SYSTEMATIC REVIEW

Risk Factor for In–Stent Restenosis in Premature Coronary Heart Disease : Systematic Review and Meta-analysis

Hotmauli Siahaan[1], Hari Basuki Notobroto[2], Yudi Her Oktaviono[3], Paulus Parholong Siahaan[4], Lidia Jane Tandra[6], Rizky Novita Anjaswanti[5], Lim Poh Ying[7], Zawiah Binti Mansor[7]

[1] Doctoral Program of Public Health, Faculty of Public Health, Universitas Airlangga, Mulyorejo, 60115 Surabaya, East Java, Indonesia
[2] Department of Epidemiology, Biostatistics, Population Studies and Health Promotion. Faculty of Public Health, Universitas Airlangga, 60286 Surabaya, East Java, Indonesia
[3] Department of Cardiology and Vascular Medicine, General Hospital Dr. Soetomo, Faculty of Medicine, Universitas Airlangga, Prof. Dr. Moestopo Street number 6-8, 60286 Surabaya, East Java, Indonesia
[4] Faculty of Medicine, Universitas Airlangga, Prof. Dr. Moestopo Street number 47, 60286 Surabaya, East Java , Indonesia
[5] Faculty of Public Health, Universitas Airlangga , 60286 Surabaya, East Java, Indonesia
[5] Faculty of Medicine, Universitas Hang Tuah, Ahmad Yani Street number 1, 60244 Surabaya, East Java, Indonesia
[7] Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor Darul Ehsan, Malaysia

ABSTRACT

Introduction: Risk factors of developing in-stent restenosis (ISR) appeared as a challenge in the young particulary in the premature coronary heart disease (PCHD) patients, therefore this systematic review aims to comprehensively analyze that may differ from the geriatrics. **Materials and methods:** This systematic review and meta-analysis followed the PRISMA 2020 guidelines to select relevant articles. In addition, the articles were retrieved from 5 global databases, namely Pubmed, Science Direct, Google Scholar, Springer, and Proquest. Analysis of 6 studies identified several risk factors for ISR in PCHD patients. **Results:** Significant factors included high body mass index (BMI) (OR=0.74, 95% CI: 0.23 - 1.25; p=0.004), smoking (OR=3.17, 95% CI: 2.34 - 4.28; p<0.001), and family history of CHD (OR=2.70 95%CI 1.62 - 4.49; p=0.001). **Conclusion:** The risk factors for in-stent restenosis (ISR) differ between patients with PCHD and those without this condition. For patients with PCHD, the primary risk factors for ISR include body mass index (BMI), smoking, and a family history of coronary heart disease (CHD).
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Keywords: Clinical outcome, In – Stent restenosis, Meta-analysis, PCHD, Systematic review

Corresponding Author:
Hotmauli Siahaan, PhD
Email: hotmauli.siahaan-2023@fkm.unair.ac.id
Tel : (+62)81331521186

INTRODUCTION

Premature Coronary Heart Disease (PCHD) is Coronary Heart Disease (CHD) characterized as occurring in those under 45 years for men and under 50 years for women (1,2). While more recent research has used higher age thresholds, such as 50 or 55 years for men and women 65 years considering the hormonal state of women before menopause (3,4). Over the last few decades, the cardiovascular risk profile in young individuals changed, seen in decreased smoking and an increased hypertension and diabetes prevalence among women. Additionally, younger populations infrequently possess common cardiovascular risk factors (5).

In-Stent Restenosis is the re-narrowing of more than 50% of the blood vessel after stenting. Studies have investigated risk factors for ISR following stent placement. An observational study done by Zhang et al. (2022), found various risk factors that might cause ISR, from the clinical aspect such as diabetes, hypertension, discontinuation of aspirin, and family history, and mechanical or anatomy factors such as calcified lesions, number of segmented stent, stent diameter, and stent length (6). Zeng et al. (2021) shown despite of second-generation drug-eluting stent implantation, patients with triple-vessel disease possess a great risk of revascularization, with progressive angiographic stenosis as a continuous hazard. The study also identified diabetes smoking as an independent risk factor for both revascularization and in-stent restenosis (7). This finding were then supported by a meta-analysis study by Rohman et al. found that diabetes mellitus, family history of CHD, and smoking were strong predictors for ISR (8) .

Many studies done on the older population have examined the risk factors for ISR. There are not much information about how the risk factors might cause ISR among the young population. In fact, the results are relatively different. In addition, there has been no systematic review study and meta-analysis on PCHD to analyze risk factors for ISR following stent implantation. Therefore, this study aims to examine the risk factors for

In-Stent Restenosis in premature coronary heart disease after stent implantation.

MATERIALS AND METHODS

Study Design

This research was conducted using a systematic review and meta-analysis study design, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. PRISMA, a tool to guide researchers in selecting relevant studies that can be advanced to data analysis. After that, a meta-analysis, a statistical technique for combining two or more original studies, was utilized to perform formal statistical analysis within the systematic review.

Eligibility Criteria

The inclusion criteria for the studies included studies that (1) employed an observational or cohort study, (2) included CHD patients undergoing PCI with DES implantation followed by restenosis assessment for at least 12 months, and (3) involved ISR in PCHD patients. On the other hand, the articles were excluded based on the following criteria: (1) duplications, (2) case reports, (3) non-English language, (4) non-coronary ISR, and (5) unclear ISR definition. The study selection process was performed by three investigators (HS, RNA, PPS).

Data Extraction

Data in this research were categorized into two groups: data used for systematic reviews and data used for meta-analysis. The data required for the systematic review included Monocyte to HDL ratio (MHR), Hba1c, METS - IR and prediabetes, and triglyceride glucose index. On the other hand, data for meta-analysis consisted of smoking, family history of CHD, BMI, stent length, multivessel, lesion at RCA, lesion at RAD, and lesion at LCX. These datasets were extracted from studies representing both PCHD and non-PCHD patients. The section covered data extraction, and the data available were summarized in tables in accordance with the systematic review and meta-analysis standards.

Literature Search

This meta-analysis involved a literature search using MeSH terminology (Supplementary Table) and was registered in the PROSPERO database, which is widely recognized for systematic observations and meta-analyses related to human health. The studies involved global scientific databases, such as PubMed, Science Direct, Google Scholar, Springer, and Proquest. The searches were performed until May 31, 2024, to identify publications comparing patients with PCHD and non-PCHD. Various terms were combined with logical connectors, including “premature”, AND “coronary heart disease”, AND “young patient”, AND “in-stent restenosis”, AND “intra-stent stenosis”, AND “repeat revascularization”, AND “prognosis”. The conceptual framework that illustrates how the literature was searched in this research is presented in Figure 1.

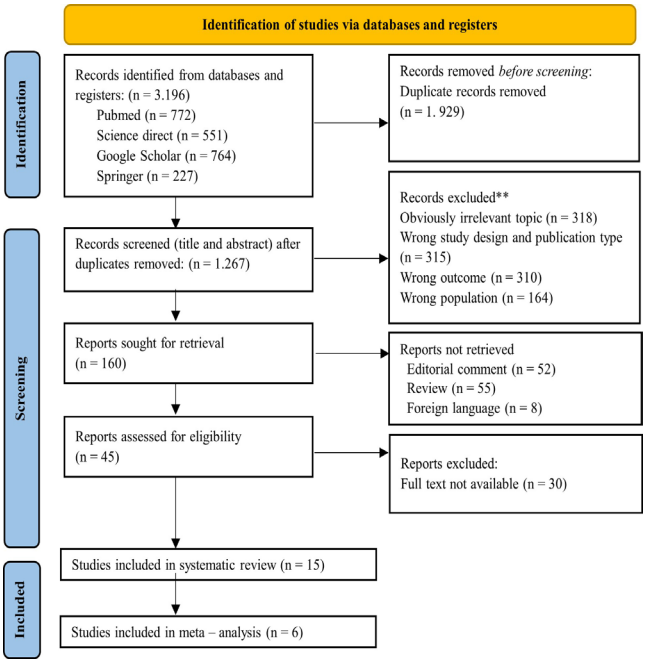

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Flow Diagram of Study Selection

Statistical and Sensitivity Analysis

In this study, we conducted a systematic review and meta-analysis using Review Manager 5.4 software. We used statistical methods like the Mantel-Haenszel method for odds ratio and the inverse variance method for continuous data. Heterogeneity was assessed using the DerSimonian and Laird random-effect model, and sensitivity analysis was used to detect outliers and changes in heterogeneity. The data analysis involved fixed and random effect models, with significance defined as a p-value below 0.05.

RESULTS

Prevalence of Premature Coronary Heart Disease

The prevalence may differ between regions of the world and ethnicities. It is notably more prevalent among Indians, with 10% to 15% of all CHD cases, in contrast to the 2% to 5% observed in Western countries. The occurrence of PCHD Indians is five times greater than that of white individuals in the UK, four times greater than that of Italians, and thirteen times greater than that of the Chinese in Singapore. In Malaysia, Indians represent 56% of CHD cases is PCHD, while in Qatar, this figure rises to 71%. Among all CHD patients, those under 45 years old make up 2-3% of cases in whites, but this percentage is significantly higher at 10-15% in India (1,9). In study by Tsao CW dan Arora, most European patients increase in the number of PCHD has been observed (2,10).

Risk Factors for In-Stent Restenosis

This study summarized 12 risk factors for In-Stent Restenosis. There were 8 risk factors that underwent

meta-analysis (e.g., smoking, family history of CHD, body mass index, stent length, multivessel, RCA lesions, LAD lesions, LCX lesions) and 4 risk factors that underwent systematic review (monocyte to HDL ratio, HbA1c , METS – IR and prediabetes, and Triglyceride Glucose Index (TyG)).

With 6 cohort studies being analyzed, the total of 2.518 patients premature coronary heart disease were included (11–16). The results of a meta-analysis carried out on five studies about smokers (Figure 2) showed that smokers have a significantly higher likelihood of having PCHD (OR=3.17 95%CI 2.34 - 4.28; p<0.001). Similarly, another meta-analysis of five studies regarding family history of CHD (Figure 3) indicated that a family history of CHD significantly increased the likelihood of having PCHD (OR=2.70 95%CI 1.62 - 4.49; p=0.001). Further, a meta-analysis conducted on three studies related to BMI (Figure 4) similarly revealed that BMI had a significantly higher likelihood of having PCHD (OR=0.74 95%CI 0.23 - 1.25; p=0.004). OR =0.74 can explain with BMI dose effect while, there may be a non-linear relationship, where a BMI that is too low or too high is risky, while a moderate BMI is more protective. Need additional analyses (e.g., stratifying by BMI category) to further understand this relationship. If this is a BMI paradox (Obesity Paradox), it still requires more studies and more samples to get clearer results. The results showed that stent lengths are not a significant risk factor in PCHD but are significant in non-PCHD (Figure 5).

Furthermore, three studies were included to analyze multivessel. Based on the results of the meta-analysis (Figure 6), it can be seen that multivessels have a significantly in non-PCHD. After that, four studies were included to analyze lesions at RCA. The meta-analysis results (Figure 7) indicated that lesions at RCA were not a significant risk factor for ISR in PCHD and non-PCHD patients (OR=0.96, 95%CI 0.86 - 1.08; p=0.51). Other four studies were also included to analyze lesions at LAD. According to the meta-analysis results (Figure 8), lesions at the LAD were not a significant risk factor for the ISR in PCHD and non-PCHD patients (OR=0.89, 95%CI 0.74 - 1.08; p=0.24). Lastly, four studies were included to analyze lesions at LCX. The meta-analysis results (Figure 9) showed that lesions at LCX had a significant association with a higher likelihood of having non-PCHD (OR=0.74, 95%CI 0.59 - 0.93; p=0.010).

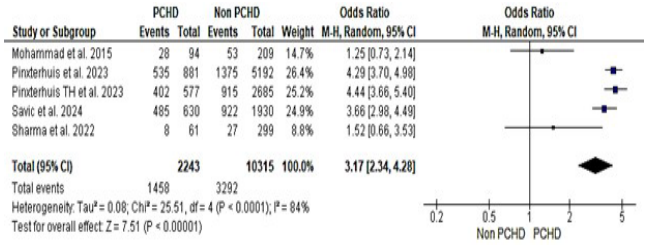

Figure 2: Smokers are more significant in PCHD patients than in non-PCHD patients (OR=3.17 95%CI 2.34 - 4.28; p<0.001)

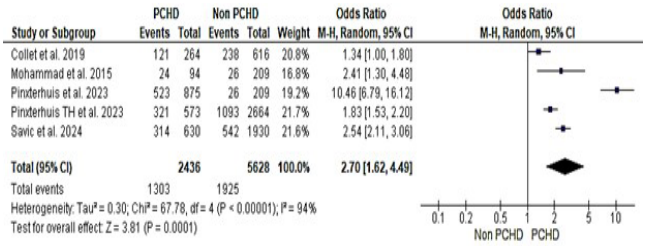

Figure 3: Family history is more significant in PCHD patients than in non-PCHD patients (OR=2.70 95%CI 1.62 - 4.49; p=0.001)

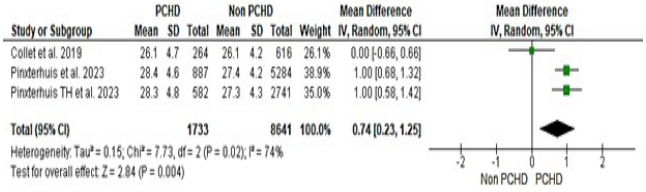

Figure 4: Body mass index is more significant in PCHD than in non-PCHD patients (OR=0.74 95%CI 0.23 - 1.25; p=0.004)

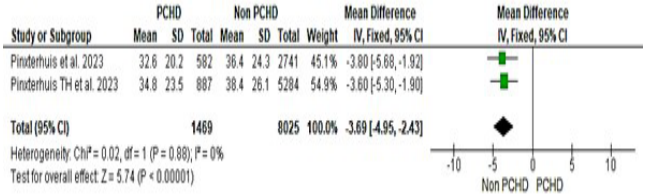

Figure 5: Stent length is more significant in non-PCHD than in PCHD patients (OR=-3.69 95%CI -4.95, -2.43; p<0.001)

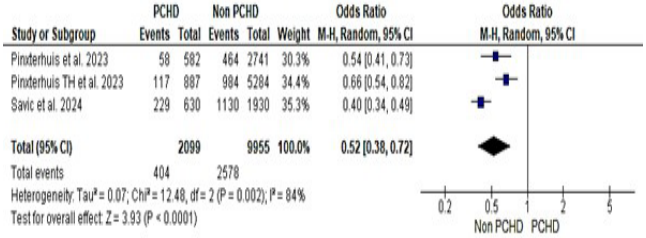

Figure 6: Multivessel is more significant in non-PCHD patients than in PCHD patients (OR=0.52 95%CI 0.38 - 0.72; p <0.0001)

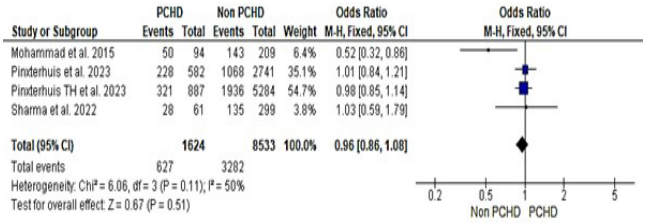

Figure 7: Lesions at RCA are not significant in both PCHD and non-PCHD patients (OR=0.96, 95%CI 0.86 - 1.08; p=0.51)

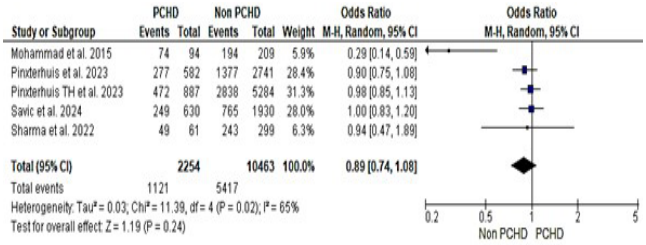

Figure 8: Lesions at LAD are not significant in both PCHD and non-PCHD patients (OR=0.89, 95%CI 0.74 - 1.08; p=0.24)

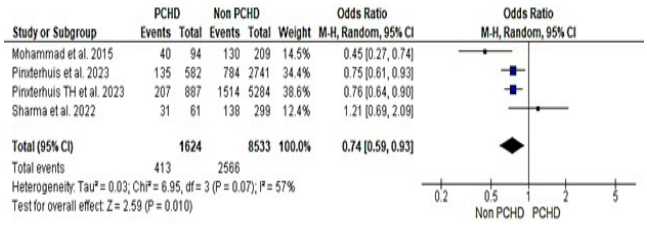

Figure 9: Lesions at LCX are more significant in non-PCHD patients than in PCHD patients (OR=0.74, 95%CI 0.59 - 0.93; p=0.010)

The risk factors for In-Stent Restenosis are not only caused by those in the meta-analysis above. The following are other risk factors that can influence the likelihood of having In-Stent Restenosis.

Monocyte to HDL ratio (MHR)

The research has extensively studied the association between MHR and coronary heart disease as well as its connection to ISR as a risk factor in various populations. Research by Avci et al. on STEMI patients and Tok et al. on unstable and stable angina patients shown that MHR is a significant risk factor for ISR in heart disease. Furthermore, a study by Chen et al. found that MHR, fibrinogen, and history of smoking is a risk factor for ISR in PCHD patients, in a study done in 257 PCHD patients who received drug-eluting stent implantation and follow-up coronary (17). The research also found that MHR can be an independent risk factor for ISR in PCHD patients. However, this study conducted only in 30 patients in a single center, therefore the results should be interpreated caustiously (3,4).

HbA1c

A recent report by Han Tang et al., examined 203 patients aged 45 years and younger with acute coronary syndrome (ACS). These patients underwent angiography twice at the Chinese General Hospital. The study aimed to assess the risk factors predicting the need for repeat revascularization in these age groups. It was found that diabetes mellitus emerged as an independent predictor of adverse cardiovascular events, irrespective of age. Additionally, there was a notable contrast between groups in both HbA1c and fasting glucose levels, highlighting the importance of glucose control in young patients with higher HbA1c. The study's results align with the ARIC Community Surveillance Study, which observed a rise in the prevalence of diabetes mellitus among young myocardial infarction patients over the past two decades. Consequently, patients with diabetes face an elevated risk of cardiovascular disease and poorer outcomes (18).

METS – IR and Prediabetes

During a 63-month study, Xu et al. found that a higher METS-IR group had increased rates of repeat coronary heart revascularization, suggesting that METS-IR is important for predicting this outcome. The study also showed that prediabetes was associated with adverse outcomes such as all-cause death, myocardial infarction, and stroke. In another study involving 1113 young patients with new-onset ACS, it was found that a higher METS-IR group exhibited significantly elevated cumulative incidence of MACE and other adverse outcomes (19).

Triglyceride Glucose Index (TyG)

Chang Liu et al. investigate the association using multivariable logistic regression analysis, revealed that these variables were potential risk factors for MACE and ISR. This suggests that the triglyceride-glucose index could be a valuable marker for identifying high-risk individuals within the young diabetic population. Furthermore, the study highlighted that managing these risk factors early could potentially decrease MACE and ISR incidence. In conclusion, the research by Chang Liu et al. emphasizes the importance of comprehensive risk factor assessment in young diabetic patients to improve their long-term cardiovascular health outcomes (20).

DISCUSSION

In this study, we aimed to explore thoroughly risk factors in premature coronary heart disease (PCHD) population for in-stent restenosis (ISR). The results showed that BMI, smoking, and family history of CHD are the significant risk factors to develop ISR. This finding align with research on similar risk factors in non-PCHD populations. For example, Zhang et al. found that family history of CHD, diabetes, hypertension, statin usage, stent diameter, stent length, ≥ 3 number of stents in an observational studies (6).

This study found that BMI as a significant risk factor for ISR in PCHD patients. However, it is slightly different from the risk factor Body mass index (BMI), which is rarely a risk factor for ISR in the general population or non-PCHD, similarly to the findings by Jones et al. in groups according to BMI status, and additionaly found that ISR increased the risk for MACE. The reason is because several genetic factors can influence PCHD. Several genes associated with lipoprotein metabolism have been identified as linked to PCHD. These genes include the cholesterol ester transfer protein (CETP) gene, the hepatic lipase gene, the lipoprotein lipase gene, the apo A1 gene, the apo E gene, and the apo B gene. Additionally, recent studies suggest that biomarkers such as lipoprotein (a), fibrinogen, D-dimer, serum Wnt, gamma-glutamyl transferase, vitamin D2, and osteocalcin may also be associated with PCHD (21). Although they also found multivessel disease and stent length are not significant risk factor(22), contrary from the finding from Zhang et al.(17) and Rohman et al.(8) in the non-PCHD population, who found that multivessel and stent length were risk factors for ISR .

Subsequently, this study do not find significant differences between LAD and RCA lesions between PCHD and non-PCHD. This finding is in contrast to research conducted

by Wang et al., where the patients typically experienced hypertension, and diabetes. In addition, the number of coronary artery lesions was more than 2 arteries. Other factors, such as LDL-C value, stent planted in the left anterior descending artery, and having unstable angina were reported as independent risk factors for ISR (24).

In this study, the lesion in the LAD found to be a significant risk factor for ISR. Lesions on the LCX are not significant as a risk factor for ISR in PCHD, whereas in non-PCHD they are significant as a risk factor for ISR, when compared with the Meta-analysis conducted by Rohman et al.(8) there are similarities, where lesions on the LAD, RCA, and LCX are not significant as a risk factor for ISR in non-PCHD.

In reviewing the current research, several risk factors were identifed for In-Stent Restenosis (ISR) in PCHD. These include the Monocyte to HDL ratio (MHR), Recently, the ratio of monocytes to HDL cholesterol (MHR) has gained significant attention as a new inflammatory marker. Inflammation and lipid accumulation are two fundamental characteristics of atherosclerosis. Monocytes serve as the primary source of pro-inflammatory substances during the development of atherosclerosis, whereas HDL cholesterol plays a protective role by preventing the oxidation of low-density lipoprotein (LDL) and directly inhibiting inflammation in monocytes. The MHR can effectively reflect the levels of inflammation and oxidative stress in the body (17). HbA1C, METS IR and prediabetes, and Tryglceride glucose index (TyG) are also several risk factors were identifed for In-Stent Restenosis (ISR) in PCHD.

Limitation

This study is subject to certain limitations. Primarily, it is observational in nature and was carried out at a single center, which may affect the generalizability of the results. Additionally, the lack of extensive research on ISR in the PCHD population undermines the strength of this study. To strengthen these findings, further research is needed, particularly multicenter studies with larger and more diverse patient populations. Such research is crucial given the increasing prevalence of PCHD and the need for effective strategies to manage ISR in this growing group of patients.

CONCLUSION

In conclusion, the risk factors for in-stent restenosis (ISR) and stents in patients with premature coronary heart disease (PCHD) are slightly different in PCHD patients compared to non-PCHD patients. For PCHD patients, key risk factors for ISR include BMI, smoking, and a family history of CHD. Additionally, emerging evidence suggests that the Triglyceride-Glucose (TyG) index, HbA1C, and METS-IR could also be significant risk factors for ISR.

The identification of these specific risk factors emphasizes the need for tailored strategies in the management of PCHD. Effective monitoring and intervention strategies should address these distinct risk profiles to reduce the incidence of ISR and adverse cardiovascular events. Future research should focus on validating these findings across diverse populations and exploring potential interventions to mitigate these risks.

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