Correlation between High-Sensitive C-Reactive Protein and High-Sensitive Troponin I with 6-Minute Walk Distance in Acute Myocardial Infarction

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ABSTRACT

Background: Biomarker has a role in diagnosis and risk stratification of ischemic heart disease patients. Troponin has become the reference biomarker for acute myocardial infarction (AMI). However, some other biomarkers have benefit on prognostic value, such as C-Reactive Protein (CRP). Six-minute walk test (6MWT) could be performed to assess functional capacity in patients with heart disease.
Aim: To assess the correlation between hsCRP and hsTroponin I with 6-minute walk distance (6MWD) in AMI patients.
Method: This is an observational analytic study with prospective cohort design, conducted in August-September 2018. The subjects were AMI patients at Dr. Moewardi district general hospital, Surakarta. The hsCRP and hsTroponin I sampling was carried out on admission. 6MWT was performed before discharge. Statistical analysis was performed to assess the correlation. Then the ROC curve was used to determine the cut-off point, sensitivity and specificity.
Result: 6MWD of 40 subjects was divided into 2 groups based on the mean distance (<378 m and ≥378 m). There was a significant negative correlation between hsCRP and 6MWD (r =-0.475, p =0.002), but no significant correlation between hsTroponin I and 6MWD (r =-0.048, p = 0.244). However, hsCRP together with hsTroponin I have a significant correlation with 6MWD (r =0.491, p =0.006). Using the ROC curve, obtained AUC of 0.725 and a cut-off point of 0.555 mg/l, as well as a sensitivity of 69.6% and specificity of 88.2%
Conclusion: There was a significant negative relationship between hsCRP and 6MWD, but no significant relationship between hsTroponin I with 6MWD.HsCRP together with hsTroponin I have a significant correlation with 6MWD in AMI.

Keywords: 6-minute walk distance; acute myocardial infarction; hsCRP; hsTroponin I

INTISARI

Latar Belakang: Biomarka memegang peranan dalam diagnosis dan stratifikasi risiko pada pasien dengan penyakit jantung iskemik. Troponin menjadi biomarka rujukan pada infark miokard akut (IMA). Namun terdapat beberapa biomarka yang bisa memberi nilai tambah dalam informasi prognostik, salah satunya adalah *C-reactive protein* (CRP). *Six-minute walk test* (6MWT) dapat dilakukan untuk menilai kapasitas fungsional pada pasien dengan penyakit jantung.
Tujuan: Untuk mengetahui hubungan antara kadar hsCRP dan hsTroponin I dengan jarak tempuh 6MWT pada pasien IMA.
Metode: Penelitian ini adalah studi observasional analitik dengan desain kohort prospektif, dilakukan pada bulan Agustus–September 2018. Subyeknya adalahpenderita IMA di RSUD Dr.Moewardi, Surakarta. Pengambilan sampel hsCRP dan hsTroponin I dilakukan saat pasien masuk IGD. 6MWT dilakukan sebelum pasien pulang. Analisis statistik dilakukan untuk menilai korelasi dengan uji korelasi ganda, kemudian dihitung *cut-off point*, sensitivitas, serta spesifisitas dengan menggunakan kurva ROC.
Hasil: Dari 40 subyek diperoleh jarak tempuh 6MWT yang dibagi 2 kelompok berdasarkan rerata, yaitu< 378 m dan ≥ 378 m. HsCRP dan jarak tempuh 6MWT memiliki hubungan negatif yang bermakna (r = -0.475, p = 0.002), sedangkan hsTroponin I tidak memiliki hubungan bermakna dengan jarak tempuh 6MWT (r = -0.048, p = 0.244). Namun, hsCRP dan hsTroponin I secara bersama-sama berhubungan dengan jarak tempuh 6MWT secara bermakna (r = 0.491, p = 0.006). Dengan kurva ROC, didapatkan AUC 0.725 dan *cut-off point* 0.555 mg/l, serta sensitivitas 69.6% dan spesifisitas 88.2%.
Kesimpulan: Terdapat hubungan negatif yang bermakna antara kadar hsCRP dan jarak tempuh 6MWT, tetapi tidak terdapat hubungan bermakna antara hsTroponin I dengan jarak tempuh 6MWT. Namun secara bersama-sama terdapat hubungan bermakna antara kadar hsCRP dan hsTroponin I dengan jarak tempuh 6MWT pada penderita IMA.

INTRODUCTION

Ischemic heart disease contributes to global burden of disease.[1] Epidemiological characteristic of acute myocardial infarction (AMI) has been changed dramatically in the last 3-4 decades.[2] In Asia-Pasific, acute coronary syndrome (ACS) has become the highest number cause of death.[3] In the last 3 decades, AMI management has developed and become more advance. AMI is necrotic condition in myocardium as a result of unstable ischemia syndrome. In practice, to establish the diagnosis of this disease is based on clinical presentation, electrocardiogram, biochemical assay, and invasive or noninvasive imaging.[4]

Biomarker has a role in diagnosis and risk stratification in ischemic heart disease patient. Troponin is the reference biomarker in ACS. Nevertheless there are some biomarkerswhich have additional value of prognostic information, one of them is C-reactive protein (CRP). CRP is acute phase reactant to predict cardiovascular risk in atherosclerotic patient.[5] Myocardial ischemia stimulates the pro-inflammatory cytokines to produce CRP. The result will be remodelling of the heart with clinical manifestations of heart failure.[6] High-sensitivity CRP (hsCRP) level has a negative correlation with left ventricular ejection fraction (LVEF).[7]

Functional capacity in heart disease is important. The assessment with 6-minute walk test (6MWT) can be performed to predict cardiovascular events in 3 months after ST elevation myocardial infarction (STEMI) with fibrinolytic therapy.[8] There was a significant relationship between the 6-minute walk distance (6MWD) and the extent of extracellular matrix in the LV myocardium.[9] This study aims to assess the correlation between hsCRP and hsTroponin I with 6-minute walk distance (6MWD) in AMI patients.

METHODS

This study was conducted at Dr. Moewardi District General Hospital, Surakarta, Indonesia from August to September 2018. The inclusion criteria were AMI patients who agreed and signed the informed consent for this study. Patients with chronic kidney disease, liver cirrhosis, infection, stroke, previous infraction, peripheral artery disease, muscle weakness, or died during hospitalization were excluded.There were 40 AMI patients who fulfilled inclusion and exclusion criterias. The diagnosis of AMI was based on typical chest pain characteristics and elevation of cardiac marker, with or wihout ST-segment changes. The hsCRP and hsTroponin I level was examined on admission. The Advia 1800 (Siemens) analyzer was used to measure the hsCRP level and Mini Vidas (Biomérieux) analyzer to measure the hsTroponin I level. The 6MWT was performed to the subjects according to the American Thoracic Society (ATS) protocolto get 6MWD, before discharged.[10]

The collected data was analyzed statistically with SPSS 23.0 software. The Shapiro-Wilk test was used to test the data normality. The qualitative datawas analyzed by the Chi square test or the Fisher`s exact test (if not fulfill the criteria for Chi square test), while the quantitative data was analyzed by the independent t-test (for normal data distribution) or the Mann-Whitney test.The linear regression test was used to analyze the correlation between hsCRP and hsTroponin I with 6MWD. To analyze each variable`s correlation with 6MWD, Pearson`s product moment correlation (for normal data distribution) or Spearman`s Rank correlation test were performed. The receiver operating characteristic (ROC) curve was used to determine the cut-off point and the value of sensitivity and specificity.

RESULT

Data with normal distribution was presented as mean ± standard deviation (SD), the normal distribution transformed data was presented as mean (95% confidence interval), and the abnormal distribution data was presented as median (table 1).

The subjects were divided into 2 groups based on the mean value of 6MWD (378 m). There were no significant difference of qualitative parameters (table 2). However, there was a significant difference in the EF variable of the quantitative parameters analysis (table 3).

Statistical analysis shows a significant negative correlation between hsCRP and 6MWD with r value = -0.475, but no significant correlation between hsTroponin I and 6MWD. In addition, hsCRP together with hsTroponin I have a significant correlation with 6MWD in AMI (table 4).Since hsCRP has the significant correlation with 6MWD, then the relative risk (RR) is analyzed.

The hsCRP parameter was divided into high and low group based on the mean value (0.45 mg/l). The result shows RR of 2.53 (95% CI 1.338 – 4.769).It means the probability of the subjects with hsCRP ≥ 0.45 mg/l to achieve a short 6MWD is 2.53 times higher than those with hsCRP< 0.45 mg/l (table 5).

The ROC curves were used to identify a cut-off point for a short 6MWD based on hsCRP and hsTroponin I level. The ROC curve for hsCRP (figure 1) shows area under curve (AUC) of 0.725 (moderate), cut-off point level of 0.555 mg/l, 69.6% sensitivity and 88.2% specificity. It means that hsCRP is good enough to identify a short 6MWD.

While the ROC curve for hsTroponin I (figure 2) shows AUC of 0.609 (weak), cut-off point level of 177.05 ng/l, 65.2% sensitivity and 58.8% specificity. It means that hsTroponin I is poorly identified a short 6MWD.

Table 1. Baseline characteristics

Parameters	Min – max	Mean±SD	Median/Mean (95% CI)
Age (years)	39 – 74	58.05 ± 9.21	-
BMI	19.1 – 31.1	-	23.15[a]
Onset (hours)	1 – 72	-	4.50[a]
eGFR	10.2 – 130	62.63 ± 25.42	-
HbA1c(%)	5 – 12.90	-	6.35[a]
Total cholesterol (mg/dl)	83 – 252	180.50 ± 38.13	-
HDL cholesterol (mg/dl)	22 – 66	40.13 ± 10.03	-
LDL cholesterol (mg/dl)	55 – 197	126.31 ± 37.09	-
Triglyceride (mg/dl)	58 – 691	-	136.96(116.81–160.58) [b]
EF (%)	21 – 74	46.99 ± 14.59	
LOS (days)	3 – 11	-	5.77 (5.16 – 6.46) [b]
hsCRP (mg/l)	0.02 – 16.79	-	0.45 (0.26 – 0.79) [b]
6MWD (m)	110 – 585	378.05 ± 90.87	

6MWD: 6-minute walk distance, BMI: body mass index, CI: confidence interval, EF: ejection fraction, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, hsCRP: high sensitive C-reactive protein, LDL: low density lipoprotein, LOS: length of stay, SD: standard deviation

[a]) Abnormal distribution data, presented as median

[b]) Normal distribution transformed data, presented as mean (95% CI)

Table 2. Comparison of qualitative parameters between 2 Groups

Parameters	6 MWD< 378 m		6 MWD ≥ 378 m		p value
	n	%	n	%	
Gender					
Male	19	59.4	13	40.6	0.702
Female	4	50	4	50	
MI type					
Anterior STEMI	4	40	6	60	0.433
Non-anterior STEMI	5	62.5	3	36.4	
NSTEMI	14	63.6	8	42.5	
Killip Class					
I	11	42.3	15	57.7	0,053
II	7	77.8	2	22.2	
III	4	100	0	0	
IV	1	100	0	0	
DM					
Yes	9	60	6	40	0.804
No	14	56	11	44	
Hypertension					
Yes	15	62.5	9	37.5	0.648
No	8	50	8	50	
Smoker					
Yes	14	60.9	9	39.1	0.616
No	9	52.9	8	47.1	
Dyslipidemia					
Yes	5	55.6	4	44.4	1.000
No	18	58.1	13	41.9	
ACEi/ARB					
ACEi	19	54.3	16	45.7	0.373
ARB	4	80	1	20	

Parameters	6 MWD< 378 m		6 MWD ≥ 378 m		p value
	n	%	n	%	
Beta blocker					
Yes	21	55.3	17	44.7	0.499
No	2	100	0	0	
Anticoagulant					
Fondaparinux	10	71.4	4	28.6	
Enoxaparin	12	52.2	11	47.8	0.351
Heparin	1	33.3	2	66.7	
Heart failure / deterioration of Killip class					
Yes	3	50	3	50	0.687
No	20	58.8	14	41.2	
Arrhythmia					
Yes	3	100	0	0	0.248
No	20	54.1	17	45.9	
Revascularization					
Nonrevascularization	11	57.9	8	42.1	
Incomplete	7	87.5	1	12.5	0.087
Complete	5	38.5	8	61.5	

6MWD: 6-minute walk distance, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, DM: diabetes melitus, MI: myocardial infarction, NSTEMI: Non ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction

Table 3. Comparison quantitative parameters between 2 Groups

Parameters	6 MWD< 378 m		6 MWD ≥ 378 m		p *value*
	Mean	SD	Mean	SD	
Age (years)	59.95	8.96	55.47	9.15	0.129
Onset (hours)	9	1 – 72	3	1 – 72	0.466
BMI	22.40	19.1 – 31.1	23.40	20.7 – 30.1	0.468
EF (%)	42.3	14.86	53.32	11.89	0.016*
eGFR	61.61	24.55	64.01	6.60	0.772
HbA1c (%)	6.50	5.3 – 12.9	6.10	5 – 10	0.143
Total cholesterol (mg/dl)	177.30	38.33	184.82	38.58	0.544
HDL cholesterol (mg/dl)	39.96	9.57	40.35	10.92	0.904
LDL cholesterol (mg/dl)	126.61	36.25	125.47	39.33	0.925
Triglyceride (mg/dl)	140	63 – 365	117	58 – 691	0.632
LOS (days)	6.30	1.94	5.88	2.39	0.542

6MWD: 6-minute walk distance, BMI: body mass index, EF: ejection fraction, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, hsCRP: high sensitive C-reactive protein, LDL: low density lipoprotein, LOS: length of stay, SD: standard deviation
*) Significant if p value < 0.05

Table 4. Correlation analysis of hsCRP and hsTroponin I with 6MWD

Parameters	Result	
	Correlation	p *value*
hsCRP with 6MWD	r = -0.475	0.002*
hsTroponin I with 6MWD	r = -0.048	0.769
hsCRP and hsTroponin I with 6MWD	R = 0.491	0.006*

6MWD: 6-minute walk distance, hs: high-sensitive, CRP: C-reactive protein
*) Significant if p value < 0.01

Table 5. Relative risk for short 6MWD in high and low hsCRP

Parameters	6MWD <378 m	6MWD ≥ 378 m	p value	RR (95% CI)
hsCRP ≥ 0.45 mg/l	16 (69.6%)	3 (17.6%)	0.001*	2.53 (1.338 – 4.769)
hsCRP< 0.45 mg/l	7 (30.4%)	14 (82.4%)		

6MWD: 6-minute walk distance, hsCRP: high-sensitive C-reactive protein
*) Significant if p value < 0.01

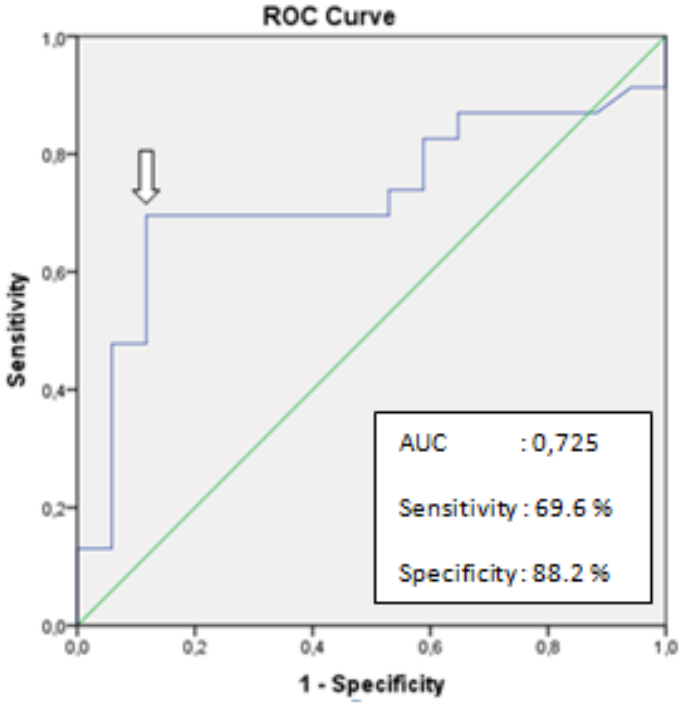

Figure 1. ROC curve for hsCRP and 6MWD
6MWD: 6-minute walk distance, AUC: area under the curve, hsCRP: high sensitive C-reactive protein, ROC: receiver operating characteristic

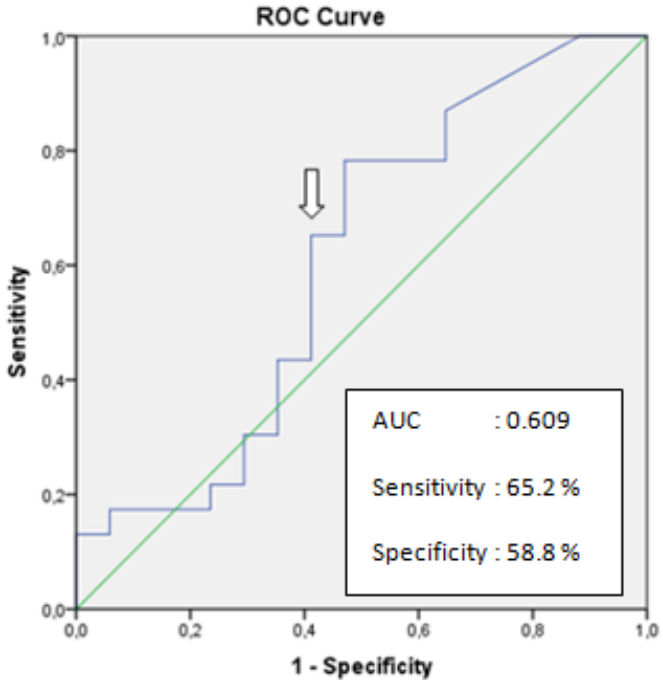

Figure 2. ROC curve for hsTroponin I and 6MWD
6MWD: 6-minute walk distance, AUC: area under the curve, hs: high sensitive, ROC: receiver operating characteristic

DISCUSSION

This study shows a significant negative correlation for hsCRP and 6MWD. It means if hsCRP level is high then 6MWD will be short, and vice versa. Furthermore, hsCRP together with hsTroponin I has a significant correlation with 6MWD. While hsTroponin I has no significant correlation with 6MWD. It might be caused by the different MI onset of the subjects. The troponin I reach the peak at 12-36 hours after MI, then it will decline.[11]

Acute myocardial infarction initiates danger-associated mollecular patterns (DAMPs) production, which activates complement cascade and stimulates toll-like receptors (TLRs), and eventually activates NF-kB. It will cause the release of various pro-inflammatory mediators, such as IL-1, IL-6 and TNF-α. The pro-inflammatory mediators will induce inflammatory cell recruitment into the infarcted zone, and increase the pro-inflammatory response after AMI. IL-6 will regulates the synthesis of CRP, while TNF-α will stimulate matrix metalloproteinase (MMP) production.[12]

Troponins are cardiac proteins, which are important for actin and myosin interaction, modulating sarcomeric contractile function in response to cytosolic calcium and protein phosphorylation.[5] Disturbance of myocyte contractility could be a cause of ventricular dysfunction in cardiac remodeling.[13]In the infarcted myocardium, the polymorphonuclear leucocytes have some roles, such as phagocytosis of the necrotic tissue, extracellular matrix degradation through MMP release, and the release of reactive oxygen species (ROS). Those will lead to the left ventricular remodelling, which will result on the short 6MWD.[9]

A study involving 118 patients with AMI onset < 6 hours, examined CRP level on admission. The early CRP level was associated with Killip class, LVEF, number of stenotic arteries, and cardiovascular events 1 month and 1 year after infarction.[14]

The increase of CRP level on early infarction also has association with the existence and the mitral regurgitation severity, and with the diastolic dysfunction. This indicates the association of inflammatory and ventricular remodelling process.[15] The extracellular matrix components will extent myocardial stiffness, and contribute to the reduction of LV compliance during diastole and the increase of LV diastolic filling pressure.[16] A study in patients with LVEF 15-45% showed that their 6MWD was shorter than normal person.[17]

This study has some limitations. First, this is a single center study, so the result may not present the condition in the other region. Second, the hsCRP and hsTroponin I level was based on 1 time sampling (on admission). The subjects came with different onset of MI, so their hsCRP and hsTroponin level may be beyond the peak level and may have decreased. A multicenter study should be done to MI subjects with onset ≤ 2 days, so the result will reflect more about the early condition of the disease.

CONCLUSION

This study showed a significant negative correlation between hsCRP and 6MWD in AMI patients. Furthermore, hsCRP together with hsTroponin I has a significant correlation with 6MWD. However, there was no significant correlation between hsTroponin I and 6MWD in AMI patients.

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