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ORIGINAL ARTICLE

HYPERLIPIDEMIA IS A DOMINANT RISK FACTOR FOR CORONARY HEART DISEASE

Hiperlipidemia Merupakan Faktor Risiko Dominan Kejadian Penyakit Jantung Koroner

I Made Sudarma Adiputra[1], Ni Wayan Trisnadewi[2], Ni Putu Wiwik Oktaviani[3], Dewa Putu Dwita[4]

[1]STIKES Wira Medika Bali, Indonesia 80239, adiputra@stikeswiramedika.ac.id
[2]Doctoral Study Program of Medicine, Udayana University, Indonesia, 80234, trisnawika09@gmail.com
[3]Nursing Program, STIKES Wira Medika Bali, Indonesia, 80239, oktaviani.wiwik@yahoo.com
[4]Cardiac Centre Care, Sanglah Hospital, Bali, Indonesia, 80114, dwita608@gmail.com
Corresponding Author: I Made Sudarma Adiputra, adiputra@stikeswiramedika.ac.id, STIKES Wira Medika, Bali, Indonesia 80239

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ABSTRACT

Background: Coronary heart disease (CHD) is a major health problem in developed and developing countries. Until now, the death rate due to CHD is the highest in the world. Its risk factors include major modifiable risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, obesity, smoking, and non-modifiable risk factors. **Purpose:** This study aimed to determine the major risk factors for the incidence of CHD. **Methods:** This study employed an unmatched case-control design, with a total sample of 43 cases and 86 controls recruited by a purposive sampling technique. Case samples were CHD patients diagnosed by a cardiologist and control samples were non-CHD patients who visited the cardiac polyclinic, with similar variables of age, sex, and residence. The samples were taken at the integrated heart center of Sanglah Hospital, Denpasar, based on the patient medical records. Data analysis was performed using the Chi-square test and logistic regression. **Results:** The results showed three risk factors that statistically and significantly increased the incidence of CHD, namely history of total cholesterol of ≥240mg/dl with adjusted OR=4.64 (95% CI: 1.60-13.49), type-2 diabetes mellitus with adjusted OR=2.85 (95% CI: 1.16-6.99), and smoking with adjusted OR=2.54 (95% CI: 1.01-6.46). **Conclusion**: The history of high total cholesterol is statistically the most dominant risk factor for the incidence of CHD.

ABSTRAK

Latar belakang: Penyakit jantung koroner (PJK) merupakan masalah kesehatan utama di negara maju dan negara berkembang. Sampai saat ini angka kematian akibat PJK menduduki urutan tertinggi di dunia. Faktor

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risiko PJK terdiri dari faktor risiko mayor yang dapat dimodifikasi, seperti hiperlipidemia, hipertensi, diabetes mellitus, obesitas dan merokok, dan faktor risiko yang tidak dapat dimodifikasi. Penelitian ini bertujuan untuk mengetahui faktor risiko mayor yang dapat dimodifikasi pada kejadian PJK. **Metode**: Rancangan penelitian adalah *unmatched case-control*, dengan jumlah sampel 43 kasus dan 86 kontrol yang diambil dengan teknik *purposive sampling.* Sampel kasus adalah pasien PJK yang sudah didiagnosis oleh dokter jantung dan sampel kontrol adalah pasien non PJK yang berkunjung ke poli jantung, yang mirip dalam variabel umur, jenis kelamin dan alamat. Sampel kasus dan kontrol diambil di pusat jantung terpadu RSUP Sanglah Denpasar berdasarkan data rekam medis pada rumah sakit tersebut. Analisis data dilakukan dengan uji Chi-square dan regresi logistik. **Hasil:** Hasil penelitian menunjukkan tiga faktor risiko yang secara statistik signifikan meningkatkan kejadian PJK, yaitu riwayat kolesterol total 240mg/dl dengan AOR = 4,64 (95% CI: 1,60-13,49), Diabetes mellitus tipe-2 dengan AOR = 2,85 (95% CI: 1,16-6,99) dan merokok dengan AOR 2,54 (95% CI: 1,01-6,46). **Simpulan:** Riwayat kolesterol total tinggi secara statistik merupakan faktor risiko paling dominan pada kejadian PJK.

INTRODUCTION

Heart disease is a degenerative disease related to lifestyle and socioeconomic conditions in the society. Heart disease is a major health problem in developed and developing countries and causes one-third of deaths in the world (1). Coronary heart disease (CHD) is the most common heart disease compared to other types of heart diseases (2). CHD is a real threat to sustainable development in this century (3). Data from the World Health Organization (WHO) in 2008 stated that more than 17 million people in the world died from heart and blood vessel diseases; around 7.3 million deaths were caused by CHD (4).

In Indonesia, there has been a shift in the incidence of heart and blood vessel diseases from 10th in 1980 to 8th in 1986. Meanwhile, the cause of death is still in the third position. Although there are no definite epidemiological data, the morbidity/mortality rate seems to be increasing. The results of the 2001 National Health Survey showed that three out of 1,000 Indonesians suffer from CHD (5). Meanwhile, the results of the Basic Health Research *(Riskesdas)* in 2018 showed that 1.5% or 15 out of 1,000 Indonesians suffer from CHD (6).

In Sanglah Central General Hospital Denpasar, based on the annual report of the integrated heart services, the number of visits of CHD patients to the cardiac polyclinic in the last three years is still relatively high. In 2017, there were 12,356 CHD patients, and in 2018, 29,181 visits were reported, with 559 (1.91%) new cases of CHD. Furthermore, in 2019, there were 20,840 visits with 569 (2.73%) new cases of CHD patients.

The exact cause of CHD is not yet known. However, several risk factors are thought to have contributed to the incidence of CHD. According to Malakar et al (7), lifestyles, environmental factors, and genetic factors play a role in the development of cardiovascular disease (1). Risk factors for CHD can be divided into two: risk factors that can be changed or modified, and biological risk factors that cannot be changed. Biological risk factors include age, sex, and family history, while modifiable risk factors include hyperlipidemia, hypertension, diabetes mellitus, smoking habits, poor diet, lack of movement, stress, obesity, and alcohol consumption (8).

Smoking history plays a role in the occurrence of CHD, and active smoking strongly correlates with the incidence of CHD (9). Smoking is a major risk factor for cardiovascular disease (CVD) and a leading avoidable cause of death worldwide (10,11). More than a quarter of adults with CVD have a lifetime smoking history (12).

Hypertension is thought to increase the risk of CHD. According to Li et al (13), people with a history of hypertension and obesity are closely related to the incidence of CHD in the future. A history of suffering from type-2 diabetes is also associated with the incidence of CHD. Type-2 diabetes mellitus (T2DM) is a major risk factor for coronary artery disease (CAD) (14). Increased levels of glucose triglyceride index (TyG) are an independent risk factor for CAD in patients with type-2 diabetes mellitus (15), and high triglyceride

levels are predictors of post-percutaneous coronary intervention (PCI) of CHD incidence (16). The history of hyperlipidemia is also thought to increase the risk of CHD incidence. According to Stewart et al (17), a history of hyperlipidemia in young adulthood increases the risk of CHD in the future.

Aging, family history, and gender are non-modifiable risk factors for CHD, and therefore, the management of CHD is done more to control risk factors that can be modified. Modernization and changes in people's lifestyles can be considered as causes of CHD. Generally, people of productive age enjoy unhealthy lifestyles in their daily life, such as poor food consumption, smoking habits, and lack of physical activity (18). The burden of CHD tends to increase along with the increasing number of its cases. CHD is burdensome for patients and their families from medical, psychological, social, and financial perspectives. Comprehensive efforts are needed to prevent CHD, so more research is needed to determine the risk factors for CHD that can be changed or modified. Accordingly, this study aimed to determine the dominant risk factors that increase the incidence of CHD.

METHODS

This study used an unmatched case-control design, in which the case and control groups were similar in terms of age, sex, and place of residence. The study was conducted from February to April 2021. Case samples were patients diagnosed with CHD by doctors in the integrated heart center of Sanglah Hospital Denpasar, while control samples were patients with non-CHD in the cardiac polyclinic of the same hospital based on the clinical diagnosis, electrocardiography, and cardiac catheterization. The number of samples was determined using the Lemeshow formula and calculated using the WHO sample size calculator 2.0. The number of case and control samples was 43 and 83, respectively. The samples were recruited using a purposive sampling technique. The inclusion criteria for the case samples were patients diagnosed with CHD by a cardiologist, while the control samples were non-CHD patients (extrasystolic, hypertension, and non-CHD/CHF patients) who underwent an examination at the cardiac polyclinic.

All variables in this study were used as categorical variables as presented in Table 2, namely history of total hyperlipidemia, history of smoking, history of hypertension and history of diabetes mellitus. Data analysis was performed using IBM SPSS software for univariate (Table 1), bivariate (Table 2) and multivariate (Table 3) analyses. Univariate analysis was performed to determine the frequency distribution of each variable. Bivariate analysis was conducted to determine crude OR with Chi-square, while multivariate analysis was used to calculate adjusted OR with the logistic regression method. Crude OR and adjusted OR significance levels were set with 95% CI.

This study obtained its ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Udayana University/Sanglah Hospital, with a reference number of 2412/ UN14.2.2.VII.14 /LT/2020. Prior to the research, the potential subjects were informed with verbal and written descriptions of the procedures and that they could withdraw from the study. Subjects who agreed to participate in the study provided consent before participation.

RESULTS

Table 1 presents the characteristics of the case and control groups based on gender, age, residence, education, and occupation. Respondents who participated in this study were predominantly males, namely 27 (62.79%) in the case group and 47 (54.65%) in the control group. The majority of respondents were aged >50 years old, as many as 28 (65.11%) in the case group and 55 (64%) in the control group. Furthermore, most respondents lived in urban areas with a total of 23 (53.49%) in the case group, and in rural areas with a total of 49 (57%) in the control group. Both case and control groups are dominated by high school graduates. Respondents' occupations are mostly self-employed, and no history of CHD in the family was reported in both groups.

In Table 2, the results of the bivariate analysis between cases and controls show that the risk factors which significantly increased the incidence of CHD were: Total Cholesterol with crude OR = 4.89 (95% CI: 1.78-13.43), Triglyceride Levels with crude OR = 4.48 (95% CI: 1.06-18.92), Type-2 diabetes mellitus with crude OR = 3.36 (95%CI: 1.46-7.77), Hypertension stage I with crude OR = 2.94 (95% CI: 1.15-7.51), Hypertension stage II-IV with crude OR = 3.42 (95% CI: 1.20-9.75), Smoking with crude OR = 3.01 (95% CI: 1.27-7.17), and Body Mass Index ≥ 25 with Crude OR = 2.86 (95% CI: 1.26-6.48).

Table 1
Baseline Characteristics of the Subjects

Baseline Characteristics	Case	Control	p-value
Gender			
Male	27 (62.79)	47 (54.65)	0.380
Female	16 (37.21)	39 (43.35)	
Age			
≥ 55	15 (34.88)	31 (36.04)	0.897
< 55	28 (65.11)	55 (63.96)	
Residence			
Rural	20 (46.51)	49 (56.97)	0.263
Urban	23 (53.49)	37 (43.03)	
Education			
None	0	2 (2.32)	0.727
Elementary	3 (6.97)	13 (15.11)	
Junior High School	5 (11.62)	11 (12.79)	
Senior High School	29 (67.44)	39 (45.34)	
University	6 (13.95)	24 (27.90)	
Occupation			
None	4 (9.30)	6 (6.97)	0.233
Employed	8 (18.60)	9 (10.46)	
Self-Employed	23 (50)	51 (59.30)	
Public Servant	8 (18.60)	20 (23.25)	
Family history of CHD			
CHD	5 (11.62)	2(2.32)	0.029
None	38 (88.38)	84(97.68)	

Table 3 shows the results of the multivariate analysis using the logistic regression method. Seven variables were found to be significant in the bivariate analysis: Total Cholesterol, Triglyceride Levels, Type-2 Diabetes mellitus, Hypertension stage I, Hypertension stage II-IV, Smoking, and Body Mass Index ≥ 25. The results of multivariate analysis showed three risk factors associated with the incidence of CHD, namely Total Cholesterol with AOR = 4.64 (95% CI: 1.60-13.49), Type-2 Diabetes mellitus with AOR = 2.85 (95% CI: 1.16-6.99), and Smoking with AOR =2.54 (95% CI: 1.01-6.46).

Table 2
Bivariate analysis results (Crude Odds Ratio) for CHD

Risk Factor	Cases	Control	Crude OR	95% CI
Total Cholesterol				
≥ 240mg/dl	13	7	4.89	1.78-13.43
< 240mg/dl	30	79		
Triglyceride Levels				
≥ 200mg/dl	6	3	4.48	1.06-18.91
< 200mg/dl	37	83		
Type-2 Diabetes mellitus				
Yes	17	14	3.36	1.46-7.77
None	26	72		
Hypertension stage I				
Yes	12	10	2.94	1.15-7.51
None	31	76		
Hypertension stage II-IV				
Yes	10	7	3.42	1.20-9.75
None	33	78		
Smoking				
Yes	15	13	3.01	1.27-7.17
None	28	73		
Body Mass Index ≥ 25				
≥ 25	17	16	2.86	1.26-6.48
< 25	26	70		

Table 3
Multivariable-Adjusted odds ratio (AOR) for CHD

Risk Factor	Adjusted OR	95%CI		*p-value*
		Lower	Upper	
Total Cholesterol ≥ 240mg/dl	4.64	1.60	13.49	0.005
Type-2 Diabetes mellitus	2.85	1.16	6.99	0.022
Smoking	2.54	1.01	6.46	0.049

DISCUSSION

The result of this study indicated that the history of hyperlipidemia has a significant correlation with the incidence of CHD, meaning that people with a history of hyperlipidemia have higher risks of suffering from CHD than those with normal lipid levels. This result is supported by the study of Liu et al (19), which showed that hyperlipidemia, hypertension, and diabetes were independent risk factors for CHD, and the difference was statistically significant ($p<0.05$). High total cholesterol in pregnant women is positively related to the incidence of CHD in future offspring with OR of 2.10 (95% CI: 1.07-4.13) (20). Although they are primary sources of energy and are required for many biological functions, foods with high cholesterols can cause detrimental effects on cardiovascular health (12).

Oxidation of LDL will attract leukocytes into the intima tunica of the coronary arteries, which will then be taken up by macrophages and there is the formation of foamy cells. The foamy cells will replicate and form lesions; this lesion will be called arteriosclerosis in the early stages. This repeated process of lipids will cause a buildup or lesions gradually in the lining of the coronary blood and eventually arteriosclerosis, which can block blood circulation in the coronary arteries and result in CAD (1). People with a history of high total cholesterol and high-density lipoprotein cholesterol levels were at risk for myocardial infarction and other cardiac disorders with adjusted hazard ratios of 1.39 (95% CI, 1.10-1.76; $p = 0.00$) (21).

Low-density lipoprotein cholesterol (LDL-C) and low-density lipoprotein cholesterol (non-HDL-C) were significant predictors of coronary artery disease (22). The risk of CHD events depends on the cumulative exposure and duration of previous exposure to LDL cholesterol; exposure to cholesterol that occurs from a young age has a greater risk of developing CHD later in life when compared to exposure to LDL cholesterol in old age (23).

The history of type-2 diabetes mellitus obtained statistically significant results with the incidence of CHD. This result is supported by the study of Si et al (15), reporting that increased levels of glucose triglyceride index (TyG) in patients with type-2 diabetes are an independent risk factor for CAD, with TyG index ≥8.2 and OR = 5.73 (95% CI: 1.72–19.07. High TyG in patients with type-2 diabetes increases the risk of CHD incidence with OR = 2.20 (95% CI: 1.55–3.11) (24). A high triglyceride level is a predictor of post-percutaneous coronary intervention (PCI) of CHD incidence (16). History of hypertension was statistically proven to be an independent risk factor for CHD ($p<0.05$) (19).

In this study, smoking history was found to be a risk factor for CHD. This result is in line with a study conducted by Grubb et al (9), reporting that smoking history has a role in the occurrence of CHD; active smokers have a strong correlation with the incidence of CHD. Smoking is a major risk factor for cardiovascular disease (CVD) and a leading avoidable cause of death worldwide (10). Smoking can cause decreased oxygen levels in the heart, increased blood pressure and pulse, decreased HDL (High Density Lipoprotein) levels, increased LDL (Low Density Lipoprotein) levels, and increased thrombogenesis and vasoconstriction. The risk of CHD due to cigarettes is strongly influenced by the duration and depth of smoking. The more cigarettes smoked in a day, the more CHD risk increases; the deeper the cigarette smoke is smoked, the higher the risk of CHD. Smoking also increases coronary artery obstruction because it produces endothelial denudation and platelet adhesion to the tunica intima layer; this increases lipid infiltration and decreases the platelet growth factor (1).

The results of this study also indicated that a history of hypertension increases the risk of CHD incidence in the future (Crude OR = 2.94 (95% CI: 1.15-7.51)), as well as hypertension stage II-IV (crude OR = 3.42 (95% CI: 1.20-9.75)). People suffering from stage II-IV hypertension had a 3.42 times greater risk of suffering from CAD than people without hypertension. The results of this study are supported by Li et al (13) reporting that people with a history of hypertension and obesity are closely related to the incidence of CHD in the future. Hypertension is related to the incidence of CHD and other heart disorders, in which men have

a greater tendency. Consistent high blood pressure can cause damage to the artery walls. The lining of the blood vessels will thicken so that it can increase the resistance to blood flow. Structural changes in the small arteries and arterioles will cause progressive blockage of blood flow. When the blood vessels are narrowed, arterial blood flow will be interrupted and can cause tissue infarction (25). According to Chen et al (21), age, gender, race, clinical location, education level, physical activity, total cholesterol level, high density lipoprotein cholesterol level, systolic blood pressure, use of antihypertensive medication, current smoking, diabetes status, body mass index, protein C level-reactive, hemoglobin A1c levels, phosphorus levels, troponin T levels, log levels of N-terminal pro-B-type natriuretic peptide, levels of fibroblast growth factor 23, estimated glomerular filtration rate, and proteinuria are associated with the incidence of myocardial infarction and other cardiac disorders with adjusted hazard ratios of 1.39 (95% CI, 1.10-1.76; p = 0.006).

Research Limitations

The limitation of this study is the wide AOR range in the analysis of risk factors for total cholesterol (95% CI: 1.60-13.49), possibly due to the small sample size. Based on the results of this study, the recommendation that can be put forward is the need for structured education to the public regarding risk factors that can still be changed to reduce or prevent the risk of CHD. Another recommendation is to conduct a study of modifiable risk factors in CHD with larger sample size.

CONCLUSION

CHD is one of the main causes of death and morbidity in developed and developing countries. However, the exact cause of CHD is still not known. This study showed four risk factors that statistically increased the risk of CHD, including the history of hyperlipidemia, type-2 diabetes, hypertension, and smoking. Of the four risk factors obtained, based on the multivariate analysis, the history of hyperlipidemia is the dominant risk factor for CHD.

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AUTHOR CONTRIBUTIONS

All persons who have made substantial contributions to the work were reported in the manuscript: IMSA (concepts, design, definition of intellectual content, clinical studies, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review), NWT (literature search, data analysis and statistical analysis), NPWO literature search, data acquisition, data analysis and statistical analysis), and DPD (Clinical Studies).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interests.

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