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High level of anti-helicobacter pylori-heat shock protein 60II3, interferon-γ, and neopterin are risk factors of cardiovascular events in acute coronary syndrome patients

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ABSTRACT

Background: Chronic inflammatory process that may cause acute myocardial infarction (AMI) has been known to play an important role in the pathogenesis of atherosclerosis and atheroma plaque instability. Based on inflammation process, several previous studies showed contradictory results in finding a relationship between infection *H. pylori* with the formation of atherosclerosis through the establishment of immunoglobulin G (IgG) anti-H. pylori-HSP60II3 (IgG anti-Hp-HSP60II3), and neopterin level due to oxidative stress. This study aims to know whether IgG anti-Hp-HSP60II3, IFN-γ and neopterin are risk factors of cardiovascular events (CVE) in patients with ACS.

Methods: A prospective cohort study was conducted among 66 patients to determine the levels of IgG anti-Hp-HSP60II3, IFN-γ, and neopterin in patients with ACS as well as the levels of IgG anti-Hp-HSP60II3, IFN-γ, and neopterin. ACS patients were grouped into two groups: patients with ACS with positive prognostic factors (high levels of IgG anti-Hp-HSP60II3, IFN-γ, neopterin, and hs-CRP) and the group of patients with ACS without prognostic factor (low level of anti-IgG levels hp-HSP60II3, IFN-γ, neopterin, hs-CRP), and then were observed for 6 months while in the hospital. Data were analyzed using SPSS version 20 for Windows.

Results: In observations over a period of 6 months, found as many as 15 (22.7%) patients with CVE, which consisted of 11 (16.7%) patients' vascular death, 3 (4.5%) patients had IMA and 1 (1.5%) patients experienced recurrent cardiac ischemia from 66 patients with ACS. Mean difference between the time of occurrence CVE subjects with high and low levels of neopterin are statistically significant (P<0.05). When confounding factors such as dyslipidemia, diabetes, hypertension, obesity, smoking, and age are controlled, only neopterin levels affect the incidence CVE with the incidence rate ratio of 6.46 (95% CI: 1.45-28.74; p = 0.014) and path analysis found the effect of neopterin on CVE incidence about 49,1%, p < 0.05. Kaplan-Meier analysis gives result that the average time of CVE on a group of subjects with high levels of neopterin is shorter (129.09 days) than the group of subjects with low levels of neopterin (168.33 days) (P=0.008).

Conclusion: This study found that the high level of anti-helicobacter pylori-heat shock protein 60II3, interferon-γ, and neopterin have a potential role in predicting risk factors of cardiovascular events in acute coronary syndrome patients.

Keywords: neopterin, IFN-γ, IgG anti-Hp-HSP60II3, ACS, CVE

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Introduction

Atherosclerosis is a chronic inflammatory process that may cause angina pectoris, myocardial infarction and cerebral infarction.[1] In recent years, inflammation has been known to have an important role in the pathogenesis of atherosclerosis and atheroma plaque instability.[2-4] Several inflammatory markers have also been studied concerning cardiovascular events (CVE) such as death due to vascular causes, AMI, stroke, and recurrent cardiac ischemia.[1] Currently one of the inflammatory markers are often used as a marker of cardiovascular disease risk is high sensitive C reactive protein (hs-CRP).[5] Pathogen infection that causes persistent immune response in the body to stimulate the host and the pathogenesis of atherosclerosis.[1] One cause inflammation which lately is often associated with atherosclerosis is an infection of *Helicobacter pylori* (*H. pylori*).[3]

H. pylori are one of the causes of gastrointestinal infections in the world that resulted in a variety of diseases ranging from chronic gastritis to gastric adenocarcinoma and lymphoma.[1,6,7] Almost all of the human population has been infected by *H.*

pylori, but most (over 70%) of the population are infected have no symptoms.[1,7] Evidence suggests that the infection of *H. pylori* usually lasts a lifetime unless eradicated by antimicrobial.[8] However, several previous studies showed contradictory results in finding a relationship between infection *H. pylori* with the formation of atherosclerosis. One hypothesis says that *H. pylori* are an indirect role in the development of atherosclerosis because these pathogens are permanently there on gastrointestinal.[3] Ameriso et al. stated that the deoxyribonucleic acid (DNA) *H. pylori* was found in 20 of 38 plaques of atheroma and not found in normal carotid arteries.[9] Pasceri et al. found the prevalence of H. pylori was significantly higher in cases (patients with ischemic heart disease) compared to controls (subjects with no history of coronary heart disease and the results of electrocardiography (ECG) was normal) with OR 2.8 (95% CI, 1.3 s / d 7, 4, P <0.001).[10] This suggests that H. pylori play a role in atherosclerosis through a persistent inflammatory process.

In atheroma plaques of human blood vessels have found a heat shock protein (HSP). HSP is the introduction of molecules that exist everywhere and is expressed by prokaryotic and eukaryotic organisms.[3] HSP in the presence of plaque pathophysiology is still unclear.[11] Pockley et al. in his research found that the serum levels of HSP60 associated with intima-media thickness.[12] HSP60 derived from pathogens is expected significant role in atherogenesis. Infection of H.pylori which resulted in the formation of chronic pylori immunoglobulin G (IgG) anti-H. pylori-HSP60 (IgG anti-Hp-HSP60) and induced polarization of T helper 1 (Th1).[3] T cells that have been activated to produce interferon γ (IFN-γ). IFN-γ then activates macrophages and cells of the blood vessels that lead to the recruitment of immune cells to the area of the lesion, increased production of chemokines and adhesion molecules, the buildup of cholesterol in foam cells and plaque formation and thrombosis.[13]

As IFN-γ activates the cells, macrophages also play an important role in the formation of atheroma plaque. Macrophages will phagocyte oxidized low-density lipoprotein (oxLDL) to form foam cells. Foam cells are a major component of early atherosclerotic lesions that are the result of the production of free radicals during metabolism oxLDL.[14] Foam cell then subjected to stress, thus forming a lot of HSP60 which can be recognized by the immune system as antigen. This immune response will eventually lead to foam cell death/lysis and subsequently will become necrotic component of atherosclerotic plaques.[14] When activated by IFN-γ, macrophages will secrete neopterin. Neopterin is a result of hydrolysis and oxidation of 7,8 dihydroneopterin triphosphate. Neopterin levels correlate with levels of oxidative stress caused by the activation of the immune system and the level of activation of macrophages.[15]

Relationship *H. pylori* with atherosclerosis encouraged to research whether the infection is H. pylori increases the risk of cardiovascular events (CVE) by examining IgG anti-Hp-HSP60 in acute coronary syndrome (ACS). In the complete sequence of amino acids that make up the HSP60, which contained two homologous peptides between Hp-HSP60 with Human-HSP60. Both of these peptides were Hp-and Hp-HSP60IV HSP60II-V. Hp-HSP60II an amino acid peptide located between Glutamat101-Serin200, while HSP60IV-V is an amino acid peptide located between Isoleusin300-Glisin435. Shorter peptide sequences that are part of the Hp-HSP60II and lies between Glutamat141-Leusin160 a candidate epitope distinguishing / distinctive associated with cardiovascular disease. This peptide is referred to as Hp-HSP60II3 or peptide B1.[1] Based on the aforementioned, this study aims to know whether the IFN-γ as a cytokine produced by Th and neopterin as macrophage activation products and anti Hp-HSP60II3 increase the risk of CVE in patients with ACS, as well as comparing the role of IgG anti-Hp-HSP60 II3, IFN-γ, and neopterin with hs-CRP as the risk factor of CVE in patients with ACS.

METHOD

This study uses a cohort design to prove the levels of IgG anti-Hp-HSP60II3, IFN-γ, and neopterin give a higher risk of CVE in patients with ACS and verify that the levels of IgG anti-Hp-HSP60II3, IFN-γ, and neopterin were offered higher risk of CVE compared with hs-CRP. ACS patients were grouped into two groups: patients with ACS with positive prognostic factors (high levels of IgG anti-Hp-HSP60II3, IFN-γ, neopterin, and hs-CRP) and the group of patients with ACS without prognostic factor (low level of anti-IgG levels hp-HSP60II3, IFN-γ, neopterin, hs-CRP), and then were observed for 6 months while in the hospital (direct observation in the Intensive Cardiac Care Unit (ICCU)), as well as at home (contact by phone or home visits when necessary).

The subject of the study were patients with ACS at ICCU, 20-80 years old, with dyspepsia and with exclusion criteria were patients with heart valve disease, congestive heart failure, acute or chronic liver disease, and received corticosteroid drugs or non-steroidal anti-inflammatory or immunosuppressive drugs. Patients managed by providing a standard therapy under AHA guidelines. This research will result in an incident

rate and survival curve of the prognostic factors for CVE. Blood samples were taken in 48 hours after admission. Examination of specimens was performed at the Laboratory of Clinical Pathology Sanglah Hospital. Data were analyzed using SPSS version 20 for Windows.

RESULTS

A total of 66 patients in the treatment of acute coronary syndrome undergoing Cardiac Intensive Care Unit Sanglah Hospital in Denpasar observed until the occurrence of cardiovascular events (CVE) or until the period of 6 months (180 days). The variables analyzed in this study were anti-HpHSP60II3, interferon-gamma, neopterin and CRP as a risk factor CVE. Of sixty-six patients ACS, there were 13 patients (19.7%) with UA, 11 patients (16.7%) had NSTEMI, and 42 patients (63.6%) had STEMI. In observations over a period of 6 months starting ACS patient admission and continued after discharge, found as many as 15 (22.7%) patients with CVE, which consisted of 11 (16.7%) patients' vascular death, 3 (4.5%) patients had IMA and 1 (1.5%) patients with recurrent cardiac ischemia (Table 1).

No different in characteristics between subjects with and without CVE, except neopterin levels. The mean neopterin levels in subjects with CVE higher than not CVE, where the mean neopterin levels in subjects with CVE and non-CVE of 29.32 (± 22.49); 14.32 (± 6, 96) respectively. The difference was statistically significant, with p <0.01 (Table 1).

Sixty-six patients with ACS (UA, NSTEMI and STEMI) were included in this study and observed over 6 months. 15 (22.7%) patients had CVE, including vascular death, IMA or recurrent cardiac ischemia. Thirteen patients with STEMI and two remainings are with UA. In these observations, CVE can occur in hospital while being treated, and after leaving the hospital. Eleven (16.7%) patients had vascular death, 3 (4.5%) patients had IMA and 1 (1.5%) patients experienced recurrent cardiac ischemia. Ten people (15%) suffered from CVE less than 30 days after hospital admission and five (7.5%) suffered from CVE more than 30 days after hospital admission. Kolmogorov-Smirnov and Shapiro-Wilk analysis results that the data are not normally distributed, and median value of which will be used as the cut-off point (Table 1).

Our study found that there is no significant difference of age, gender, total cholesterol, HDL, LDL, and triglyceride levels between CVE and non-CVE patients (P>0.05) (Table 2). Dyslipidemia profile tends to be higher in a non-CVE group (92.15%) compared to the CVE (86.67%). However, the obese prevalence seems to be more prominent on CVE group (60.00%) compared to non-CVE (50.98%) group. Besides, smoking history is predominant in the non-CVE group (56.86%). The recent findings also found that the neopterin levels are significantly higher (P<0.01) in CVE group (29.32 ± 22.49 nmol/L) compared with non-CVE group (14.32 ± 6.96 nmol/l) (Table 2).

Incidence rate CVE on a group of subjects with a high level of neopterin is 5.216 times greater than the incidence rate CVE on a group of subjects with low levels of neopterin., p = 0.005. Incident rate CVE in subjects with high levels of anti-HpHSP60II3 is 0.832 (95% CI: -0.257 - 2.627) with a p-value = 0.7310 (not significant). Incident rate CVE in subjects with high levels of hs-CRP is 0.820 (95% CI: 0.253 to 2.587) with a value of p = 0.709 (not significant) (Figure 1). Kaplan-Meier analysis gave results that the average time of CVE on a group of subjects with high levels of neopterin was shorter than the group of subjects with low levels of neopterin (Figure 1). In group of subjects with high neopterin levels, CVE occurred in 129.09 days, whereas in the group of subjects with low levels of neopterin, CVE occurred in 168.33 days, p = 0.008 (Figure 1).

CVE cumulative incidence in the group of subjects with high neopterin levels are always higher than the group of subjects with low levels of neopterin, and CVE in the group of subjects with high neopterin levels occur earlier compared with subjects with low levels of neopterin. Kaplan-Meier analysis showed no significant difference in the cumulative incidence CVE between subjects with high levels of IFN-g and low levels of IFN-g

Table 1. Baseline characteristic of respondents, classical risk factors, and inflammatory markers

Variables	Mean	SD	Median (Cut-off)
Age (years)	57.29	11.33	-
Systole (mmHg)	118.97	25.45	-
Diastole (mmHg)	75.65	14.99	-
Total cholesterol (mg/dL)	118.97	25.45	-
HDL cholesterol (mg/dL)	39.96	10.51	-
LDL cholesterol (mg/dL)	130.30	47.66	-
Triglyceride (mg/dL)	147.60	82.06	-
Fasting glucose (mg/dL)	102.71	27.01	-
Post-prandial glucose (mg/dL)	126.39	48.14	-
Neopterin (nmol/L)	17.73	13.65	15.18
IFN gamma (pg/mL)	0.75	0.09	0.73
Anti-HpHSP60$_{II3}$ (OD)	1.24	0.25	1.26
Hs-CRP (mg/L)	31.64	36.34	17.92

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Table 2. Baseline characteristics of respondents based on the classical risk factors and inflammation after grouped according to CVE

Characteristics	CVE (N=15)		Non-CVE (N=51)	
	Mean±SD	N (%)	Mean±SD	N (%)
Age (years)	58.73 ± 11.28		56.68 ± 11.42	
Gender				
Male		12 (80.00)		41 (80.39)
Female		3 (20.00)		10 (19.61)
Total cholesterol (mg/dL)	200.96 ± 61.03		193.58 ± 46.29	
HDL cholesterol (mg/dL)	41.57 ± 10.53		39.49 ± 10.56	
LDL cholesterol (mg/dL)	130.95 ± 60.42		130.11 ± 43.93	
Triglyceride (mg/dL)	162.76 ± 70.83		143.14 ± 85.21	
Dyslipidemia				
Yes		13 (86.67)		47 (92.15)
No		2 (13.33)		4 (7.85)
Obese		9 (60.00)		26 (50.98)
Non Obese		6 (40.00)		25 (49.01)
Systole (mmHg)	112.67 ± 28.96		120.82 ± 24.33	
Diastole (mmHg)	77.07 ± 17.17		75.24 ± 14.46	
Fasting glucose (mg/dL)	109.62 ± 21.22		100.71 ± 28.35	
Post prandial glucose (mg/dL)	123.78 ± 25.33		127.16 ± 53.20	
Smoking History				
Smoking		6 (40.00)		29 (56.86)
Non smoking		9 (60.00)		22 (43.14)
Neopterin (nmol/L)	29.32 ± 22.49		14.32 ± 6.96	
IFN gamma (pg/mL)	0.75 ± 0.08		0.75 ± 0.09	
Anti-HpHSP60$_{II3}$ (OD)	1.24 ± 0.24		1.24 ± 0.25	
Hs-CRP (mg/L)	24.75 ± 32.00		33.64 ± 37.57	

SD: standard deviation; IFN: interferon; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CVE: cardiovascular events

(P>0.05) (Figure 1). In addition, the Kaplan-Meier analysis also showed that the average time of CVE in subjects with high levels of anti-HpHSP60II3 is 152.42±10.38 days and in subjects with low levels of anti-HpHSP60II3 is 145.00±12.59 (P-value = 0.782). No significant difference in the cumulative incidence CVE between both groups (P>0.05). Kaplan-Meier analysis showed that the average time of CVE in subjects with high levels of hs-CRP was 153.54 (± 11.10) days and in subjects with low CRP levels at 143.88 (± 11.85) days, P-value = 0.705. No difference in the cumulative incidence CVE between the two (Figure 1).

The influence of neopterin, IFN-g, anti-HpHSP60II3 and hs-CRP for CVE incidence rate ratio in patients with ACS (UA, NSTEMI and STEMI), were analyzed by the Cox regression model. Results of this analysis indicate that only neopterin levels affect the incidence of CVE (Table 3). Incidence rate ratio is 5.44 (95% CI: 1.46 to 20.33) with P-value = 0.012. In contrast, the other three variables, IFN-g, anti-HpHSP60II3 and hs-CRP were not proven with P values > 0.05, as shown in Table 3. When confounding factors such as dyslipidemia, diabetes, hypertension, obesity, smoking and age are controlled, only neopterin levels have affected the incidence CVE, with the incidence rate ratio 6.46 (95% CI: 1.45 to 28.74) with P-value = 0.014 (Table 3)

DISCUSSION

The study included all types of clinical features of patients with ACS (UA, NSTEMI and STEMI). The third type of clinical picture mechanism has the same pathomechanism, namely inflammation continues with the imbalance between supply and demand of myocardial O2 / heart muscle causing chest pain. Anatomical changes that occurred between the three different clinical picture ACS. At UA coronary vasospasm occurs (dynamic and progressive mechanic obstruction) and can also be followed by the formation of thrombus. While the IMA (NSTEMI and STEMI) occurring is partial obstruction in NSTEMI, STEMI and total obstruction may continue with the establishment of thrombus.[16,17]

Patients who experience CVE ACS has an average age higher than the average age of patients who did not experience CVE. Dyslipidemia was found in 91% of subjects and 86.6% subjects with dyslipidemia CVE is. Obesity was found in 53% of subjects and 60% of subjects with CVE is obese. 53% of the study were smokers and 40% of subjects with CVE are smokers. Of sixty-six patients ACS that is the subject in this study, there were 13 men (19.7%) with UA, 11 people (16.7%) had NSTEMI, and 42 people (63.6%) suffered from STEMI. In one study conducted by Nazer et al. found that different characteristics of the subjects, 58.2% study subjects were women, 18% had diabetes, 50% had hypertension, and 37% smoked.[18] Third of the study subjects suffered from STEMI, NSTEMI another third and the remainder UA.[18]

Results of this study indicate that neopterin levels affect the incidence of CVE. Mean difference between the time of occurrence CVE subjects with high and low levels of neopterin are statistically significant. When confounding factors such as dyslipidemia, diabetes, hypertension, obesity, smoking and age are controlled, then got down only neopterin levels which affect the incidence CVE the incidence rate ratio of 6.46 (95% CI: 1.45 to 28.74), p = 0.014 and path analysis found the effect of neopterin on CVE incidence of 49.1% (P <0,05).

Neopterin examination is used to determine

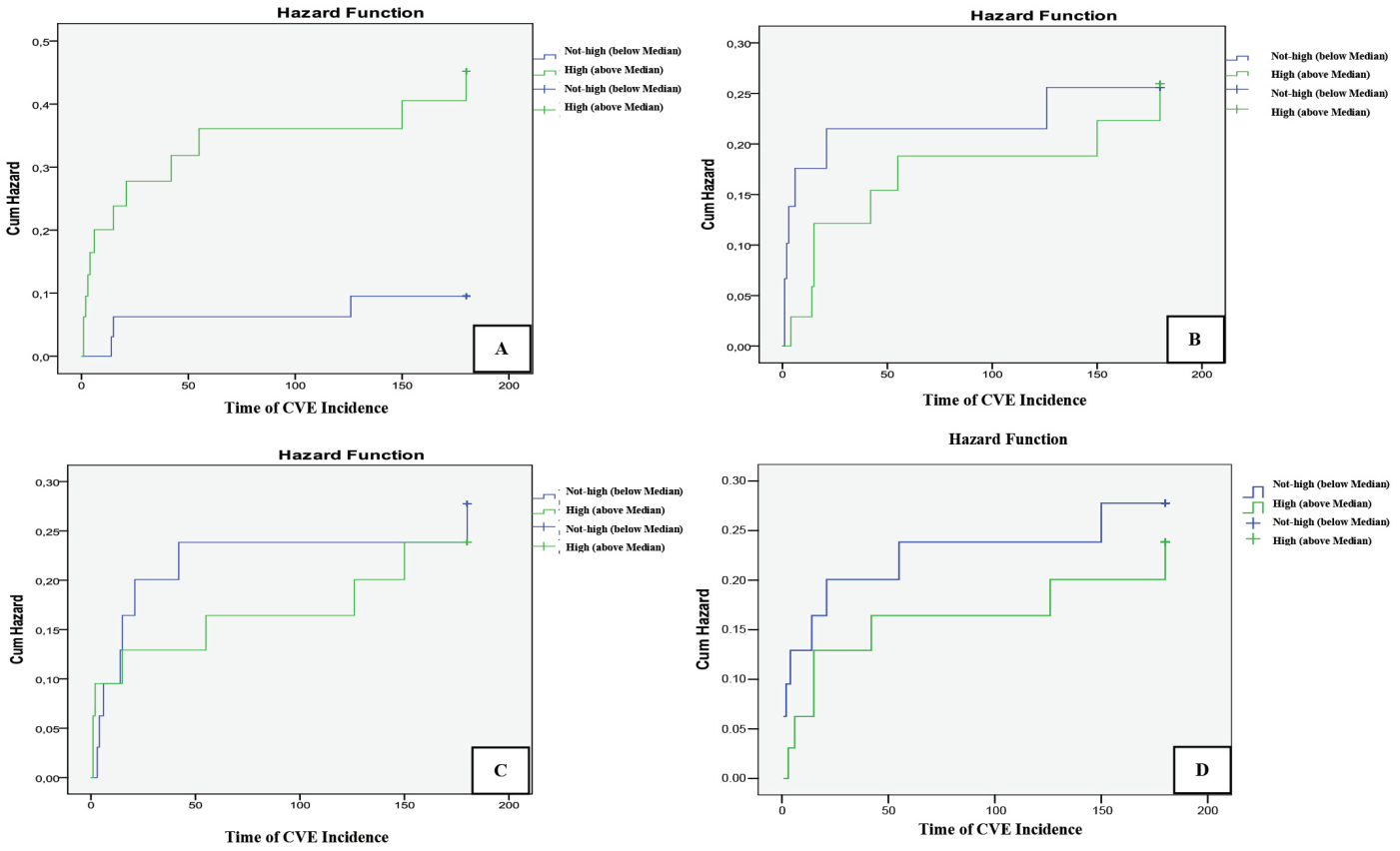

Figure 1. Cumulative incidence curves of CVE according to time between subject groups with (A) high and low levels of neopterin; (B) high and low levels of IFN-g; (C) high and low levels of Anti-HpHSP60II3; and (D) high and low levels of hs-CRP.

Table 3. Cox Regression Analysis for Effect of neopterin, IFN-g, Anti-HpHSP60II3 and hs-CRP for incident CVE

Exposure factor	P-value	Hazard Ratio	CI 95% HR	
			Lower	Upper
Neopterin	0.012	5.438	1.455	20.325
IFNg	0.394	0.630	0.218	1.823
Anti-HpHSP60$_{II3}$	0.888	1.082	0.362	3.228
Hs-CRP	0.653	0.779	0.263	2.308

the cellular immune activation and oxidative stress estimates. Neopterin is a marker of macrophage activation. Neopterin play a role in increasing the cytotoxicity of macrophages by reacting with reactive oxygen, nitrogen and chloride. When macrophages stimulated by IFN-γ, guanosine triphosphate (GTP) GTP cyclohydrolase broken down by enzymes into intermediate products (7-8 dihydro neopterin), which is then oxidized to form neopterin.[18] Amount secreted neopterin correlated with spending reactive oxygen radicals by cells that describe levels of oxidative stress caused by the activation of the immune system.[15] In an in vivo study, it was found that neopterin can stimulate apoptosis of vascular smooth muscle cells and stimulates the formation of plaque. This poses a clinical correlation between elevated levels of neopterin with risk factors CVE after ACS. Neopterin levels on average increased at day 4-9 after the attacks, with an average level of 11.2 nmol / L (6.39 to 20.41).[18] In contrast to the study, blood samples for examination neopterin in this study were taken 48 hours after admission to hospital. The average levels of neopterin in patients who have not experienced CVE CVE and also higher at 29.3 nmol/L and 14.3 nmol/L. In vivo studies also showed that neopterin levels in patients with UA, NSTEMI and STEMI are not much different, so it is suspected that neopterin is not associated with myocardial necrosis.[18] Kaski et al. in his study also found the same thing that neopterin levels in UA and NSTEMI are not much different from the 8.3 and 7.9 nmol / L.[19] Neopterin is considered capable of being a long-term prognosis marker because its concentration is not significantly different when examined day 30, four months and two years.[19] This is in contrast to the only high CRP in the

acute state.[15] Neopterin levels are associated with coronary atheroma plaques that rupture easily. Neopterin can predict the occurrence of ACS in patients with chronic stable angina.[19] Ray et al. mention that neopterin levels 7 days after the ACS = 12.11 nmol / L and is a risk factor for death (HR 1.86; 1.24 to 2.77).[20] Kaski also said that about 14.9% of patients/research subjects suffered repeated attacks, with a hazard ratio of 1.762 (1023 to 3.036), whereas in this study, the number of subjects who experienced CVE 22.7% and a hazard ratio of 5.44 (1.46 to 20.33), higher than that found in studies Ray and Kaski.[19,20]

Results of this study showed that the mean difference between the time of occurrence CVE levels of with high and low IFN-γ subjects is not statistically significant. Provision of recombinant IFN-γ increased 2-fold lesion area, increasing the number of T lymphocytes and increased MHC class II. These things prove the role of IFN-γ proatherogenic. In animals lacking IFN-γ receptors and apolipoprotein E compared with experimental animals that lacked only apolipoprotein E, turns out to be the development of atherosclerosis occurs less experimental animals lacking IFN-γ receptors and apolipoprotein E compared with the only deficiency apolipoprotein E alone.[21] The role of IFN-γ as proinflammatory atherosclerosis is also evidenced by the discovery of mRNA and IFN-γ protein in atherosclerotic lesions of mice and humans. IFN-γ receptor deficiency causes a decrease in the severity of atherosclerosis and administration of recombinant IFN-γ stimulates atherogenic processes.[21]

The role of IFN-γ in the pathogenesis of atherosclerotic lesions is still debatable. IFN-γ is proatherogenic cytokines, which are expressed in arterial plaque and T cells in the circulation in patients with atherosclerosis. But IFN-γ plasma is difficult to detect because of the limited secretion likely systemic, short half-life, or tied all by endothelial cytokine receptors, and has a low affinity for heparan sulfate binding. The role of IFN-γ in atherosclerosis is the accumulation of fat in the case/foam cell formation, cell structure in the plaque and other roles.[21] His role in determining the structure of cells in the plaque consists of stimulating the proliferation of smooth muscle cells, activation of macrophages, stimulates macrophage apoptosis, stimulation of Th 1 cells (autocrine), Th 2 inhibits cell stimulation and increased expression of MHC II on macrophages and smooth muscle cells.[22] When linked with the formation of neopterin, IFN-γ is a central stimulus for activation of GTP siklohidrolase I, which will convert guanosine triphosphate into the intermediate form of neopterin.[19]

One of the autoantigens that play a role in atherosclerosis is HSP. Detection of antibodies to HSP60 is closely related to the severity of coronary artery disease. Past research has shown that there is a relationship between atherosclerosis with multiple pathogens such as Chlamydia pneumoniae, herpes simplex and cytomegalovirus. Pathogens are found in atherosclerotic lesions. Further research is needed to determine the relationship between atherosclerosis with pathogens as well as associated factors or the complication management caused by atherosclerosis.[22-24] Similarly, the relationship between atherosclerosis with *H.pylori* in this study is one step to prove the relationship between pathogens with atherosclerosis, which is still a matter of controversy. Okada et al. found that levels of anti-HpHSP60II3 an independent diagnostic marker for cardiovascular disease.[1] In our study, there were no differences between groups of subjects with high levels of anti-HpHSP60II3 and low. Median levels of anti-HpHSP60II3 subject of the study were 1.26 OD, 0.69 OD with the lowest levels, which means that all subjects had high levels of anti-HpHSP60II3 or above the cut-off Okada. Two possibilities could explain it. The first possibility is that the anti-HpHSP60II3 indeed this is a marker of cardiovascular disease diagnosis so that all subjects ACS patients in this study had high levels or the second possibility is the levels of anti-HpHSP60II3 Indonesian people indeed all higher than the cut-off Okada, due to infection of H. pylori infection is endemic in Indonesian society.

Hs-CRP is a nonspecific marker of inflammation. Results of this study showed that the mean difference between the time of occurrence CVE subjects with high levels of hs-CRP and low is not statistically significant. There were no differences between groups of subjects with high levels of hs-CRP and low. Nazer et al. in his article mentioned that a good time to check out the hs-CRP to predict heart failure is within 2 days after ACS or 1 month after ACS.[18] For this purpose, neopterin has a better predictor of function than hs-CRP 1.6 (1.47 to 1.74) vs 1.34 (1.47 to 1.74) and neopterin remained a predictor of the outcome at a concentration factor of hs- low and high CRP.[15] In the study conducted Kaski et al. hs-CRP levels did not differ significantly between patients with ACS who suffered repeated attacks by not having repeated attacks, with a hazard ratio of 0.98, p = 0.89 CI 0.8 to 1.21.[19] In the univariate analysis, hs-CRP showed a significant role in predicting repeated attacks, but on multivariate analysis, the role becomes meaningless. A non-significant results of hs-CRP in this study is in line with the results of several other studies, so that the predictive value of hs-CRP to predict the existence

of ACS in patients with repeated attacks require further study, although the CDC and the AHA has established the role of hs-CRP as an independent marker for cardiovascular risk .

CONCLUSION

Our study found that the high level of anti-helicobacter pylori-heat shock protein 60II3, interferon-γ, and neopterin have a potential role in predicting risk factors of cardiovascular events in acute coronary syndrome patients. However, only neopterin levels were found to be statistically significant higher in predicting CVE among respondents.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript

ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Faculty of Medicine, Universitas Udayana prior to the study being conducted.

AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study from conceptual framework, data gathering, data analysis, until reporting the results of study.

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