Risk Factors of Coronary In–Stent Restenosis in Drug-Eluting Stent: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *In-stent restenosis (ISR) is an event of coronary atherosclerosis re-budling following the stent implantation in percutaneous coronary intervention. The events of ISR have been significantly reduced since the introduction of drug-eluting stents. However, ISR could still occur, and factors affecting the incident have not yet been discovered. This study aims to evaluate the risk factors of coronary in-stent restenosis in drug-eluting stents.* ***Methods:*** *Studies on the factors and risks of ISR in patients with drug-eluting stents were systematically searched in databases (PubMed, ScienceDirect, Springer, Google Scholar, and ProQuest) on September 20th, 2023. The odds ratio (OR) and mean difference (MD) were analyzed using Review Manager 5.4.* ***Results:*** *Diabetes mellitus (OR 1.73 [95%CI 1.56, 1.91] p < 0.00001) and smoking (OR 1.24 [95%CI 1.13, 1.36] p<0.0001) are the patients' clinical characteristics that are associated with ISR in DES. It is closely related to the contribution of diabetes mellitus in promoting platelet adhesion and smoking in enhancing intimal hyperplasia. As in the angiography characteristics, stent lesion at LAD (OR 1.20 [95%CI 1.07, 1.35] p = 0.002) and stent length (MD 3.61 [95%CI 1.81, 5.42] p < 0.0001) are correlated with the events of ISR. Every millimeter excess of stent length significantly increases the risk of ISR. Therefore, reducing the excess stent length may contribute to the reduced risk of ISR in DES.* ***Conclusion:*** *The identification of risk factors contributing to ISR in DES may help cardiologists modify the attributable factors and prevent the occurrence of ISR.*

Keywords**:** *Drug-eluting stents, Meta-analysis, Risk factor ISR, Systematic review.*

INTRODUCTION

Percutaneous coronary intervention (PCI) has become one of the effective methods for the treatment of coronary heart disease (CHD). However, it is easy to have in-stent restenosis (ISR), even cardiovascular events after PCI, which affects the therapeutic effects. In-stent restenosis is a corollary of the improved durability of modern-day coronary inter. After performing percutaneous coronary intervention (PCI), patients are still at risk of developing new stenosis, such as intra-stent restenosis (ISR).[1] The widespread application of new anticoagulants and drug-eluting stents has

significantly decreased the incidence of coronary ISR. Nevertheless, large-scale clinical trials have confirmed that a 5% probability of restenosis exists despite the use of drug-eluting stents.[2]

The first and especially second-generation drug-eluting stents (DES) were specifically designed to reduce hyperproliferation within stents as a mechanism to overcome the high rate of ISR.[3] Nevertheless, the prevalence of ISR is estimated to vary from 3 to 20% in the current DES era, depending on coronary anatomy, and patient- and procedure-related factors.[3] This suggests that the type of stent is only one factor to consider when searching for additional promoters of ISR. The results of previous research concluded that the factors associated with ISR after PCI have not been clearly defined. In previous studies, several risk factors for ISR have been found, but not much research data on risk factors for ISR in drug-eluting stents (DES). For this reason, we systematically review the latest evidence to detect the risk factors of in-stent restenosis with drug-eluting stents (DES).

METHODS

This meta-analysis is conducted based on PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 guidelines**.** This study had been registered on the PROSPERO database (CRD42023465249).

Eligibility Criteria

Studies were selected based on inclusion criteria, which are: (1) observational study with human subjects, (2) investigated the association between risk factors and ISR after stent implantation (DES), (3) ISR was defined as ≥50% diameter stenosis of the culprit lesion by quantitative coronary analysis. The exclusion criteria were: (1) CAD without implantation stent, (2) RCT study. Two independent reviewers screened for the included studies (PS and PBTS). Our senior reviewer (HS) made the final decision when there were differences in the screening results.

Search Strategy and Selection of Studied

Electronic databases include PubMed, ScienceDirect, Springer, Google Scholar, and Proquest. The search terms have diabetes mellitus, ISR, in-stent restenosis, PCI, risk factor, and drug-eluting stent. Databases were searched using terms (('risk factors')) AND (('drug eluting stent')) AND (('in stent restenosis')) on September 20th, 2023. Newcastle-Ottawa Scale was used to evaluate the risk of bias for each study independently, with each bias assessment consisting of the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest, with the assessment of good, fair, and low quality of a study.

Data Extraction

The following data: age, patient's status of hypertension, diabetes mellitus, smoking, dyslipidemia, and family history of CAD, and the paramount data of lesion at LAD, lesion at LCX, lesion at RCA, stent diameter, and stent length, each representing ISR and Non-ISR patients were collected and recorded in a formatted table.

Statistical Analysis

The software Review Manager 5.4 was used to conduct statistical analyses, dichotomous data (risk ratio and odds ratio) used Mantel-Haenszel statistical method for hypertension, diabetes mellitus, smoking, dyslipidemia, and family history of CAD, and the paramount data of lesion at LAD, lesion at LCX, lesion at RCA, and continuous data (mean difference) used inverse variance statistical method for stent length and diameter. Heterogeneity was analyzed using the DerSimonian and Laird random-effect model.

Sensitivity analysis should also be done, by using the leave-one-out approach to detect study outliers and changes in heterogeneity (I2), with I2 values of 0-50% representing low heterogeneity, 50-75% representing moderate heterogeneity, and 76-100% representing substantial heterogeneity. The data analysis employed either the fixed or the random effect model. All statistical analysis with a p-value < 0.05 was considered statistically significant. Leave-one-out sensitivity analysis was conducted to find the source of statistical heterogeneity and demonstrate how each study affected the overall result.

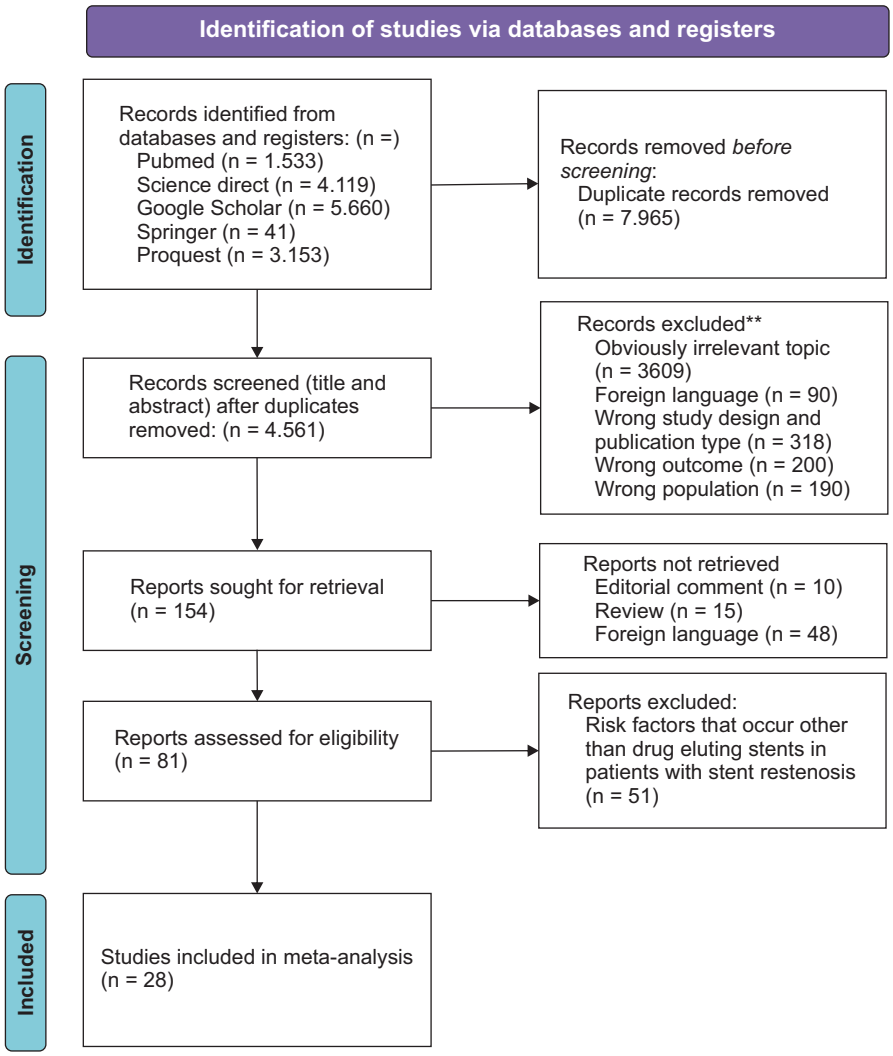


Figure 1. The study selection process in the PRISMA diagram

RESULTS

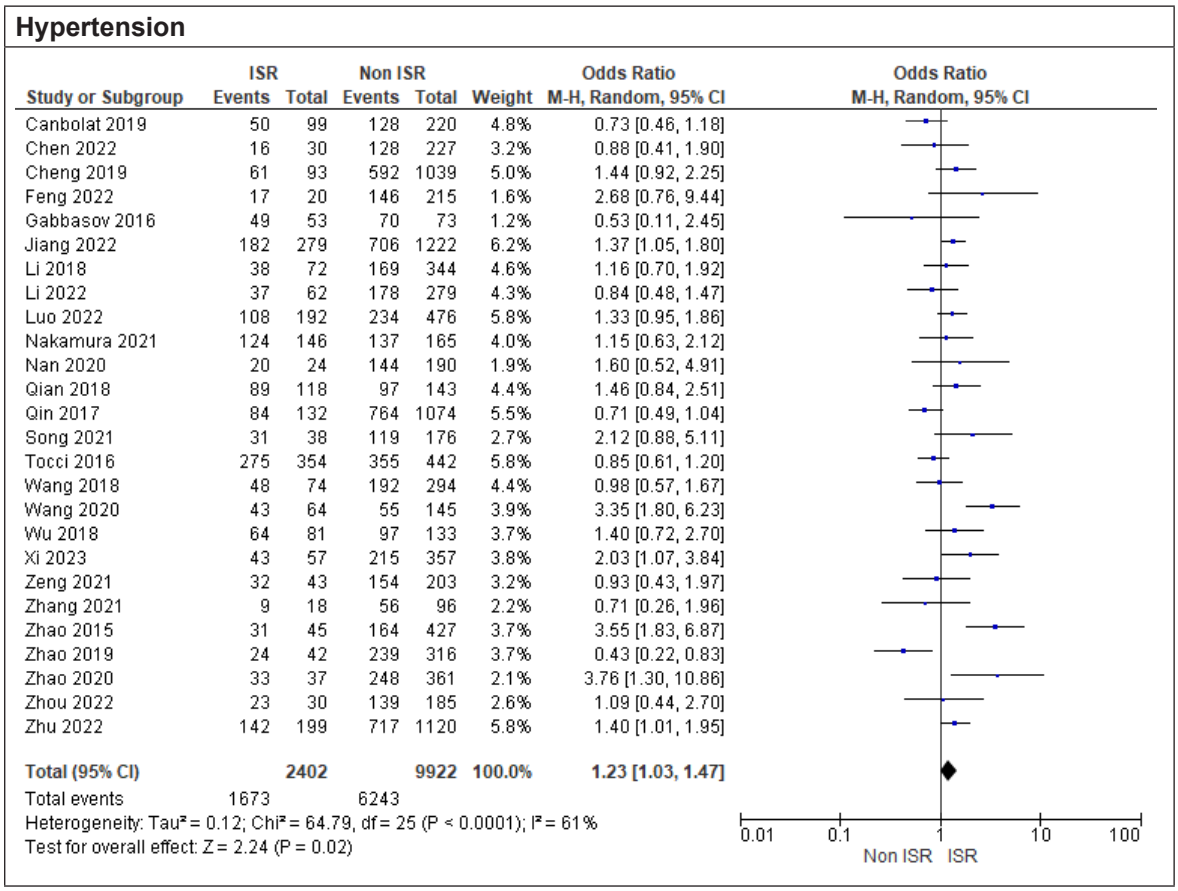
Characteristics of Studies

Among 12,526 studies gathered from databases, 28 articles were included.[4-31] The risk of bias from 26 articles was assessed to be good, while the other 2 studies were fair. This study involved a total of 12.559 patients, where 2.701 patients developed ISR and the rest 9.858 were non-ISR patients as controls. Most of the studies originated from China, while there was one study from Turkiye, one study from Japan, and the rest one study was from Italy. Data were collected from patients from 2004 to 2020. Moreover, the quality of the included studies was assessed using the Newcastle-Ottawa Scale and summarized in Supplementary Materials (**Table S2**).

Table 1. Characteristics of subjects.

No	Outcomes	No of Studies	Type of TE	TE (95% CI)	P	I^2	P for I^2
1.	Hypertension	26	OR	1.23 (1.03, 1.47)	0.02	61%	< 0.0001
2.	Diabetes Mellitus	25	OR	1.73 (1.56, 1.91)	< 0.00001	43%	0.01
3.	Smoking	27	OR	1.24 (1.13, 1.36)	< 0.0001	33%	0.05
4.	Family history of CAD	10	OR	1.27 (1.02, 1.58)	0.03	0%	0.77
5.	Dyslipidemia	19	OR	1.12 (0.89, 1.41)	0.33	71%	<0.00001

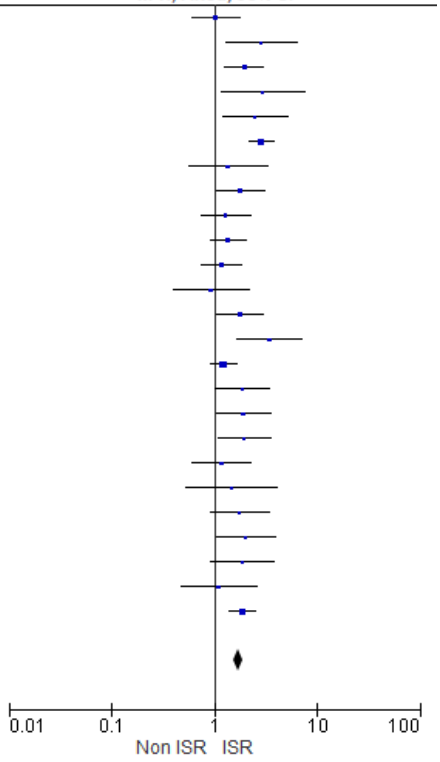
26 articles discuss hypertension and the incidence of ISR. The results of the study stated that hypertension showed a significant relationship with the incidence of ISR (OR 1.23; CI 95% 1.03-1.47; I2 61%; p < 0.0001). However, the prevalence of hypertension between ISR and non-ISR was 2402 versus 9922, which shows an increased rate of restenosis in hypertension. In the diabetes mellitus variable, 25 articles discuss the relationship between diabetes mellitus and ISR incidence. This study found a significant correlation between diabetes mellitus and ISR events (OR 1.73; 95% CI 1.56-1.91; I2 43%; p<0.00001). The research we have conducted from 27 articles states that there is a significant correlation between smoking and the incidence of ISR (OR 1.24; 95% CI 1.13-1.36; I2 33%; p <0.0001). Research conducted on 10 research articles found a significant relationship between ISR and family history of CHD (OR 1.27; CI 95% 1.02-1.58; I2 0%; p= 0.03). Meanwhile, research between ISR and dyslipidemia stated that there was no significant relationship between the two (OR 1.12; CI 95% 0.89-1.41; I2 71%; p= 0.33) (**Figure 2)**.



Diabetes Mellitus

Study or Subgroup	ISR Events	ISR Total	Non ISR Events	Non ISR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Canbolat 2019	29	99	63	220	5.0%	1.03 [0.61, 1.74]
Chen 2022	13	30	48	227	1.1%	2.85 [1.30, 6.28]
Cheng 2019	42	93	308	1039	5.0%	1.95 [1.27, 3.00]
Feng 2022	10	20	54	215	0.8%	2.98 [1.18, 7.55]
Gabbasov 2016	30	53	25	73	1.6%	2.50 [1.21, 5.18]
Jiang 2022	171	279	433	1222	11.2%	2.89 [2.21, 3.77]
Jing 2015	15	50	12	50	1.5%	1.36 [0.56, 3.30]
Li 2018	27	72	86	344	3.4%	1.80 [1.05, 3.08]
Li 2022	28	62	109	279	3.9%	1.28 [0.74, 2.24]
Luo 2022	47	192	91	476	7.1%	1.37 [0.92, 2.05]
Nakamura 2021	86	146	91	165	6.3%	1.17 [0.74, 1.83]
Nan 2020	11	24	91	190	2.0%	0.92 [0.39, 2.16]
Qian 2018	51	118	43	143	4.0%	1.77 [1.06, 2.95]
Song 2021	20	38	43	176	1.3%	3.44 [1.67, 7.09]
Tocci 2016	141	354	155	442	15.0%	1.23 [0.92, 1.64]
Wang 2020	36	64	59	145	2.9%	1.87 [1.03, 3.40]
Wu 2018	29	81	30	133	2.6%	1.91 [1.04, 3.52]
Xi 2023	22	57	87	357	2.7%	1.95 [1.09, 3.50]
Zeng 2021	24	43	105	203	2.9%	1.18 [0.61, 2.29]
Zhang 2021	8	18	34	96	1.1%	1.46 [0.53, 4.04]
Zhao 2015	17	45	63	247	2.2%	1.77 [0.91, 3.46]
Zhao 2019	17	42	79	316	2.0%	2.04 [1.05, 3.97]
Zhao 2020	14	37	89	361	1.9%	1.86 [0.92, 3.77]
Zhou 2022	9	30	52	185	1.8%	1.10 [0.47, 2.55]
Zhu 2022	97	199	379	1120	10.6%	1.86 [1.37, 2.52]
Total (95% CI)		**2246**		**8424**	**100.0%**	**1.73 [1.56, 1.91]**
Total events	994		2629			

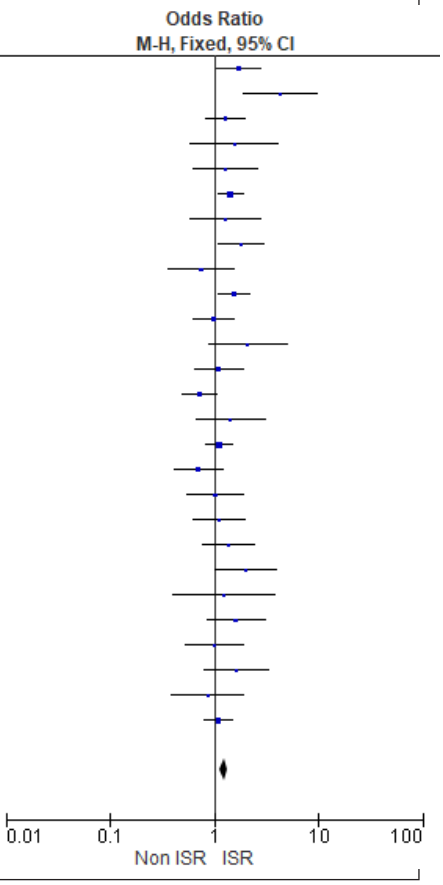
Heterogeneity: Chi² = 41.97, df = 24 (P = 0.01); I² = 43%
Test for overall effect: Z = 10.61 (P < 0.00001)



Smoking

Study or Subgroup	ISR Events	ISR Total	Non ISR Events	Non ISR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Canbolat 2019	62	99	108	220	3.3%	1.74 [1.07, 2.82]
Chen 2022	20	30	72	227	0.7%	4.31 [1.92, 9.67]
Cheng 2019	35	93	332	1039	4.5%	1.29 [0.83, 1.99]
Feng 2022	7	20	55	215	0.8%	1.57 [0.59, 4.13]
Gabbasov 2015	28	53	34	73	1.8%	1.28 [0.63, 2.61]
Jiang 2022	118	279	413	1222	11.8%	1.44 [1.10, 1.87]
Jing 2015	26	50	23	50	1.5%	1.27 [0.58, 2.79]
Li 2018	39	72	136	344	2.9%	1.81 [1.08, 3.01]
Li 2022	10	62	57	279	2.3%	0.75 [0.36, 1.56]
Luo 2022	96	192	187	476	7.2%	1.55 [1.10, 2.17]
Nakamura 2021	67	146	76	165	5.1%	0.99 [0.64, 1.55]
Nan 2020	14	24	76	190	0.9%	2.10 [0.89, 4.97]
Qian 2018	38	118	43	143	3.5%	1.10 [0.65, 1.87]
Qin 2017	44	132	440	1074	8.6%	0.72 [0.49, 1.06]
Song 2021	12	38	43	176	1.4%	1.43 [0.66, 3.07]
Tocci 2016	124	354	145	442	11.2%	1.10 [0.82, 1.48]
Wang 2018	26	74	128	294	4.5%	0.70 [0.41, 1.19]
Wang 2020	22	64	49	145	2.6%	1.03 [0.55, 1.91]
Wu 2018	30	81	46	133	2.9%	1.11 [0.63, 1.98]
Xi 2023	24	57	123	357	2.6%	1.38 [0.78, 2.44]
Zeng 2021	22	43	70	203	1.6%	1.99 [1.02, 3.87]
Zhang 2021	13	18	65	96	0.8%	1.24 [0.41, 3.79]
Zhao 2015	19	45	77	247	1.8%	1.61 [0.84, 3.09]
Zhao 2019	21	42	157	316	2.5%	1.01 [0.53, 1.93]
Zhao 2020	14	37	98	361	1.5%	1.63 [0.81, 3.30]
Zhou 2022	11	30	74	185	1.7%	0.87 [0.39, 1.93]
Zhu 2022	74	199	392	1120	9.9%	1.10 [0.80, 1.50]
Total (95% CI)		**2452**		**9792**	**100.0%**	**1.24 [1.13, 1.36]**
Total events	1016		3519			

Heterogeneity: Chi² = 38.91, df = 26 (P = 0.05); I² = 33%
Test for overall effect: Z = 4.39 (P < 0.0001)



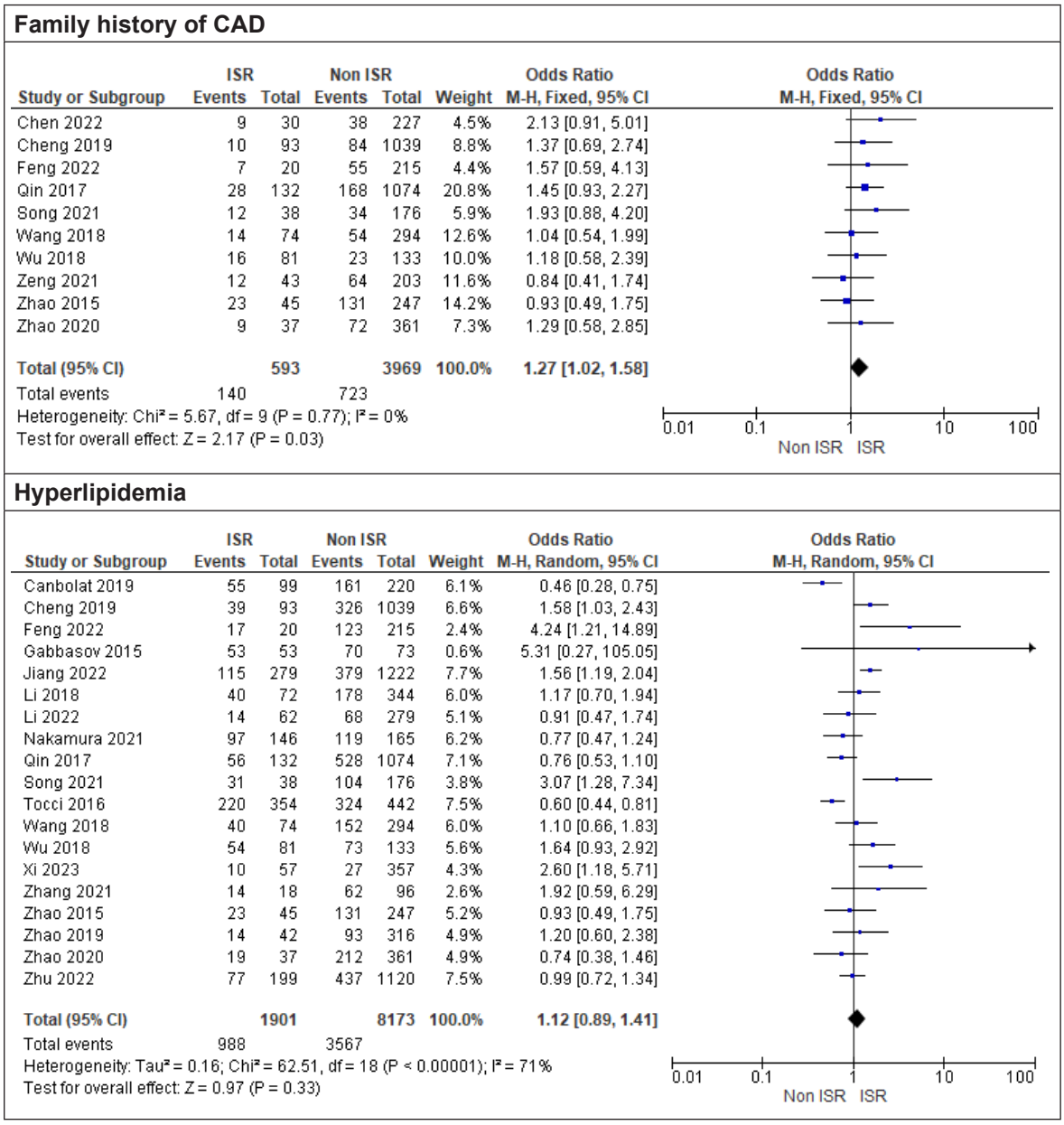


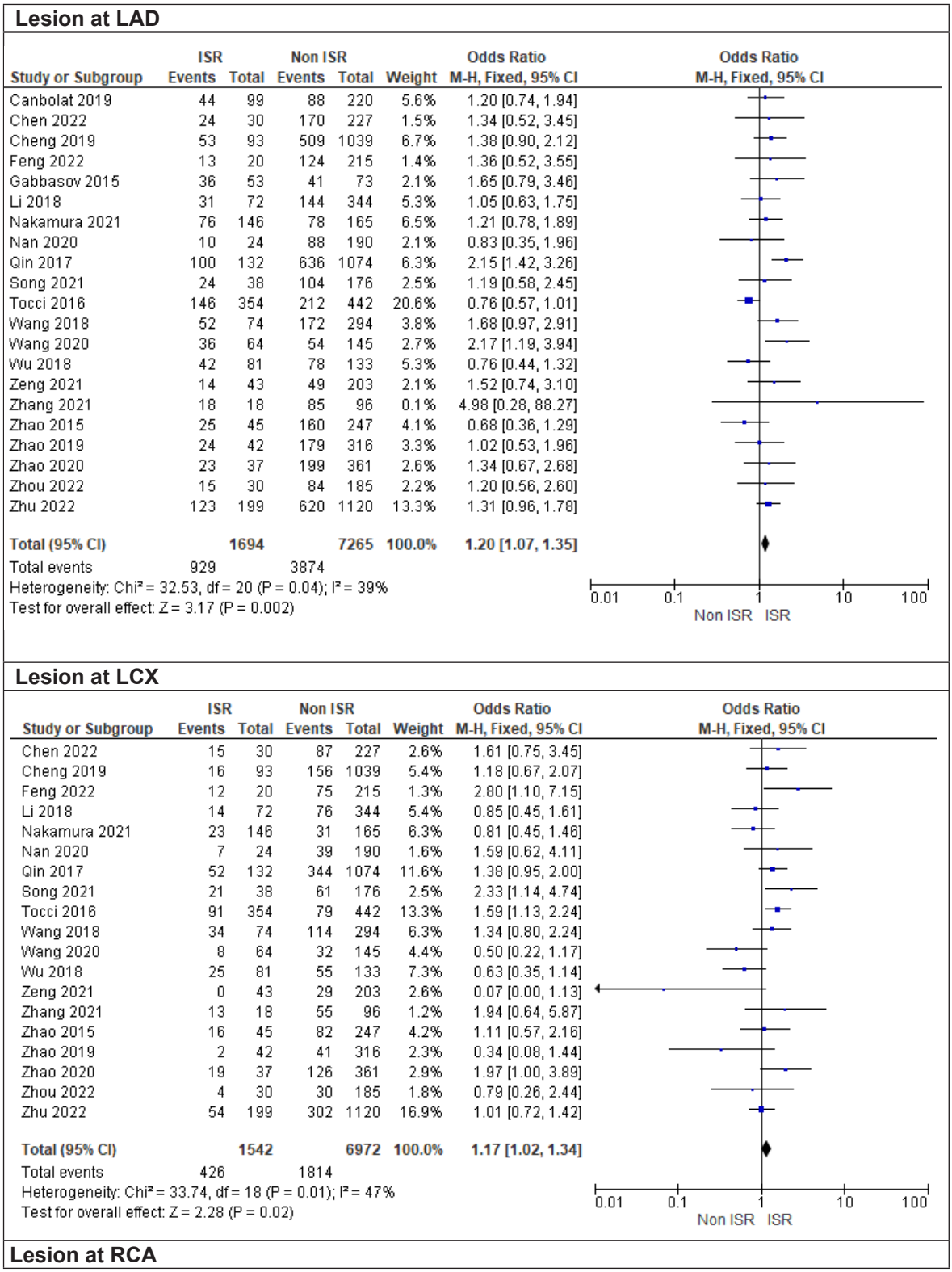
Figure 2. Forest plot of the relationship between patient characteristics and ISR incidence

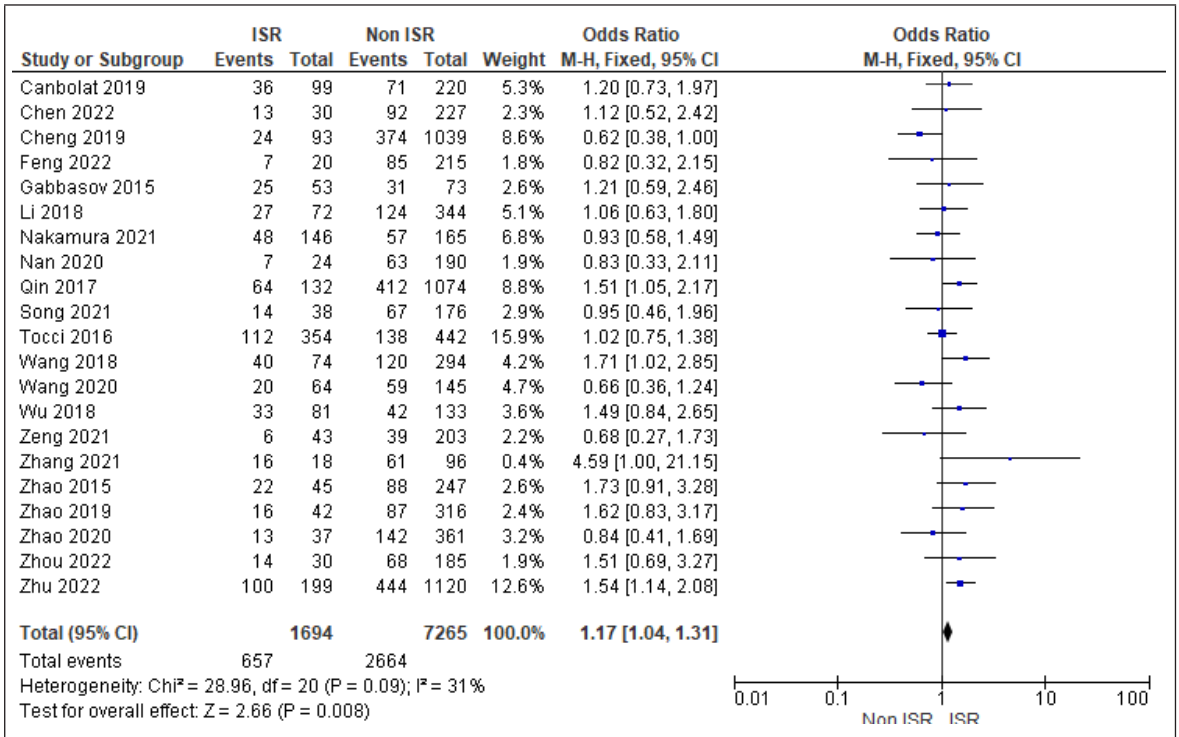
Table 2. Angiography characteristics

No	Outcomes	No of Studies	Type of TE	TE (95% CI)	P	I^2	P for I^2
1.	Lesion at LAD	21	OR	1.20 (1.07, 1.35)	0.002	39%	0.04
2.	Lesion at LCX	19	OR	1.17 (1.02, 1.34)	0.02	47%	0.01
3.	Lesion at RCA	21	OR	1.17 (1.04, 1.31)	0.008	31%	0.09
4.	Stent Diameter	13	MD	-0.12 (-0.22, -0.03)	0.009	94%	<0.00001
5.	Stent Length	13	MD	3.61 (1.81, 5.42)	<0.0001	93%	<0.00001

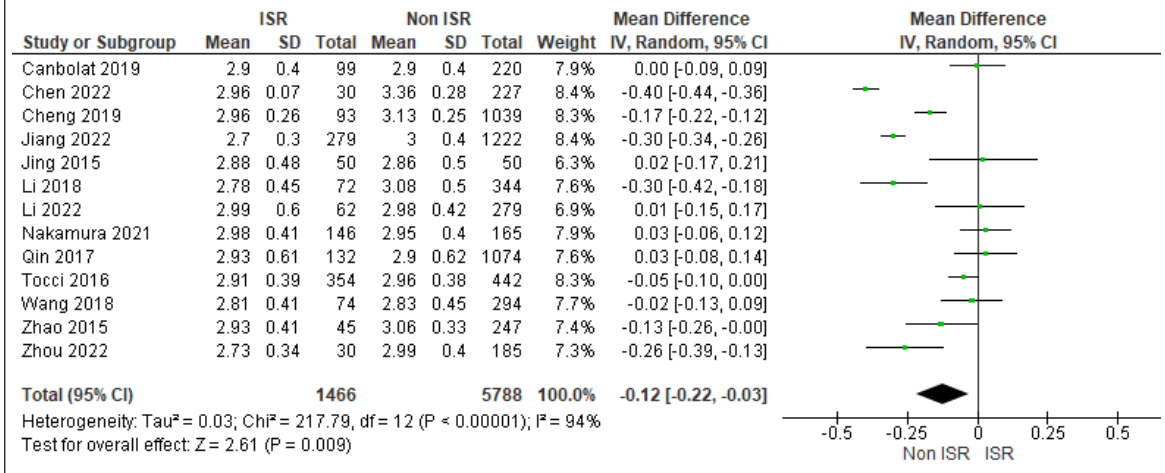
LAD is a lesion location that shows a significant correlation with the incidence of ISR (OR 1.20; 95% 1.07-1.35; I2 39%; p= 0.002). Apart from that, lesions located in the LCX also have a significant relationship with the incidence of ISR (OR 1.17; 95% 1.02-1.34, I2 47%; p = 0.02). Lesions in the RCA were significantly correlated with the incidence of ISR (OR 1.17;

95% 1.04-1.31; I2 31%; p = 0.008). On the other hand, we have found that ISR is more likely to occur in patients with small stent diameters. The research we conducted on 13 articles stated that there was a significant relationship between stent diameter and ISR (MD -0.12; 95% CI –0.22, -0.03; I2 94%; p 0.009). The research we have conducted in 13 articles states that there is a significant relationship between stent length and the incidence of ISR (MD 3.61; 95% CI 1.81-5.42; I2 93%; p <0.0001) **(Figure 3)**.





Stent Diameter



Stent Length

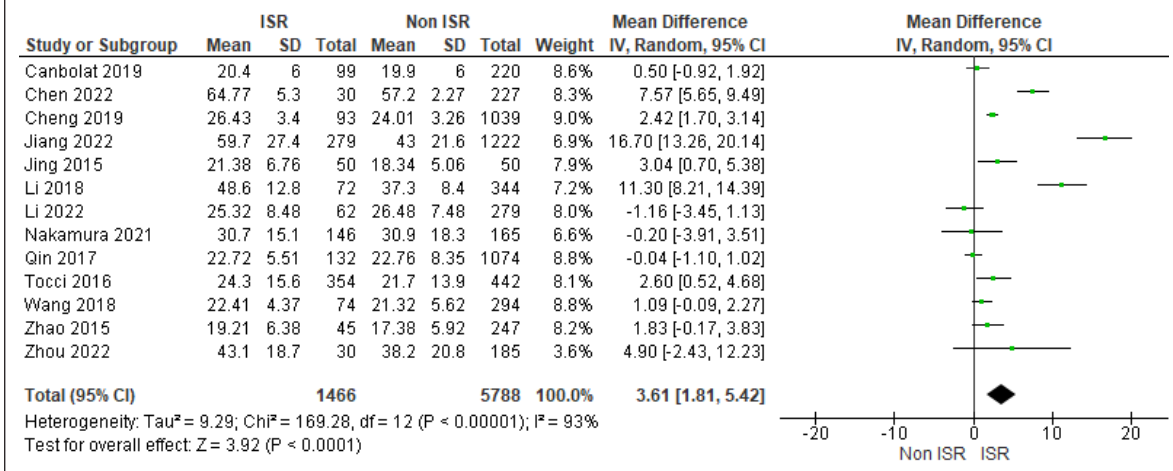


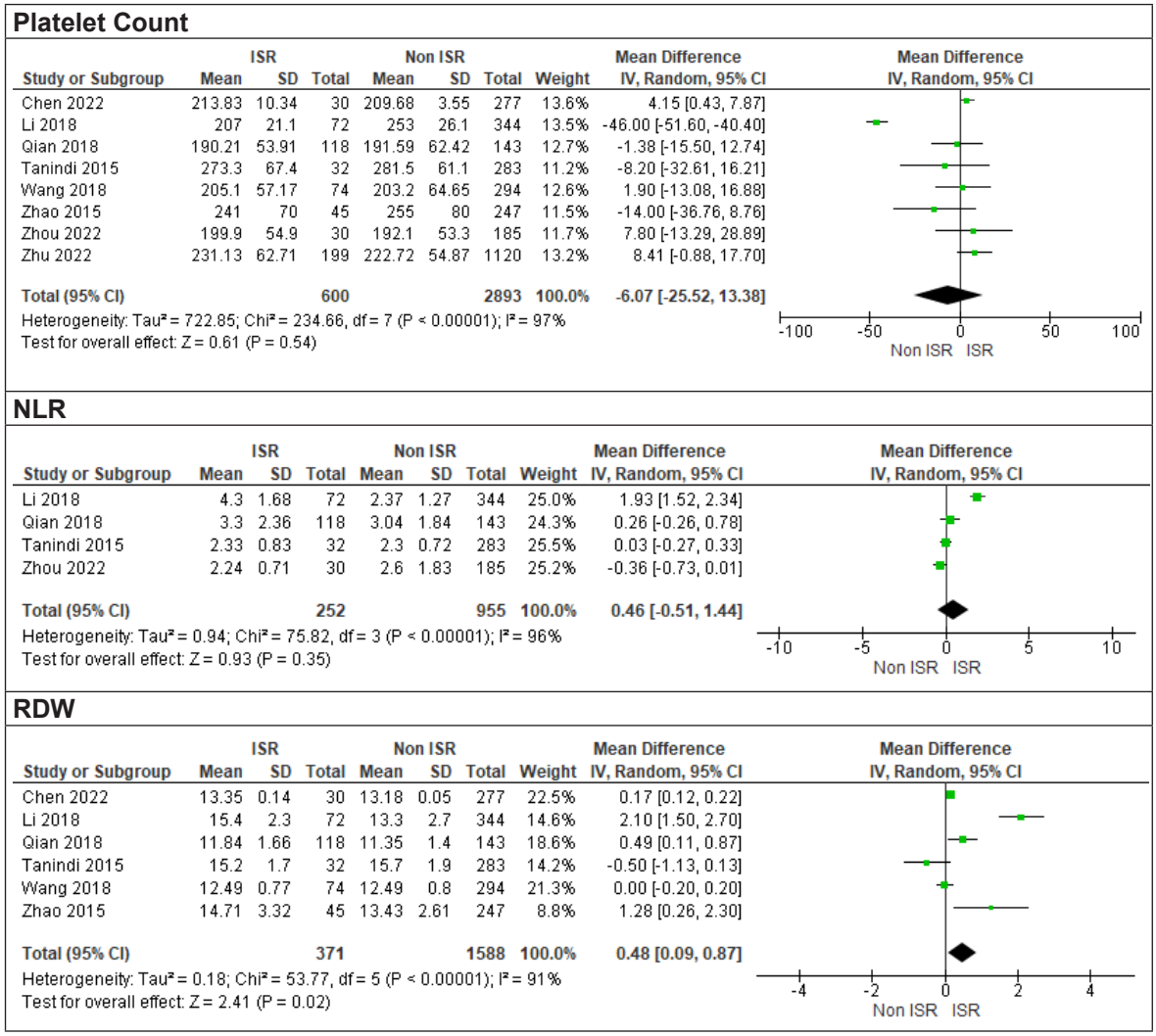
Figure 3. Forest plot of the relationship between angiography characteristics and ISR incidence

Blood Parameters

Table 3. Blood parameters

No	Outcomes	No of Studies	Type of TE	TE (95% CI)	P	I^2	P for I^2
1.	Platelet Count	8	MD	-6.07 (-25.52, 13.38)	0,54	97%	<0.00001
2.	NLR	4	MD	0.46 (-0.51, 1.44)	0.35	96%	<0.00001
3.	RDW	6	MD	0.48 (0.09, 0.87)	0.02	91%	<0.00001
4.	Creatinine	8	MD	0.20 (-0.12, 0.52)	0.22	78%	<0.0001

Based on research that has been conducted from 8 articles, it is stated that there is no significant relationship between platelet count and the incidence of ISR (MD -6.07; CI 95% -25.52-13.38; I2 97%; p=0.54). In addition, research conducted on the Neutrophil Lymphocyte Ratio stated that there was no significant relationship with the incidence of ISR (MD 0.46; CI 95% -0.51-1.44; I2 96%; p=0.35). Meanwhile, research on red cell distribution width (RDW) stated that there was a significant relationship with the incidence of ISR (MD 0.48; CI 95% 0.09-0.87; I2 91%; p=0.02). Creatinine did not have a significant relationship with the incidence of ISR (MD 0.20; CI 95% -0.12-0.52; I2 78%; p=0.22) **(Figure 4)**.



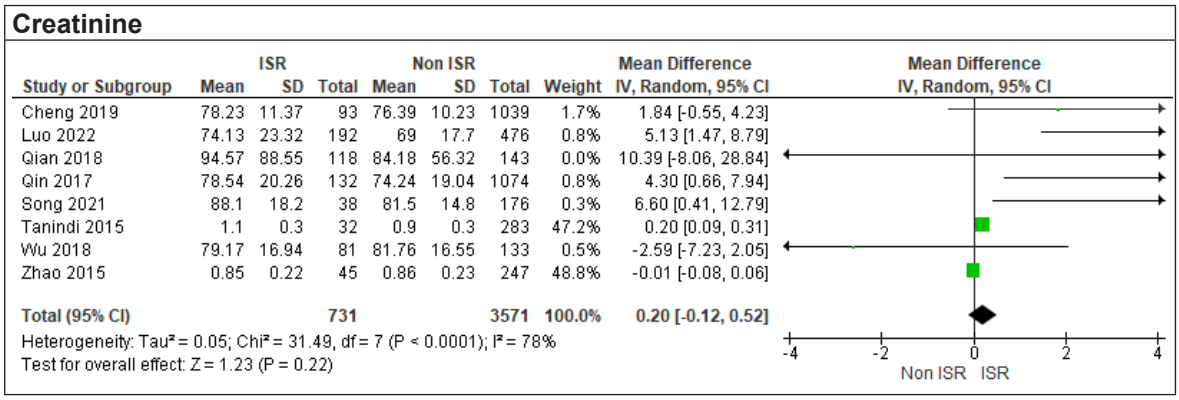


Figure 4. Forest plot of the relationship between blood parameters and ISR incidence

DISCUSSION

Hypertension is a predisposing factor for coronary artery disease. High or fluctuating blood pressure causes acceleration of blood shear force on the vessel wall, therefore damaging the endothelial cells lining and stimulating restenosis.[15,32] So, patients who underwent PCI are advised to strictly control their blood pressure to avoid restenosis. Both hypertension and diabetes mellitus complicate vascular lesions and unstable endothelial function.[33] During PCI intervention, coronary intimal tear or dissection tends to occur and promotes platelet adhesion.[34] Additionally, blood glucose may directly disrupt coronary endothelial cells, thus promoting ISR occurrence.[35] Unstable glucose metabolism activates an inflammation cascade in the endothelial wall, which is a predisposing factor for plaque formation. Inadequate blood glucose control following the PCI procedure will aggravate protein glycosylation and oxidation processes, thus stimulating ISR.[36] Moreover, cigarette smoking is closely related to the development and progression of coronary arterial disease. Our study reported a significant correlation between (OR 1.24; 95% CI 1.13-1.36; I2 33%; p < 0.0001). This result is coherent with the study by Huang et al., which reported a microstructural change of the coronary artery after stenting in smoking vs non-smoking patients. Patients with persistent smoking demonstrated increased neointimal coverage, while smoking cessation retarded neointimal hyperplasia process.[37] This phenomenon is expected due to the nature of nicotine in cigarettes, which has been proven to stimulate proliferation and migration of endothelial cells, therefore accelerating intimal hyperplasia.[38,39] Family history may provoke ISR due to differences in immune response and genetic factors.[40] This study states that a family history of CAD has a significant effect on the incidence of ISR. This is in contrast to research conducted by Cheng *et al*, which stated that family history of CAD was not significantly related to the incidence of ISR (p>0.05).[5] Dyslipidemia may also predispose to ISR, because, in particular, high LDL-C stimulates inflammation, damages endothelial cells, and promotes deposition of cholesterol in the blood vessel wall.[40]

LAD is the lesion location that demonstrated significant correlation with ISR incidence (OR 1.20; 95% 1.07-1.35; I2 39%; p= 0.002). This result is similar to the previous studies, which also imply that the most common site of restenosis is the lesion in the LAD.[41,42] Originally, bypass grafting was determined as superior compared to PCI in the LAD stenosis, because a significantly higher incidence of restenosis and revascularization was found in PCI compared to grafting.[43-45] However, the start of DES has dramatically reduced the incidence of restenosis in LAD.[46] But still, with the treatment of PCI using DES, the ISR event was found to occur mostly in LAD lesions. In a study conducted by,[9] stated that the incidence of ISR in ACS patients after successful PCI during angiographic follow-up of more than 2 years. The average time from stent placement to the occurrence of ISR was 32.8 months, and ISR tended to occur in LAD and LCX. Several other studies have shown that stent length is an important determinant of

ISR. Our study found a significant correlation between stent length and ISR incidence (MD 3.61; 95% CI 1.81-5.42; I2 93%; p < 0.0001). It shows that patients with longer stent lengths are more likely to experience ISR. Previous studies have shown similar results, where stent length is described as an important risk factor for ISR.[47] Research conducted by Hong et al. found that stent length (>40 mm) was an independent predictor of the development of ISR.[48] Mauri et al.[49] stated that each 10 mm increase of stent length was associated with an absolute increase of 7.7% stenosis diameter (p<0.0001).[49] On the other hand, we found that ISR was more likely to occur in patients with small stent diameter, however, this correlation is not significant (MD -0.12; 95% CI –0.22, -0.03; I2 94%; p= 0.009). HORIZONS-AMI study reported that vascular caliber ≤3 mm increased ISR significantly.[50]

The NLR (neutrophil count divided by lymphocyte count) is a potential biomarker of inflammation. Neutrophils play a major role in endothelial injury and platelet aggregation in acute coronary events. Lymphocytes represent the immunomodulatory response. Moreover, low lymphocyte counts in patients with CAD reflect the physiological stress of cortisol and correlate with a worse prognosis.[51] NLR is an effective biomarker of systemic inflammation and is considered a predictor for the prognosis of different cardiovascular diseases, especially for CAD. CHD patients with high NLR have the potential for unstable plaque and inflammatory conditions.[52] In a recent study, NLR was independently associated with early ISR after stent implantation in patients with femoropopliteal CTO.[53] The study conducted by Turak et al investigated the relationship of NLR before PCI and found that the NLR value predicted a higher incidence of ISR in ACS patients [54]

Red blood cell distribution width (RDW) is a parameter that reflects the size of red blood cells. An increase in RDW indicates a greater heterogeneity of red blood cells in the peripheral blood.[55] Red cell distribution width is a measurement of the variability and size of erythrocytes. By deforming the red cell membrane, Inflammation may induce changes in red blood cell maturation, leading to increased RDW.[56] In a recent study, an increased RDW predicted BMS restenosis, suggesting potential as a useful screening tool to stratify patients by higher or lower risk of ISR.[57] The mechanisms underlying the relationship between RDW restenosis and DES remain unclear. In this study, it was stated that RDW had a significant relationship with the incidence of ISR. This is different from research conducted by which stated that although RDW was higher in the ISR group, it did not show significance in multivariate analysis.[31]

Creatinine is a product of the hydrolysis reaction of phosphocreatine that occurs in muscles, which occurs with a fairly constant rhythm. A large amount of creatinine contained in the blood circulation will be filtered out with the urine, and not reabsorbed into the blood. Research conducted has found that serum creatinine in the ISR group was higher than in the non-ISR group, indicating that serum creatinine may be correlated with the occurrence of PCHD.[26] Creatinine is considered an indicator that can reflect kidney function. Research by Okada[58] found that serum creatinine was closely related to ISR in CHD patients.

Limitation the Study

Finally, this systematic review and meta-analysis have several limitations. First, the included studies were predominantly observational. Second, the small sample size makes the trial underpowered to detect small differences in some risk factors, such as hyperlipidemia, platelet count, and NLR. At last, further well-powered studies with more extensive adjustment of confounders are warranted to address some limitations of our current meta-analysis.

CONCLUSION

From our study, we found that diabetes mellitus and smoking are associated with the incidence of ISR in DES. In addition, as the angiography characteristics, stent lesion at LAD, RCA, and stent length may contribute to ISR in DES. By identifying the risk factors of ISR in DES, cardiologists may modify the attributable factors. Thus,

ISR in DES could be prevented. Further studies need to be conducted to explain the mechanism behind each risk factor in contributing to the event of ISR.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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