HIGH RATIO OF MONOSIT: HIGH-DENSITY LIPOPROTEIN AS A RISK FACTOR OFCHRONIC TOTAL OCCLUSION IN PATIENTS CORONARY ARTERY DISEASE

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ABSTRACT

Objective: Chronic total occlusion (CTO) is frequently found in coronary heart disease (CHD) with multivessel lesions. Patients with CTO are associated with an increased mortality rate. Management CTO requires specialized techniques, more resource utilization, and high cost. The progression of atherosclerosis can be prevented by controlling for risk factors. Monocyte to high-density lipoprotein ratio (MHR) is one of the new biomarkers used to assess the incidence of a major adverse cardiovascular event, the severity of coronary lesions, and the incidence of in-stent restenosis. This study was aimed to determine the role of MHR levels as a risk factor for the occurrence of CTO in CAD patients.

Methods: This research is a matched case–control located in Sanglah General Hospital from August 2017 until October 2017. This research consisted of 47 cases with CTO and 47 control without CTO. Case and control samples were adjusted by sex, age, and number of blood vessels involved in CAD.

Results: The cutoff value of MHR was also determined by analyzing the receiver operating curve. The optimal cut off point was 14.33 with sensitivity 83% and specificity 80.9%. Bivariate analysis showed high MHR was found strongly associated with the risk of CTO in CHD patients with odds ratio (OR)=61; IK 95% (OR)=3.211–114.15; p≤0.001. Multivariate analysis showed that high levels of MHR were significantly associated with risk of CTO after other traditional risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking were controlled with OR=20,306; 95% IK (OR)=6.05–68.05; p≤0.001.

Conclusion: High levels of MHR were significantly associated with the risk factor of CTO in CAD patients.

Keywords: Chronic total occlusion, Monocyte to HDL ratio, Coronary artery disease

INTRODUCTION

Patients with coronary heart disease (CHD) have high morbidity and mortality rates. Every year in America, 660,000 new cases of CHD are found and 305,000 cases of recurrent attacks are found [1]. In 2010, CHD was the cause of 80,000 deaths in the UK [2]. In 2016, there were 35% of CHD cases from all cardiovascular cases handled at Pelayanan Jantung Terpadu (PJT) Sanglah Hospital Denpasar [3].

In the initial phase, CHD patients can be asymptomatic. Atherosclerotic plaques that continue to develop can rupture and cause thrombus blockage in coronary arteries. This can cause unstable angina, acute coronary syndrome, to sudden cardiac death. The development of atherosclerotic plaque together with fibrotic tissue and old thrombus can form chronic total occlusion (CTO) [4]. CTO is the progression of CHD accompanied by severe fibrosis and calcification tissue. CTO events are often found in CHD with complex lesions and have a prevalence rate of 12–20% [5]. In a study conducted in Texas, the United States found a 46% incidence of CTO cases in CHD patients [6]. The prevalence of CTO in CHD patients treated at PJT Sanglah Hospital Denpasar is 15% [3].

A prospective study of CHD risk factors found that monocytes have the strongest relationship of all white blood cell subtypes [7,8]. Monocytes or macrophages have an important role in the initiation and propagation of the atherosclerotic process. Monocytes have been shown to play a role in the early process of atherosclerotic plaque formation which is accelerated by different risk factors such as smoking, hypertension, hyperglycemia, and dyslipidemia [9]. Activated monocytes and damaged endothelium can trigger the overexpression of adhesion molecules and pro-inflammatory cytokines [10].

In contrast, high-density lipoprotein (HDL) can reduce the accumulation of macrophages and prevent oxidized cholesterol from entering the arterial wall. This process is mediated by the ability of HDL to reduce the expression of adhesion molecules and chemotaxis molecules on the surface of monocytes or macrophages which causes the expression of CD14 on monocytes to decrease [11]. This causes HDL to resist the inflammatory and oxidation processes caused by monocytes. In the case of patients who have low HDL levels, it will reduce the protective effect against atherosclerosis resulting in an increased risk for vascular disorders [12]. This is supported by research conducted by the multi-ethnic study of atherosclerosis found that patients with low HDL values have a higher risk of developing CHD than patients with optimal lipid profiles [13]. HDL concentrations also decrease during the inflammatory process. In the acute phase of inflammation, HDL becomes unstable and loses its protective ability [14].

One of the pathogenesis of atherosclerosis is an inflammatory process. The pro-inflammatory effects of monocytes and the anti-inflammatory effects of HDL can be used as markers of the body's inflammatory status. At present, monocyte to HDL ratio (MHR) can be used as a new predictive marker and prognosis in cardiovascular disease. Both of these tests are easily available in the laboratory and are routine checks performed on CHD patients.

Based on the background described above, research will be conducted on the role of high MHR as a risk factor in patients with CTO. This

research was conducted because there are no studies that examined the increase in monocytes and decreased levels of HDL indicated by high MHR values as a risk factor in patients with CTO.

METHODS

This study is a retrospective case–control study to prove the role of high MHR as a risk factor for CTO events in CHD patients. Patients with CHD are grouped into two groups: CTO patients with high MHR and CTO sufferer with not high MHR according to the results of the cut point values in the receiver operating curve (ROC) curve analysis. All patients receive treatment management according to the European Society of Cardiology guidelines. The location and time of the study were in the cardiac catheterization laboratory of the integrated heart service (PJT) and Sanglah Denpasar Hospital medical record unit, carried out from August 2017 until the number of samples was reached. This study has received a Certificate of Eligibility for Ethics from the Ethics Commission of the Faculty of Medicine of Udayana University with Protocol number: 2017.02.1.1065. The sample is determined consecutively, i.e., taking the sample by specifying subjects who meet the criteria as a research sample until it reaches the required number of samples, which is by following the sample calculation of 47 people in each group, with inclusion criteria: All CHD patients with CTO who perform angiographic actions coronary hospital, and exclusion criteria: Patients with the following criteria: Malignancy, septic patients, patients with liver disorders, thyroid dysfunction, chronic kidney failure, autoimmune disease, CHD patients with in-stent restenosis (ISR), and finally incomplete.

RESULTS

To stratify the MHR value, it is necessary to limit the value obtained by making a ROC curve. Based on the analysis of the ROC curve obtained a threshold value in expressing high MHR levels in predicting the incidence of CTO in CHD patients. The threshold value obtained was 14.33 with an area under the curve (AUC) 0.926 (p<0.001), a sensitivity of 83% and a specificity of 80.9%. An illustration of the characteristics of the threshold study population obtained from the ROC curve is shown in Fig. 1.

Odds ratio (OR) values will be calculated by cross-tabulating the case–control pairs as Table 2.

Table 2 shows a significant relationship between high MHR and the risk of CTO in CHD with a risk of 61 times compared to patients with low MHR (OR=61; 95% confidence interval [CI] (OR)=3.211–114.15; p≤0.001). This shows a significant MHR as a risk factor for CTO events in CHD patients.

DISCUSSION

Some traditional risk factors influence the progression of atherosclerosis such as diabetes, smoking, dyslipidemia, hypertension, and obesity. In this study, it was found that smoking, hypertension, and obesity were not significantly different between the case and control groups. Diabetes and dyslipidemia are risk factors that have a significant influence on CTO with p=0.032 and p≤0.001. This study found that 46.8% of patients with diabetes mellitus (DM) suffer from CTO (Table 1). Similar results were found in multicenter studies in Canada that the incidence of DM with CTO was 34% [15].

This can occur because in patients with DM, complex inflammatory processes and endothelial dysfunction occur making it easier to process atherothrombosis which can play a role in the process of restenosis and new coronary lesions [16]. In this study, almost the majority of CTO patients who had dyslipidemia were 95.7%. In the European registry of CTO data obtained that dyslipidemia is the most common risk factor of 74.9% [17]. Dyslipidemia acts as an inhibitor of arteriogenesis which will worsen the process of ischemia. The accumulated cholesterol is a component of arterial plaque which is a pathogenesis of atherosclerosis [18].

ROC curve analysis

In this study, the AUC value for MHR obtained in this study was 0.926 with a standard error of 0.0025; (95% CI=0.878–0.974), p<0.001 sensitivity 83% and specificity 80.9%. In this study, the MHR cut value
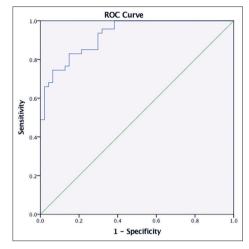

Fig. 1: Characteristics of the threshold study population

Table 1: Description of research subject characteristics based on case and control groups

Variable	Case (*n*=47)	Control (*n*=47)
Age (years)	58.23±SD 8.422	57.70±SD 7.953
18–65 (%)	37 (78.7)	39 (83)
66–79 (%)	10 (21.3)	8 (17)
Sex		
Male *n* (%)	37 (78.7)	37 (78.7)
Female *n* (%)	10 (21.3)	10 (21.3)
Vessel amount		
Single vessel (%)	3 (6.4)	3 (6.4)
Multi vessel (%)	44 (93.6)	44 (93.6)
Traditional risk factor		
DM type 2		
Yes	22 (46.8)	12 (25.5)
No	25 (53.2)	35 (74.5)
Dyslipidemia		
Yes	45 (95.7)	24 (51.5)
No	2 (4.3)	23 (48.9)
Smoking		
Yes	16 (34)	21 (44.7)
No	31 (66)	26 (55.3)
Hypertension		
Yes	35 (74.5)	33 (70.2)
No	12 (25.5)	14 (29.8)
BMI		
Obese	4 (8.5)	3 (6.4)
Non obese	43 (91.5)	44 (93.6)
Statin therapy	47 (100)	47 (100)

DM: Diabetes mellitus, BMI: Body mass index

Table 2: Cross tabulation between MHR variables and CTO variables

Groups	Control		Total
	High MHR	**Low MHR**	
Case			
High MHR	9	30.5	39
Low MHR	0.5	8	8
Total	9	38	47

OR=61; CI 95% (OR) = 3.211–114.15; *P*≤0.001. OR: Odds ratio, CTO: Chronic total occlusion, MHR: Monocyte to high-density lipoprotein ratio, CI: Confidence interval

was 14.33. Almost the same value was obtained in previous studies that used a cut value for high MHR of 14.1 which was used to predict the incidence of ISR in patients undergoing BMS stents [19]. In the MHR study to predict the incidence of mortality in patients with ACS who performed a primary PCI using a cutoff value of 17.1 [20].

Relationship of high MHR as a predictor of CTO events in CHD patients

The results of this study show a significant relationship between MHR and the risk of CTO changes in CHD. In this study showed that a high MHR has an OR of 61 (OR=61; 95% CI [OR]=3.211–114.15; p≤0.001). This shows CHD patients who have MHR values who have a high risk of 61 times higher than CTO. The results taken by MHR are submitted as a factor that lends CTO.

The mechanism underlying MHR as a risk factor for CTO is the inflammatory process caused by monocyte activation and the anti-inflammatory effect possessed by HDL. The initial stage of the process of atherosclerosis is monocyte activation. In the early stages of the atherosclerosis process in endothelial dysfunction. After endothelial dysfunction, monocytes and T lymphocytes attach to the endothelium which then migrates into the subendothelial chamber. This interaction will also cause overexpression of adhesion molecules and pro-inflammatory cytokines such as intracellular-1 adhesion molecules, cell-1 molecule adhesion molecules, and chemotactic ligand-1 monocyte proteins [21].

Monocytes then turn into macrophages which can carry out phagocytosis of oxidized low-density lipoprotein (LDL) cholesterol molecules through the SR-A and CD-36 scavenger receptors [22]. The foam cell will then form fat bubbles which will secrete pro-inflammatory cytokines which will improve the local inflammatory response in the lesion area, the metalloproteinase matrix, the tissue factor will turn into a local matrix, and the growth factor will stimulate the replication of smooth muscle cells. Increased metalloproteinase will cause internal elastic disruption, causing plaque prone to rupture. Tissue factor is located in an area rich in macrophages in the necrotic nucleus of plaque. Tissue excretion and contact with blood circulation will cause thrombus formation [23]. This thrombus will join the granulation tissue and repair infiltration by smooth muscle cells by collagen and proteoglycan deposition. This process is then followed by the formation of fibrous plaques that are returned calcified which develops into CTO [24-26].

HDL works in preventing direct responses to activated monocytes and repairing adhesion molecules in endothelial cells, thereby preventing the recruitment of new monocytes and indirectly completing macrophage collection on blood transfer [27]. The important function of HDL is as an antioxidant through oxidation of free radicals in LDL, activated lipid hydroperoxides and through reductions that inhibit the redox-active of apolipoprotein A-I in favor of inactive hydroxides [28]. Furthermore, HDL can increase the expression of nitric oxide synthase in endothelial tissue and cause vasorelaxation. Low HDL levels will reduce the protective effect against atherosclerosis and are often associated with a worse prognosis.

This study found that patients who had significantly high MHR as predictors of CTO events in CHD patients. It can be explained that a high MHR is a sign of a high inflammatory and oxidant process while the protective effect on atherogenic is decreased. This is very important as the initial process and progression of atherosclerosis. This progressivity will increase the severity of coronary artery lesions.

CONCLUSION AND SUGGESTION

This research has proven that high MHR as a risk factor in the occurrence of CHD on CTO. The decrease in HDL is a component of the high MHR value so that it can be a target for therapy in the management of CHD to prevent the progression of atherosclerosis.

AUTHORS' CONTRIBUTIONS

Prof. Wita, Dr. Ida, and Dr. Junior are the guarantor of this study designed and supervised the research process. Dr. Raditya has carried out the research and analyzed the results. Dr. Sundari has contributed to preparation and revision of the manuscript.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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