRP and high sensitivity cardiac troponin I peak post-PCI.

Conclusion: Elevated baseline CRP was an independent risk factor for the incidence of the 2007 and the 2012 universal PMI rather than minor necrosis. However, CRP may not correlate with the severity of minor myocardial necrosis in patients with PMI. (*Anatol J Cardiol* 2018; 20: 310-7)

Keywords: C-reactive protein, percutaneous coronary intervention, complications, prediction, periprocedural myocardial infarction

Introduction

Percutaneous coronary intervention (PCI) is the most predominant treatment for coronary revascularization. Although technical advances in PCI result in a safe procedure with minimal complications, a considerable part of patients undergoing elective PCI suffer periprocedural myocardial infarction (PMI) arising from the procedure itself (1, 2). Besides, several definitions have been established over the last 10 years (3-5), mainly including periprocedural myocardial minor necrosis (PMN, defined as 1-3 fold elevations of cardiac enzymes post-PCI), the 2007 universal PMI (simply defined as cardiac enzymes >3-fold elevations), the 2012 universal PMI (cardiac enzymes >5-fold el-

evations with at least one clinical evidence, such as chest pain, ECG changes or imaging diagnosis of heart ischemia) and the Society for Cardiovascular Angiography and Interventions (SCAI) new PMI definition (defined as creatine kinase-myocardial band isoform (CK-MB) >10-fold elevations or cardiac troponin (cTn) >70-fold elevations with new pathologic Q-waves in 2 contiguous leads or new persistent left bundle branch block).

It has been well established that PMI is associated with a higher risk of mortality and adverse cardiac events, even with minor necrosis. There is a dose-response relationship between cardiac enzymes release (1-3-fold, >3-fold, >5-fold) and the ratio of subsequent events according to previous studies (6-9). Idris et al. (10) indicated that the rates of death/myocardial infarction at 2 years in patients based on the SCAI definition were higher than

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that based on the 2012 and the 2007 universal PMI. Therefore, it was important to routinely screen for PMI, particularly for the patients belonging to higher risk stratifications.

As an acute-phase reactant and the most widely used marker of systemic inflammation, C-reactive protein (CRP) plays an important role in the procedure of thrombogenesis and thromboembolism (11), which associates with the incidence of PMI (9, 12). Some studies have demonstrated that increased baseline high-sensitivity C-reactive protein (hs-CRP) before PCI may influence subsequent clinical outcomes (13-15). However, the role of CRP and post-PCI myocardial injury is still debatable, with previous studies presenting conflicting results (16-22).

On the basis of significantly different risk stratifications of PMI as mentioned above, the distinction of PMI of higher stratifications is equally important. However, no comprehensive study about the association of CRP with subsequent PMI of different risk classifications has been performed. Thus, we aimed to reveal the possible role of CRP in PMI of varying standards and tried to explore the potential mechanism in this procedure.

Methods

Study population and design

Our investigation was designed as a retrospective cohort study. A total of 7,096 consecutive patients of coronary stenosis with angiographic testified who underwent PCIs with drug-eluting stents at our hospital from May 2014 to April 2017 were considered. About 2,670 patients were excluded according to the criteria presented in Figure 1, and finally 4,426 patients were included. Interventions were performed according to the current practice guidelines. The choices of specific types of drug-stents

were made according to the discretion of operators and consent of patients. All patients undergoing PCI were prescribed 100 mg/day aspirin and 75 mg/day clopidogrel maintenance therapy for more than 7 days; a 300 mg loading dose of aspirin or clopidogrel before the index procedure was administered if patients were not pretreated. And 10 mg/day rosuvastatin or 20 mg/day atorvastatin was conventionally given before the procedure. All the procedures were performed in accordance with the Declaration of Helsinki. Each patient signed the informed consent form to participate in the study.

Data collection

Blood samples were collected for the measurement of baseline CRP, cTnI, CK-MB and other serum biochemical indices in the last 24 h before the procedure. All interventions were performed using standard techniques. The cTnI and CK-MB levels were evaluated every 8 h within 24 h after PCI, and a 24–48 h dynamic monitoring after the procedure was used if necessary. All the factors implicated for higher incidence of PMI according to previous studies were also collected before the end of the procedure (23, 24).

End points and definitions

The primary end point was to investigate the role of CRP in subsequent PMI of various standards mentioned above. The secondary endpoint was to evaluate whether it can influence the severity of myocardial injury.

Based on the cut-off point suggested in the previous studies (13, 25, 26), CRP >3 mg/L was considered as elevated. As a more hyper-sensitive cardiac enzymes, elevated cTnI peak (indexed by upper reference limit), was used to assess the severity of myocardial injury post-PCI.

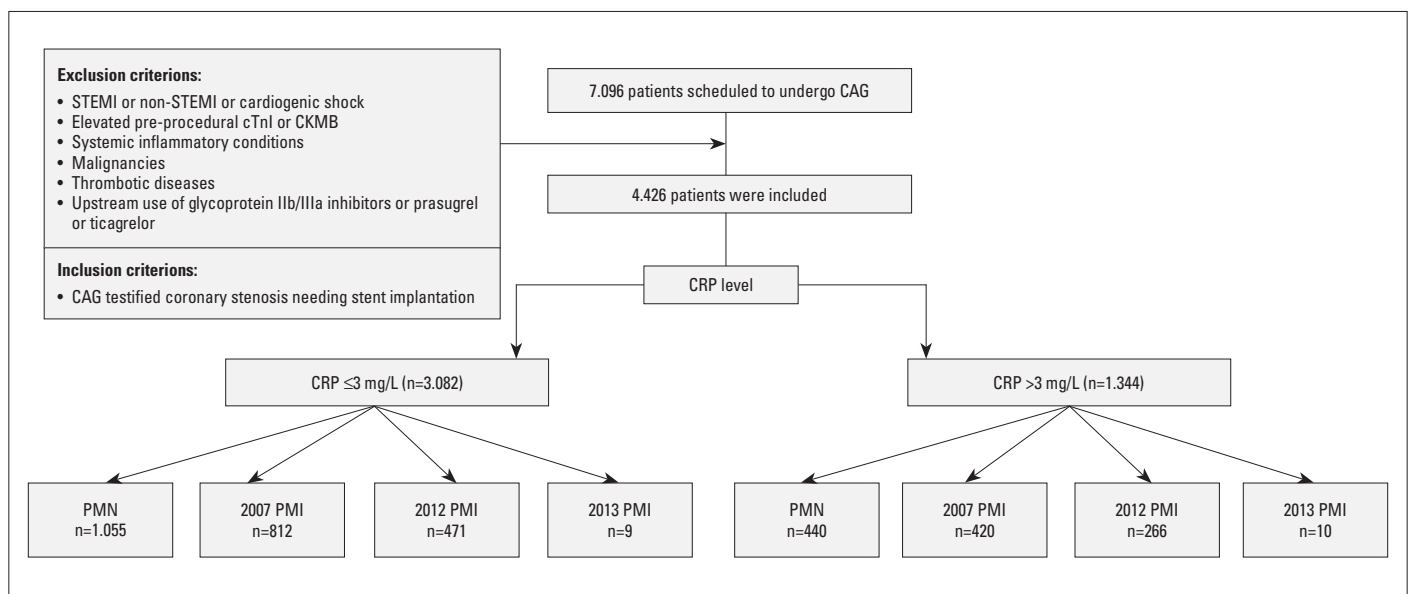


Figure 1. Research process

CAG- coronary angiography; CK-MB- the MB fraction of creatine kinase; cTnI- cardiac troponin I; CRP- C-reactive protein; PMI- periprocedural myocardial infarction; PMN- periprocedural myocardial minor necrosis; STEMI- ST-segment elevation myocardial infarction

Statistical methods

Categorical variables were expressed as percentages (%) and continuous variables were presented as medians with interquartile ranges; the normality test of the continuous variables was routinely conducted by standard normal curve testing with the Kurtosis and Skewness coefficients. The statistical method multiple imputation was used to deal with the random missing data for some covariates. Continuous variables were compared by using Mann-Whitney U test, and noncontinuous were determined using χ^2 statistical test. The predictive value of CRP for PMI was investigated with the use of multiple logistic regression analysis. Elevated cTnI peak post-PCI was identified in each group of various PMI standards, and its relationship with the continuous variable of CRP was evaluated by using multiple linear regression analysis. In these models, odds ratio (OR) and 95% confidence intervals (95% CIs) were confirmed by Schoenfeld tests, and no relevant violations were found. All calculations were performed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois, the United States), and 2-sided p values <0.05 were considered significant.

Results

Patient baseline data and PMI ratios

All the clinical, angiographic and procedural characteristics were recorded as shown in Tables 1-3. Elevated CRP (>3.0 mg/L) was observed in 30.4% of the study population. Of the included patients, 72.3% were males, 69.7% had hypertension, 27.6% had diabetes, 43.3% had acute coronary syndrome (ACS), 54.2% had the American College of Cardiology and the American Heart Association (ACC/AHA) class B2 or C lesions, and 47.6% had multi-stents interventions.

About 2,727 patients (61.61%) had cardiac enzymes elevations [1,867 (60.58%) for low CRP group and 860 (63.99%) for the high group]. The ratios of various types of periprocedural myocardial injury are shown in Figure 2. The incidence of PMI was elevated in hyper baseline CRP level for the 2007 (1.2 fold) and the 2012 universal PMI (1.32 fold) rather than PMN (0.96 fold). As for the 2013 SCAI definition, the incidence in each group was much lower (only 0.74% versus 0.29%) although it was much higher in high CRP.

Association between CRP and the ratio of PMI

Based on the 2007 universal definition (Fig. 3), high baseline CRP (OR, 1.19; 95% CI, 1.008-1.414; p=0.04) was an independent predictor of PMI. Applying the 2012 third universal PMI definition and using the same model, high baseline CRP played a more

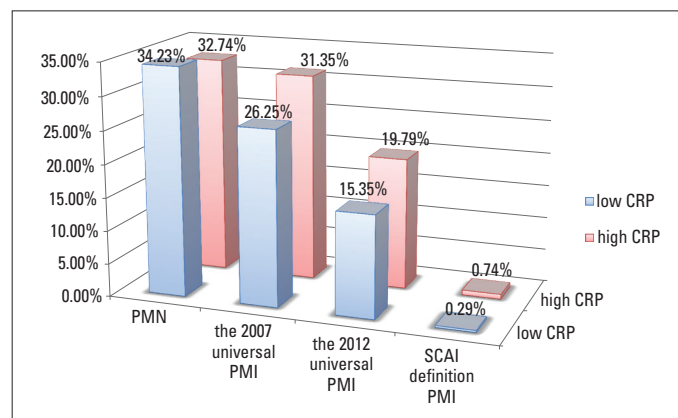


Figure 2. Incidence of PMI according to varying definitions
CRP- C-reactive protein; PMI- periprocedural myocardial infarction; PMN- periprocedural myocardial minor necrosis; SCAI- the Society for Cardiovascular Angiography and Interventions

Table 1. Main clinical features according to CRP levels

Variables	Low CRP level (CRP ≤3 mg/L) (n=3082)	High CRP level (CRP >3 mg/L) (n=1344)	P value
Age, y	66 (59, 73)	68 (60, 76)	<0.001
Serum LDL-C, mmol/L	1.82 (1.42, 2.44)	2.05 (1.56, 2.69)	<0.001
Cardiac insufficiency, % (n)	5.4% (133/2462)	15.7% (175/1116)	<0.001
Hypertension, % (n)	68.5% (2079/3036)	72.4% (957/1321)	0.009
Renal insufficiency, % (n)	3.3% (100/3016)	8.8% (115/1304)	<0.001
Diabetes, % (n)	26.3% (798/3032)	30.7% (404/1318)	0.003
Previous PCI, % (n)	34.9% (1055/3025)	26.4% (348/1317)	<0.001
Previous AMI, % (n)	8.8% (266/3082)	6.4% (84/1316)	0.007
Previous CABG, % (n)	0.7% (21/3025)	1.3% (17/1318)	0.053
ACS, % (n)	41.7% (1257/3014)	46.9% (610/1301)	0.002

Data are expressed as number (%) / number or with interquartile range.

ACS- acute coronary syndrome; AMI- acute myocardial infarction; CABG- coronary artery bypass surgery; CRP- C-reactive protein; LDL-C- low-density lipoprotein cholesterol; PCI- percutaneous coronary intervention

Table 2. CAG characteristics according to CRP

Variables	Low CRP level (CRP ≤3 g/L) (n=3082)	High CRP level (CRP >3 g/L) (n=1344)	P value
Lesion location: LM, % (n)	8.7% (263/3013)	7.5% (99/1322)	0.174
LAD,% (n)	57% (1717/3013)	53.5% (707/1322)	0.032
LCX,% (n)	24% (724/3013)	21.8% (288/1322)	0.108
RCA,% (n)	28.6%(861/3013)	33.1% (438/1322)	0.003
Multivessel lesions, % (n)	15.8% (476/3013)	14.2% (188/1322)	0.159
Lesion Characteristics:			
Bifurcation lesion, % (n)	11.3% (341/3013)	10.5% (139/1322)	0.438
Lesion length ≥20 mm, % (n)	61.4% (1849/3013)	64.2% (849/1322)	0.074
Calcification, % (n)	18.0% (543/3013)	22.3% (295/1322)	0.001
Eccentricity, % (n)	59.2% (1784/3013)	61.2% (809/1322)	0.220
Tortuosity, % (n)	5.2% (158/3013)	5.6% (74/1322)	0.634
Diameter ≥25 mm, % (n)	80.3% (2420/3013)	81.8% (1081/1322)	0.264
Chronic total occlusion, % (n)	7.3% (221/3013)	9.4% (124/1322)	0.022
Type B2/C lesion, % (n)	53.8% (1620/3013)	55.1% (728/1322)	0.429

Data are expressed as number/number (%).
 CAG- coronary angiography; CRP- C-reactive protein; LAD- left anterior descending; LCX- left circumflex; LM- left main artery; RCA- right coronary artery; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

Table 3. PCI procedures according to CRP

Variables	Low CRP level (CRP ≤3 g/L) (n=3082)	High CRP level (CRP >3 g/L) (n=1344)	P value
Balloon pre-dilation, % (n)	80.9% (2437/3013)	82.1% (1086/1322)	0.326
Direct PCI, % (n)	16.2% (487/3013)	14.9% (197/1322)	0.294
Atherectomy,%(n)	1.2% (37/3013)	0.8% (11/1322)	0.251
Post ballooning, % (n)	88.9% (2680/3013)	89.9% (1188/1322)	0.371
Stent average length, mm	24 (20, 30)	25 (20, 30)	0.150
Stent number ≥2, % (n)	47.3% (1396/2953)	48.2% (623/1292)	0.534
TIMI grade <3 after PCI, % (n)	1.2% (37/3013)	1.1% (15/1322)	0.795

Data are expressed as number/number (%) or with interquartile range.
 CRP- C-reactive protein; PCI- percutaneous coronary intervention; TIMI- thrombolysis in myocardial infarction

important predictive role (OR, 1.26; 95% CI, 1.032-1.545; p=0.023) (Fig. 4). As for the 2013 SCAI standard (Fig. 5), the OR of 2.903 maybe a little debatable (95% CI, 0.799-10.547; p=0.106). However, it showed no statistical significance (OR, 0.095; 95% CI, 0.815-1.127; p=0.607) with the same model for PMN (Fig. 6). Therefore, elevated CRP might be helpful for the prediction for the 2007 and 2012 universal PMI, but not for PMN.

On this basis, we tried to evaluate whether higher CRP levels associated with more frequencies of PMI using multiple logistic regression analysis (Table 4): the occurrence rates of PMI el-

evated as the level hyper baseline CRP (beta=0.010, p=0.006 for the 2007 and beta=0.009, p=0.011 for the 2012 universal PMI). All the other covariates listed were associated with PMI expect for low-density lipoprotein cholesterol (LDL-C) and diabetes.

Association between CRP and the severity of PMI

To study the mechanism of how CRP increases the incidence of PMI, we analyzed the relationship between the baseline CRP level and the severity of myocardial injury evaluated by the cTnl peak using multiple linear regression analysis in patients with the

Table 4. The multiple logistic regression analysis adjusting for continuous variable of baseline CRP level for the incidence of PMI

Variables	The 2007 PMI		The 2012 PMI	
	Beta	95% CI	Beta	95% CI
Renal insufficiency, 5%	0.388	1.048-2.075	0.228	0.855-1.844
Cardiac insufficiency, 8.6%	0.492	1.233-2.171	0.612	1.348-2.520
Hypertension, 69.7%	0.182	1.003-1.436	0.290	1.071-1.668
Diabetes, 27.6%	-0.040	0.803-1.15	0.035	0.808-1.281
Type B2/C, 54.2%	0.401	1.273-1.753	0.393	1.220-1.799
Age ≥65 y, 57.9%	0.370	1.221-1.715	0.320	1.121-1.693
LDL-C, mmol/L	0.007	0.923-1.10	0.032	0.931-1.145
Multi-vessel PCI, 47.6%	0.591	1.538-2.121	0.509	1.391-1.989
ACS, 43.3%	0.211	1.055-1.447	0.191	1.003-1.463
CRP, mg/L	0.010	1.003-1.017	0.009	1.002-1.017

Data are expressed as number/number (%) or with interquartile range.
ACS- acute coronary syndrome; CRP- C-reactive protein; LDL-C- low-density lipoprotein cholesterol; PMI- periprocedural myocardial infarction; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

Table 5. The linear relationship between elevated CRP levels and cTnI peaks post-PCI for the 2007 and the 2012 universal PMI

Variables	The 2007 PMI		The 2012 PMI	
	P value	Beta	P value	Beta
Renal insufficiency	0.205	0.049	0.560	0.029
Cardiac insufficiency	0.035	0.081	0.124	0.074
Hypertension	0.341	0.032	0.523	0.028
Diabetes	0.033	0.072	0.042	0.089
Type B/2C	0.616	-0.016	0.572	-0.024
Age ≥65 y	0.986	0.001	0.627	-0.022
LDL-C	<0.001	0.123	<0.001	0.155
Multi-vessel PCI	0.766	-0.10	0.841	-0.009
ACS	0.028	0.073	0.046	0.086
CRP	0.989	<0.001	0.963	-0.002

Data are expressed as number/number (%) or with interquartile range.
ACS- acute coronary syndrome; CRP- C-reactive protein; cTnI- cardiac troponin I; LDL-C- low-density lipoprotein cholesterol; PCI- percutaneous coronary intervention; PMI- periprocedural myocardial infarction; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

2007 and 2012 universal PMI (Table 5). No significant linear relationship between CRP and cTnI peak was found. However, LDL-C and diabetes were related to the cTnI peak, which had no significant predictive value to the incidence ratio of PMI as shown previously.

Discussion

It is increasingly important to distinguish PMI of higher stratifications with the recognition of its poor prognosis. Previous studies have demonstrated the dose-response relationship between cardiac enzymes release (1-3 fold, >3-folds, >5-folds)

and the ratio of subsequent events using any cardiac enzyme, including CK-MB, cTn I and cardiac troponin T (cTnT) (6-8). According to Idris et al. (10), the rates of death/myocardial infarction at 2 y in patients with PMI were 14.7%, 16.9% and 29.4% respectively, based on the 2007, the 2012 and the 2013 definition, which were much higher than those patients without PMI. Thus, more frequent late death/myocardial infarction occurrences are associated with the 2013 SCAI definition; relative more occur with the 2012 and 2007 universal PMI, whereas, much lesser are associated with PMN. Thus, the prediction for PMI of higher risk stratifications is much more important than that for slight enzyme elevations.

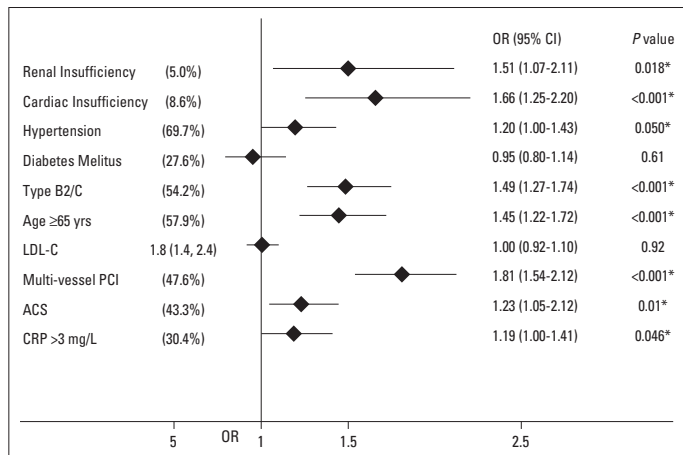


Figure 3. OR for the 2007 PMI

*indicate $P < 0.05$

ACS- acute coronary syndrome; CRP- C-reactive protein; LDL-C- low-density lipoprotein cholesterol; OR- odds ratio; PMI- periprocedural myocardial infarction; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

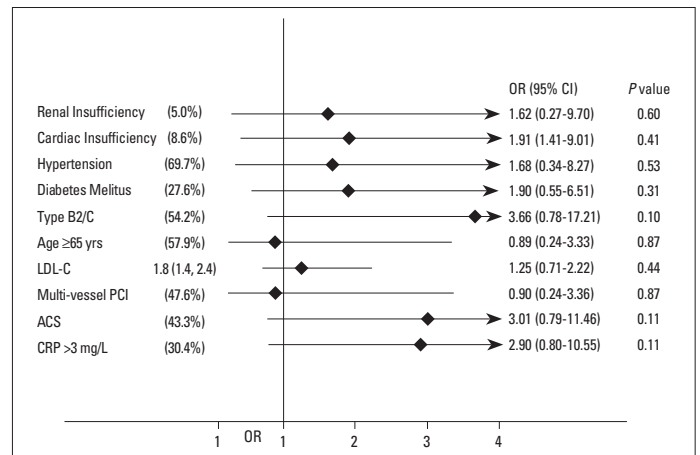


Figure 5. OR for SCAI

ACS- acute coronary syndrome; CRP- C-reactive protein; LDL-C- low-density lipoprotein cholesterol; OR- odds ratio; PMI- periprocedural myocardial infarction; SCAI- the Society for Cardiovascular Angiography and Interventions; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

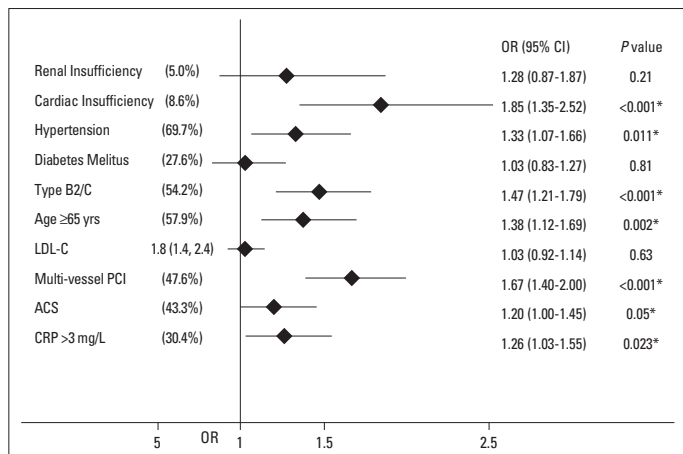


Figure 4. OR for the 2012 PMI

*indicate $P < 0.05$

ACS- acute coronary syndrome; CRP- C-reactive protein; LDL-C- low-density lipoprotein cholesterol; OR- odds ratio; PMI- periprocedural myocardial infarction; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

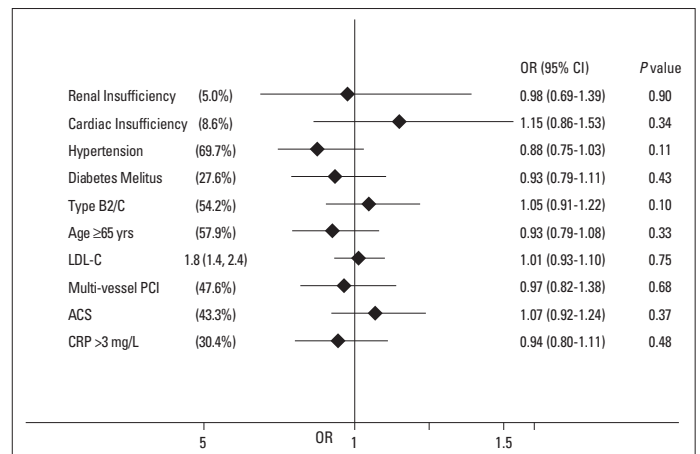


Figure 6. OR for PMN

ACS- acute coronary syndrome; CRP- C-reactive protein; LDL-C- low-density lipoprotein cholesterol; OR- odds ratio; PMN- periprocedural myocardial minor necrosis; Type B2/C- type C lesion or more than 2 characteristics of type B lesions

However, previous studies examining the relationship between preprocedural CRP level and periprocedural myocardial injury (mainly minor PMN and the 2007 universal PMI) reported controversial conclusions, with different cardiac enzymes, various cut-offs of CRP, and relatively smaller samples (16-18, 20, 22, 27, 28). For instance, the results from the study done by Goldberg et al. (22) which used >4.6 mg/L as a CRP cutoff was contradictory to that from other previous large sample size studies which used >3 mg/L as a CRP cutoff in patients with stable angina (13, 25, 26). However, altogether 208 patients were included in the study done by Goldberg et al. (22), thus, the relatively smaller sample size may influence the authenticity of their study. Similar studies aiming at the relation between CRP and troponin elevations reached opposite conclusions (16, 17, 20, 28).

In our large cohort of 4426 patients with drug-stent implantation, we made a comprehensive study about the predictive value

of elevated CRP to the subsequent PMI based on significant different risk classifications. Our data suggested that elevated CRP level was associated with a significant incremental risk for the 2007 and the 2012 universal PMI, but not for PMN. This finding is important because PMI of the 2007 and the 2012 universal standards are associated with more incidences of adverse events than PMN during follow-up (6, 7). Although the predictive value with SCAI definition (OR, 2.9, $p=0.11$) was not cogent enough, the limited data of our study indicated that the incidence was much higher in high CRP group (2.55-fold).

For the post-PCI myocardial enzymes elevation, in contrast with previous findings (20, 22), the incidence rates in our study were similar between the low CRP group and the high CRP group. The smaller sample size might account for controversial results of those previous studies for the predictive value of CRP to myocardial injury based on simple cardiac enzymes elevation.

In our findings, no significant predictive value was found between elevated CRP and PMN or for all the other patient characters, or the lesion-related factors. The results above may imply that PMN was more related to intervention procedure, and further studies about the predictive value of other related procedural factors on the minor cardiac enzymes release are necessary.

However, the limited data of PMI based on the 2013 SCAI definition showing a more important predictive role (OR, 2.9; $p=0.11$) of CRP, was not convincing enough for the lower incidence of this standard (0.29% in low CRP group and 0.74% in high group) caused by the strict criterion. On comparing with a previous study (2.6% in the study of Idris et al. (10), but only 1.47% with normal pre-PCI cTn), another reason for the lower incidence was probably that we excluded patients with elevated baseline cardiac enzymes ahead of schedule. Further, larger sample and comprehensive studies needed to be performed to definitively confirm the correlation with SCAI standard PMI.

To further investigate whether a dose-response relation between CRP and PMI existed, we incorporated the continuous variable of CRP into the multiple regression analysis model *de novo*. We found the PMI ratios increased with the level of CRP, which could explain why PMI incidences were much higher in the studies using higher CRP cut-offs (16, 17, 22).

By contrast, no linear relation between the continuous variable of CRP and cTnI peaks was found; however, the most interesting result of our study was that LDL-C and diabetes related to the release of myocardial enzymes, regardless of little independent predictive value for PMI of the 2007 and the 2012 universal standards. Thus, LDL-C and diabetes may not predict a higher incidence of PMI independently, but could associate with the severity of myocardial injury.

On the basis of our findings, CRP may help predict the incidence rate of PMI before PCI procedures, and which is indicated that the prevention of PMI by correcting basal hyper inflammation may translate into an improvement in prognosis during follow-up. The view is supported by reinforcing anti-inflammatory drug therapy, i.e., statins (29, 30), the interleukin-6 receptor antagonist (31), vitamin C (32), and interventional nicorandil pharmacology (33) to reduce PMI for selective patients with PCI. We believe more drugs with anti-inflammatory properties will be put into practice to reduce PMI in the near future.

Study limitations

First, as a single-center, retrospective cohort study, some unknown confounding factors may have affected the outcomes, regardless of in-order patient recruitment and analytical adjustments. Second, although some variables showing $p<0.05$ in the univariate analyses were excluded in multivariate analyses for clinical considerations; it is possible that these parameters affect the occurrence of cardiac events. Third, in some patients, transient hs-CRP may be affected by the underlying disease or undetected infection independently. Next, we failed to ascertain the predictive role in the 2013 SCAI standard PMI because of the rela-

tively smaller number of events due to the strict criterion and the exclusion of preprocedural elevated cardiac enzymes. Finally, we did not collect the detailed information about other medications except for antiplatelet drugs and statins on admission and more procedural risk factors that may influence the incidence of PMI.

Conclusion

Elevated baseline CRP level is an independent risk factor for the 2007 and 2012 standard PMI rather than PMN, and the risk increased in accordance with the level of preprocedural elevated hs-CRP. However, CRP may not correlate with the severity of myocardial injury in patients with PMI.

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