

Correlation of Serum Levels of Matrix Metalloproteinase-9 to Acute Heart Failure Event as a Complication of Acute Coronary Syndrome

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Abstract

Background: Acute heart failure (AHF) after acute coronary syndrome (ACS) is the biggest complication with a poor prognosis in a long term. The influence of MMP-9 as proteolytic enzyme that degrades extracellular matrix in remodeling left ventricle was recognized. However, according to researcher's knowledge, evaluation of the MMP-9 as a predictor of AHF after ACS was never reported. **Objective:** To find out the serum level of MMP-9 in ACS with AHF higher than that without it, as well as to find out the level of MMP-9 with risk of AHF after ACS. **Method:** The study used a cross-sectional study. Samples were collected by using a consecutive sampling technique among patients with ACS treated in ICCU of Public Hospital Dr Sardjito Yogyakarta, since June 2008 to August 2010. Questionnaires were used to collect sample raw data. The level of MMP-9 was examined a time at admission in ICCU before thrombolysis was done. The heart failure had Killip II- IV scores. Factors influencing the incidence was analyzed by using multivariate analysis technique. A significance level was at $p < 0.05$. The relative risk of acute heart failure at a certain level of MMP-9 (from cut-off value) was obtained after it was adjusted. **Result:** Among 122 subjects, 75 was without AHF and 47 with AHF. Median of the level of MMP-9 in the whole sample of ACS was 1248.55 ng/mL with a minimum of 170.50 ng/mL and maximum of 3058.40 ng/mL. Moreover, the level of MMP-9 in ACS with AHF (1700.81 ± 740.43 ng/mL) was significantly higher than ACS without AHF (1189.55 ± 654.60 ng/mL) with p value = 0.000. Independent risk factor after the multivariate analysis was done indicates the level of MMP-9 above 1444 ng/mL (RR= 4.2) and the location of anterior infarction (RR= 2.9). **Conclusion:** In patients with ACS treated in ICCU of RSUP Dr Sardjito, the level of MMP-9 with AHF was higher than that without it. If the level of MMP-9 above 1444 ng/mL, the possibility of AHF was 4.2 times.

Keywords: ACS, MMP-9, AHF after ACS

Introduction

Kyne et al. (2000) stated that heart failure is the biggest complication of ACS and a clinical problem with a poor prognosis in the long run about 50% to 70% among elderly patients¹. Acute heart failure is associated with post-AMI mortality rates as expressed in ESC (2005) in a large randomized control trial study on patients hospitalized with decompensated heart failure, 60-days mortality of 9.6%, combined death and 60-days rehospitalization of 35%. The largest of death in acute heart failure was due to IMA of 30% in 12 months².

Remodeling as a concept that underlies the occurrence of heart failure has widely been studied, one of which was associated with the involvement of matrix metalloproteinase (MMP), especially after the ACS. There are 25 types of MMP and MMP-9 with gelatinase activity, which

has wide influence on ventricular remodeling and heart failure (Armstrong, 2006 and Phatharajaree et al., 2007)^{3,4}. According to Jong et al. (2006) the levels and activities of MMP-9 increased in patients with post-AMI acute heart failure, while those of MMP-2 did not show any difference⁵.

The purposes of this study are to find out difference in serum levels of MMP9 at ACS between with and without acute heart failure, and to examine the effect of increase in serum levels of MMP-9 at ACS on acute heart failure.

METHOD

The cross sectional study was conducted at the Intensive Cardiac Care Unit (ICCU) of Public Hospital Dr. Sardjito Yogyakarta from June 2008 to August 2010. The subjects of the study were recruited consecutively until the required number of samples was reached. Anamnesis, physical

examination, 12 lead EKG examination, Killip score assessment, thoracic X-ray examination, serial CKMB and troponin I examination, standard laboratory tests including CBC, liver function (SGOT, SGPT, albumin), renal function (ureum, creatinine, uric acid), electrolytes, blood glucose, coagulation function (PPT and aPTT), lipid profile examination, and examination of MMP-9 were done to each patient with a diagnosis of ACS at admission and meeting the inclusion criteria of study. The examinations were performed using the standard ELISA method in Central Prodia Laboratory of Jakarta, because the laboratory department of Public Hospital Dr. Sardjito could not been able to do.

The diagnosis of ACS (in this study, they were STEMI and NSTEMI) was done with minimum of two of three myocardial infarction criteria, i.e. the presence of typical chest pain, EKG pattern changes, and increased markers of heart muscle damage (cardiac enzymes) (Jaffe, 2007)⁶. Acute heart failure is determined by Killip criteria, namely the class II, III or IV, which was firstly done at admission to ICCU and evaluated until the seventh day of treatment, to find out whether or not there was change in Killip class of the class I (no acute heart failure) into class II, III or IV.

Inclusion criteria for this study: (a) patients with diagnoses of STEMI, either with thrombolysis or without thrombolysis, and of NSTEMI with the onset of attacks in both groups of = 7 days associated with the incidence of acute heart failure as a complication of ACS, (b) male and female patients with age >18 and <75 years, and (c) patients are willing to participate in the study with informed consent. Meanwhile, the exclusion criteria in this study were: (a) patients with Primary PCI; (b) patients with chronic heart failure before, (c) patients are pregnant.

Outcomes assessed were difference in serum levels of MMP-9 between ACS with complication of acute heart failure and that without acute heart failure and the relative risk of acute heart failure at certain levels of MMP-9. The ethical feasibility of study was obtained from the Ethical Committee of Medicine and Health Research in Faculty of Medicine, Gadjah Mada University.

The basic characteristics of subjects were presented in the average or median. Average difference in levels of MMP-9 was found in the two groups of ACS with heart failure and to be are not tested by Student's T Test or Mann-Whitney U Test.

The significance was accepted at p value <0.05, while the cut-off value of MMP-9 was determined by the ROC curve. The relative risk (RR) of MMP-9's influence on post-ACS acute heart failure was obtained after multivariate analysis was done using other risk factors (age, location of infarction).

Results

From June 2008 to August 2010, 135 patients of ACS were obtained. There were 122 subjects that met the criteria of study. The average age was 56.75 ± 9.82 years with the youngest age of 32 and the oldest one of 75. Average age with acute heart failure was 59.2 ± 9.2 years, while that without it was 55.2 ± 9.9 years with a significance value of $p=0.027$. Most of the subjects were 104 male patients (85.2%), while the remaining was 18 female ones (15.8%). No difference was found in the variables of thrombolysis, ACE inhibitors, diagnosis and the content of c Troponin I, while a significant difference was found in location of infraction ($p = 0.003$). In this study, the overall level of MMP-9 on the condition of ACS was 1248.55 ng/mL, a minimum of 170.50 ng/mL and a maximum of 3058.40 ng/mL. Levels of MMP-9 were obtained at ACS with acute heart failure (1700.81 ± 740.43 ng/mL) and that without acute heart failure (1189.55 ± 654.60 ng/mL) with a value of $p = 0.000$, as shown in Table 1.

To find out the effect of the increased levels of MMP-9 on the incidence of heart failure, the cut-off levels of MMP-9 was determined previously. From these ROC curves, it can be known that the cut-off value of the levels of MMP-9 was 1444 ng/mL. In the cut-off value, the sensitivity of 67% and the specificity of 62% were found. Based on the cut-off value of the levels of MMP-9, the subjects of this study were classified into two groups, i.e. group with the levels of MMP-9 above the cutoff value, amounting to 58 subjects (47.5%) and the group with high levels of MMP9 under the cut-off value, amounting to 64 subjects (52.5%). The proportion of area under curve of the ROC curve was equal to 69.5%, meaning that there was a weak relationship between MMP-9 and post-ACS acute heart failure as shown in Figure 1.

Table 2 indicates that the subjects with the levels of MMP-9 > 1444 with acute heart failure was 66%, while those with the levels of MMP-9 < 1444 with heart failure was 31% with a significance level of $p = 0.000$. It can be concluded that there

Tabel 1. The characteristics of the subjects of study

Variable	n (%)		P
	No acute heart	Acute heart failure	
failure			
Average age (year)	55.2±9.9	59.2±9.2	0.027
< 60 year	49(65.3)	23(48.9)	0.073
> 60 year	26(34.7)	24(51.1)	
Male	63(84)	41(87)	0.624
Female	12(16)	6(13)	
ACE inhibitor, Yes	46(61.3)	31(66.0)	0.357
No	29(38.7)	16(34.0)	
Trombolysis, Yes	20(26.7)	15(31.9)	0.533
No	55(73.3)	32(68.1)	
Troponin I < 7.17 ng/mL	40(53.3)	22(46.8)	0.483
> 7.17	35(46.7)	25(53.2)	
Diagnosis STEMI	38(50.7)	27(57.4)	0,465
NSTEMI	37(49.3)	20(42.6)	
Location of infarction	43(57.3)	14(24.8)	0.003
Non anterior			
Anterior	32(42.7)	33(70.2)	
MMP-9 ng/mL	1189.55±654.60	1700.81 ±740.43	0.000

Table 2. The level of MMP-9 with the incidence of acute heart failure after ACS.

Variable ng/mL	Heart failure n(%)	No heart failure n(%)	n(%)	P
MMP-9> 1444	31(66.0)	25(33.3)	56(47.5)	0.000
MMP-9< 1444	16(34.0)	50(66.7)	66(52.5)	
Total	47(38.5)	75(61.5)	122(100)	

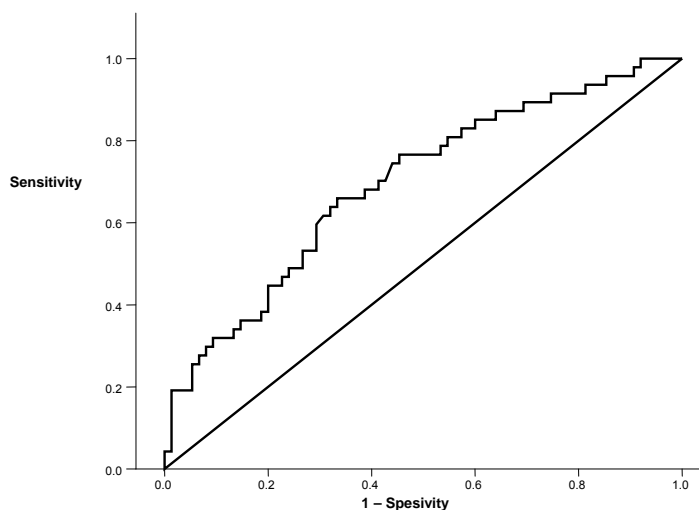


Figure 1. The ROC curve to determine the cut-off value of the levels of MMP-9

Table 3. Multivariate analysis on the variables of age, location of infarction, and the serum level of MMP-9 with acute heart failure after ACS

Variable	P	RR/Exp(B)	95% C.I.	
			Lower	Upper
Age	0.053	2.277	0.991	5.232
Location of infarction	0.010	2.963	1.298	6.765
The level of MMP-9	0.001	4.217	1.843	9.646

was a relationship between MMP-9 and the post-ACS acute heart failure.

By making a multivariate analysis with other risk factors lain, it can be found out that MMP-9 has the RR of 4,2 and the location of anterior infarction with the RR of 2.9, as shown in Table 3.

Discussion

In this study, there was difference in mean age between the groups with acute heart failure and those with a significance value of $p = 0.027$, while those with acute heart failure was older than those without it. According to Tayebjee et al. (2005) the activities of TIMP and MMP has positive correlation, while TIMP-1 has a negative correlation if associated with age. The study use healthy subjects, so that the higher the age, the higher the risk of atherosclerosis or ACS, because the balance of MMPTIMP changed⁷.

Sundström et al. (2004) shows that there was a very clear difference between MMP-9 and left ventricular remodeling, and the relationship was only significant for patients male patients⁸. The result was different from our result of the study, because no difference was found in sex between the groups with acute heart failure and those without acute heart failure.

Result of the study shows that the groups using the ACE inhibitor have larger proporsion, but acute heart failure did not show difference between those with ACE inhibitor and those without it ($p = 0.357$). It was different from results of the study conducted by Franzosi et al. (1998), indicating that the early use of ACE inhibitors (the acute phase was 0-36 hours of the onset of myocardial infarction, followed by 46 weeks) significantly reduced the incidence of nonfatal heart failure in 30 days, i.e. 6.1 cases per 1000 pasien⁹. This was because the size of sample was much greater in the study (6687 in groups with ACE inhibitor and 6937 in control group).

In the study, no more thrombolysis was done, and there was no significant difference in the incidence of post-ACS acute heart failure between groups with thrombolysis and those without it ($p = 0.533$). This was different from Werf et al. (2003), stating that of 150,000 patients that were randomized to receive fibrinolytic therapy and the control of onset under 12 hours, fibrinolytic therapy still given better benefit than control¹⁰.

Results of the study were consistent with those of previous studies, i.e. there were the

increased levels of MMP-9 on the condition of ACS, amounting to 1248.55 ng/mL with a minimum of 170.50 ng/mL and a maximum of 3058.40 ng/mL. In addition, the levels of MMP-9 on the ACS with heart failure (1700.81 ± 740.43 ng / mL) were significantly higher than those on the ACS without acute heart failure (1189.55 ± 654.60 ng/mL) with p-value of 0.000.

Savic et al. (2010) stated that other independent predictors of the increased risk of acute heart failure wee: anterior infarction and 3-vessel disease CAD¹¹. The proportion of age > 60 years was higher with the complications of acute heart failure, but it was statistically insignificant ($p = 0.073$). After multivariate analysis was done, it can be known that the role of MMP-9 as an independent predictor of acute heart failure indicates that the levels of MMP-9 above 1444 ng/mL in patients with ACS influenced on the incidence of acute heart failure by 4.2 times compared to the ACS with the levels of MMP-9 under 1444 ng / mL. According to our knowledge, there was no data about it before. Therefore, it becomes the contribution of knowledge on the influence of MMP-9 on the incidence of heart failure.

Conclusion

The serum levels of MMP-9 in patients of ACS with acute heart failure were higher than those without acute heart failure in ICCU department of RSUP Dr. Sardjito Yogyakarta. The ACS patients with the serum levels of MMP-9 > 1444 ng/mL had a possibility of acute heart failure by 4.2 times compared to those of ACS with the MMP-9 of <1444 ng/mL.

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