HIGH MYELOPEROXIDASE LEVEL AS A PROGNOSTIC FACTOR CARDIOVASCULAR EVENTS AT SIX MONTH IN PATIENTS PRESENTING WITH ACUTE CORONARY SYNDROME

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ABSTRACT

Cardiovascular disease (CVD) is the highest leading cause of death worlwide. Inflammation has been implicated in all stages in the evolution of atherosclerotic plaques. Myeloperoxidase (MPO) is an enzyme linked to both inflammation and oxidative stress. The aim of this study was to assess wether high level of MPO is a prognostic factor of cardiovascular events at six month in patients presenting with acute coronary syndrome (ACS). This study was a prospective cohort study, which took place at Sanglah General Hospital Denpasar from 10 December 2011 until 10 December 2012. Subjects of this study were 60 ACS patients which were enrolled by consecutive sampling. MPO levels was measured at the first admission and the cardiovascular events during six month were observed. Sixty samples were involved in this study, 9 unstable patients (11%), 11 NSTEMI patients (18.3%), and 40 STEMI patients (66.7%). In 6 months observation, there was 14 (23.3%) patients had cardiovascular events. Nine patients (15%) had high MPO levels and 51 patients (85%) had low MPO levels. The result of this study were the ACS patients with high levels of MPO were tend to have more adverse cardiac events [hazard ratio (HR) 1.4; 95 % confidence interval (CI) 0.39 to 5.22; P = 0.591]. The relationship between MPO levels and incident cardiovascular event according to ARR (absolute risk reduction) was 11.76 % and NNT (number need to treat) was 8. High MPO levels gives benefit of long term prognostic in patients with acute coronary syndrome. **[MEDICINA 2015;46:16-21].**

Keywords : *acute oronary syndrome,* MPO

KADAR MYELOPEROXIDASE YANG TINGGI MERUPAKAN PETANDA PROGNOSTIK KEJADIAN KARDIOVASKULAR DALAM 6 BULAN PADA PENDERITA SINDROM KORONER AKUT

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ABSTRAK

Penyakit kardiovaskular merupakan penyebab kematian tertinggi di seluruh dunia. Inflamasi memegang peranan pada stadium pembentukan plak aterosklerosis. *Myeloperoxidase* (MPO) adalah enzim yang berhubungan dengan inflamasi dan stres oksidative. Tujuan penelitian ini adalah untuk mengetahui kadar MPO yang tinggi sebagai faktor prognostik kejadian kardiovaskular dalam 6 bulan pada penderita sindrom koroner akut (SKA). Penelitian ini merupakan kohort prospektif, yang bertempat di RSUP Sanglah dari 10 Desember 2011 sampai 10 Desember 2012. Sampel penelitian adalah 60 orang yang diambil secara *consecutive sampling*. Sampel yang memenuhi kriteria inklusi diperiksa kadar MPO saat masuk rumah sakit dan diamati kejadian kardiovaskular (KKV) selama 6 bulan. Enam puluh penderita SKA yang dilibatkan dalam penelitian ini terdiri dari 9 orang pasien APTS (15 %), 11 orang pasien NSTEMI (18,3 %) dan 40 orang pasien STEMI (66,7 %). Dalam pengamatan selama 6 bulan, didapatkan sebanyak 14 (23,3 %) orang pasien yang mengalami KKV. Sebanyak 9 orang (15%) dengan kadar MPO tinggi dan 51 orang (85%) dengan MPO rendah. Pada penelitian ini didapatkan bahwa pasien SKA dengan kadar MPO tinggi memberikan *outcome* yang lebih tinggi dibanding dengan kadar MPO yang rendah (HR 1,4; IK 95 % 0,39-5,22; P = 0,591). Besar efek dari MPO terhadap KKV yang diukur dengan ARR (*absolute risk reduction*) adalah 11,76 % dan NNT (*number need to treat*) sebesar 8. Kadar MPO yang tinggi memberikan manfaat dalam prognostik jangka panjang pada pasien SKA. **[MEDICINA 2015;46:16-21].**

Kata kunci : *sindrom koroner akut,* MPO

INTRODUCTION

Coronary artery disease is wellknown as the leading cause of morbidity and mortality both in developed and developing countries.[1] In Indonesia, cardiovascular diseases is the leading cause of death in 2000.[2]

Coronary artery disease almost always caused by or without lumen thrombosis and vasospasm. Lumen thrombosis plays significant role in pathogenesis of acute coronary syndrome, such as ST-Segment Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI), and unstable angina pectoris (UAP).[3]

Clinical studies showed inflammation markers in atherosclerosis were tested directly in human. Increase of inflammation markers can predict cardiovascular events in acute coronary syndrome. [4]

Leucocyte affects to corocary artery disease through several pathologic mechanism and trigger inflammation process, cause oxidative stress to endothelial cells, and extend infarct area.[5]

Myeloperoxidase (MPO) is an enzyme released from leucocyte that catalyzes reactive oxidant species (ROS) production. Evidences showed oxidant from MPO contributes to tissue damage during inflammation. MPO catalytic reaction play role in proatherogenic process of cardiovascular diseases, by initiation, propagation, and acute complication phase of atherosclerotic process.[6]

Study about MPO levels as risk predictor of cardiovascular events was conducted in 604 consecutive patients with chest pain suspected cause by coronary disease. MPO levels measurement when patients were admitted to emergency unit, with mean 4 hours after onset, is a independent predictor of cardiovascular events in 30 days (infarct myocardial, needs revascularisation, or death) and 6 months.[7, 8]

CAPTURE study evaluated MPO levels as prognostic factors in 1090 acute coronary syndrome patients and recurrent angina which had percutaneous coronary intervention. MPO levels correlated with traditional risk factors, but not with troponin T, CD-40 soluble ligand, C-reactive protein (CRP), and electrocardiography changes. Patients with high MPO levels (31.3% from samples), showed increase risk of reinfarction and death in 72 hours until 6 months RR 2.25 (1.32 to3.8).[8, 9]

Many studies revealed that MPO can be used as prognostic value in coronary artery disease patients.[10,11] Multimarker study, including MPO marker, found that there's no prediction value of long term outcome, including death events and myocardial infarction,[12] and in another multimarker study showed there's no difference of cause of death between normal MPO levels and increase MPO levels. During 4 months observation, MPO concentration was statistically significant if combined with with troponin I levels.[13]

TACTICS-TIMI 18 study analyzed cardiovascular events in 30 days in NSTEMI patients, showed that MPO levels was correlated with short term risk of ischemia events and was not influenced by traditional risk factors, troponin levels, and another biochemical markers such as BNP, sCD40L, and hsCRP.[14]

Based on those facts, this study was conducted to evaluate the role of MPO levels in cardiovascular events for 6 months in acute coronary syndrome (ACS) at Cardiology and Vascular Medicine Departement, Udayana University Medical School/Sanglah Hospital, Denpasar Bali.

METHODS

This was a cohort study to prove or reevaluate high proinflammatory activity of MPO could increase risk of cardiovascular events in ACS.

The study have been conducted at emergency unit and Intensive Cardiac Care Unit (ICCU) Cardiology and Vascular Medicine Departement, Udayana University Medical School/ Sanglah Hospital Denpasar since 10 December 2011 until 10 December 2012.

The subjects were 60 ACS patients that fulfilled inclusion and exclusion criterias with consecutive sampling method.

The inclusion criterias for the study were: 1) all acute myocardial infacrtion patients with age 25-80 years old and admitted at emergency unit and treated at ICCU Sanglah Hospital 2) willing to participate in this study and signed informed consent. The exclusion criterias were 1) valvular heart diseases, 2) congestive heart failure, 3) acute and chronic liver diseases, 4) chronic kidney disease (creatinine clearance with Cockroft Gault formula <60 ml/1.73 m^2/minute), 5) acute or chronic infection, 6) sepsis, 7) malignancy, 8) treated with corticosteroid or antiinflammation drugs or immunosuppresive drugs more than 1 week.

ACS patients were divided into two groups based on cut off point of MPO levels with ROC curve: group ACS patients with positive prognostic factor (high MPO levels) and group ACS patients without prognostic factor (low MPO levels), then followed for 6 months at hospital (direct observation), outside hospital/at home by phone contact or home visit, and coordination with family, doctor who treated the patients. The outcomes that were evaluated were cardiovascular events such as vascular death, myocardial infarction, stroke, and recurrent cardiac ischemia.

Data were collected from medical record and observtion for 6 months. Data were analyzed with SPSS 17 program and described with tables and naration.

RESULTS

Sixty ACS patients were conducted in this study and treated at ICCU Sanglah Hopsital, observed until had cardiovascular events or until 6 months period. The subjects were treated with ACS management based on ACS management guideline from Indonesian Heart Association.

Sixty ACS patients were participated in this study, consisted of 9 unstable angina pectoris patients (15 %), 11 NSTEMI patients (18.3 %), and 40 STEMI patients (66.7 %) (**Table 1**). During 6 months observation, 14 patients (23.3 %) had cardiovascular events, 1 in unstable angina patients (7.1 %) with recurrent cardiac ischemia, 3 STEMI patients (21.4%) with acute myocardial infarction, and 10 STEMI patients (71.4 %) had vascular death.

Based on ROC curve analysis, cut off point value of high MPO levels to predict cardiovascular events was 406.0057 pg/ml (**Figure 1**). With cut off point 406.0057 pg/ml, there were 9 patients with high MPO levels and 51 patients with low MPO levels.

High MPO levels as cardiovascular events predictor

To assess influence of high MPO levels with cardiovascular events, Kaplan Meier estimation method was used.

Survival rate ACS patients with high MPO levels was compared with ACS patients with low MPO levels. In another word,

Table 1. Sample characteristics based on MPO levels

Characteristics		MPO Levels	
		High (n=9)	Low (n=51)
Age Sex		55.44 ± 7.03	57.63 ± 11.56
	Male	9 (100 %)	42 (82.4 %)
	Female	0 (0 %)	9 (17.6 %)
ACS			
	UAP	2 (22.2 %)	7 (13.7 %)
	NSTEMI	0 (0 %)	11 (21.6 %)
	STEMI	7 (77.8 %)	33 (64.7 %)
Smoking			
	Yes	5 (55.6 %)	25 (49 %)
	No	4 (44.4 %)	26 (51 %)
Diabetes			
	Yes	2 (22.2 %)	10 (19.6 %)
	No	7 (77.8 %)	41 (80.4 %)
Hypertension			
	Yes	4 (44.4 %)	30 (58.8 %)
	No	5 (55.6 %)	21 (41.2 %)
Dyslipidemia			
	Yes	8 (88.9 %)	46 (90.2 %)
	No	1 (11.1 %)	5 (9.8 %)
Obesity			
	Yes	6 (66.7 %)	27 (52.9 %)
	No	3 (33.3 %)	24 (47.1 %)
Revascularisation Therapy			
	Yes	7 (77.8 %)	25 (49 %)
	No	2 (22.2 %)	26 (51 %)

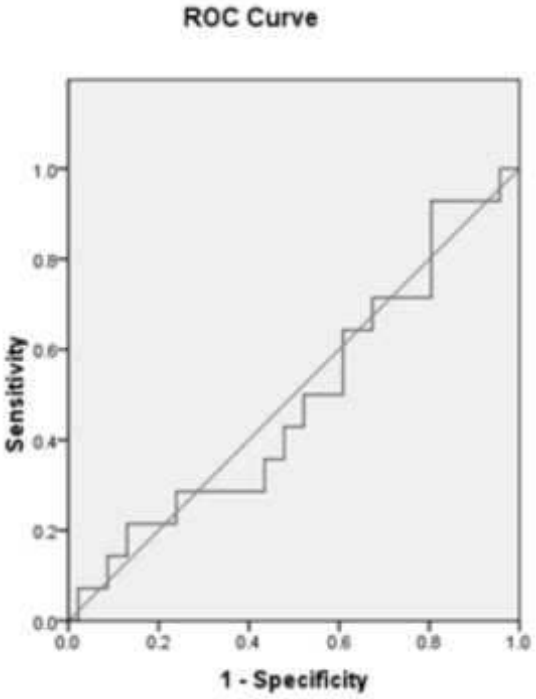

Figure 1. ROC curve to determine cut off point of MPO levels.

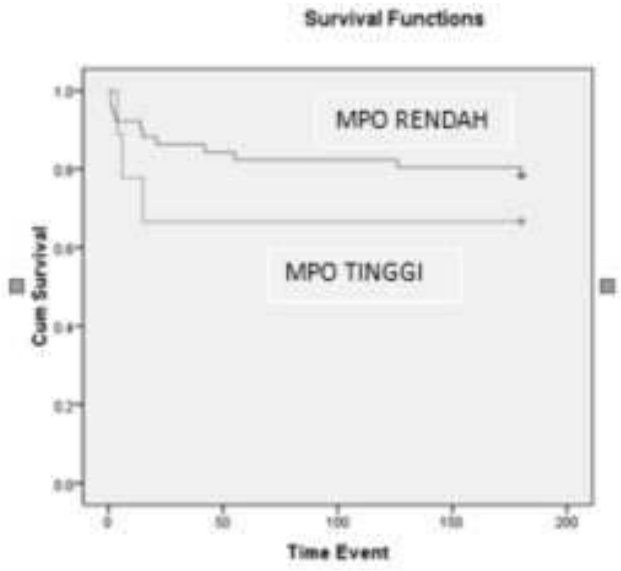

Figure 2. Kaplan Meier survival estimation curve of cardiovascular events based on MPO levels.

risk of death in ACS patients was higher in patients in patients with high MPO levels although not statistically significant (P= 0.403; **Figure 2**).

Effect of MPO levels to cardiovascular events after controlled with another variables

From independent variables that calculate with cox regresion model, both were not statistically significant (P>0.05; **Table 2**), but revascularisation therapy had stronger effect to cardiovascular events.

Effect of MPO levels to cardiovascular events based on ARR and NNT

The magnitude of MPO effect to cardiovascular events was measured with ARR (the difference of cardiovascular risk percentage in high MPO levels with cardiovascular risk precentage in low MPO levels) = 11.76 %. Meanwhile, number needed to treat (NNT) 100 : ARR = 8.5, which meant 8 patients with high MPO levels cause 1 added cardiovascular events (**Table 3**).

DISCUSSION

Statistically, there was no characteristic difference between high MPO levels and low MPO levels (P > 0.05). The subjects were 25-70 years old, with mean in high MPO group was 55.44 (SD 7.03) and 57.63 (SD 11.56) in low MPO group. This mean of age was not different with another studies.[13]

Until now, there's no standard value as cut off point for MPO, compared with another cardiac biomarkers. This is really important in determine wether someone has high or low MPO levels if associate with long term prognosis in management of those patients. This study used cut off point 406 pq/ml, differed with Morrow et al study who used 884 pq/ml.[14] The effect was in what value MPO levels would cause cardiovascular events. Another studies used different unit such as ng/ml,[15-17] µg/l,[9,13,18] and pmol/l based on reagent from factories.[19]

This study used EDTA tube, whereas Morrow used citrat tube, but both could stabilized blood samples. Blood samples were kept in temperature -15 to -40^{0}C, whereas Morrow used temperature -20 to -80^{0}C.[14,20] High MPO levels was better obtainde from culprit lesion than peripheral vessels.[22]

The result from Kaplan Meier estimation graph showed that sample survival rate was different in first 10-20 days. After 20th day, survival rate in ACS patients with high MPO levels clearly lower than ACS patients with low MPO levels. Hazard ratio was 1.4 to assess independent effect of high MPO levels to cardiovascular events, although statistically insignificant with P value = 0.415. A metaanalysis study found that RR between 1.69-1.99 with outcome difference statistically significant between high MPO levels and low MPO levels (P < 0.0001).[20]

Another study with mean of observation 30-2000 after ACS reported risk of myocardial infarction, hospitalisation because of ACS, PCI, CABG, and sudden cardiac death, was found more in ACS patients with high MPO levels.[20] In patients with acute chest pain, serial MPO with troponin I levels measurement could predict major adverse cardiac events (MACE) in 6 months than troponin I levels measurement alone.[23]

In multivariate analysis that assess true HR by controlled potential confounding factors, reported cox regression analysis result was not significant (P>0.05), but revascularisation therapy was stronger than MPO to cardiovascular events. Conflicting evidence was found in another study of STEMI patients undergo primary PCI, that reported high MPO levels was an independent predictor MACE in 30 days, beside low LVEF and high leucocyte count.[15]

This study showed ARR 11.76 %, which meant if we could prevent increase of MPO levels in patients with high MPO levels, so we could decrease cardiovascular evens risk for 11.76 %. Whereas NNT 8 meant for every 8 person with high MPO levels, could add 1

Table 2. Base model cox proportional hazards regression analysis high MPO levels as cardiovascular events in patients with ACS

Variables	HR	95% CI	P
MPO	1.427	0.390 to 5.222	0.591
Revascularisation	2.288	0.706 to 7.419	0.168

Table 3. ARR and NNT Value

MPO Levels	Total	Cardiovascular Events	(%)	ARR(%)	NNT
Low	51	11	21.57		
High	9	3	33.33		
Total	60	14	23.33	11.76	8.5

cardiovascular events, so we need to control this together.

The limitation of this study was to get result that statistically significant, need more samples and longer observation time. There's no cut off point of MPO levels, so author determined it with ROC curve (using median value will cause imbalance data distribution between ACS patients with high and low MPO levels and can cause bias). Measurement of MPO levels from peripheral blood samples can not reflect the true MPO levels in culprit lesion. Beside that, using different unit to determine MPO levels and different storage from previous study. The difference in revascularisation management will affect cardiovascular events.

CONCLUSION

Cohort prospective study was done to prove the role of inflammation in ACS progresivity. High MPO levels is a prognostic marker of cardiovascular events during 6 months in patients with ACS. More samples and longer observation time are needed in order to get significant result. MPO levels cut off point must be determine carefully to minimize bias eventhough there's no standard yet. Blood sample should collected from culprit lesion to reflect true MPO levels. All patients should get same revascularisation procedure based on indication, therefor it will not affect cardiovascular events.

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