Impact of anemia on in-stent restenosis after percutaneous coronary intervention

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Abstract

Background Anemia is a well-recognized risk factor for adverse events after percutaneous coronary intervention (PCI), but data regarding the association between anemia and in-stent restenosis (ISR) remain limited.

Methods A total of 538 patients who underwent PCI between January 2018 and September 2019 and performed follow-up angiography 9–12 months after the initial PCI was enrolled in the study. Baseline clinical and procedural characteristics were compared between ISR and non-ISR group. Multivariate logistic regression analysis was employed to determine the independent predictors of ISR.

Results The incidence of anemia in patients with ISR was 53.5% and 19.0% in the non-ISR group, which was significantly different ($P = 0.001$). The rate of diabetes, chronic kidney disease (CKD), bifurcation lesion and calcification was significantly higher in ISR group. In addition, low-density lipoprotein cholesterol (LDL-c), multiple stenting and stent diameter were also significantly related with ISR. After multivariate logistic analysis, anemia (odds ratio [OR], 2.786; 95% confidence interval [CI], 1.091 to 7.115; $P = 0.032$) together with LDL-c (OR, 1.682; 95% CI, 1.145 to 2.469; $P = 0.008$), diabetes (OR, 3.582; 95% CI, 1.406 to 9.125; $P = 0.007$), CKD (OR, 2.841; 95% CI, 1.006 to 8.027; $P = 0.049$), multiple stenting (OR, 2.823; 95% CI, 1.184 to 6.731; $P = 0.019$), and stent diameter (OR, 2.778; 95% CI, 1.069 to 7.194; $P = 0.036$) were closely associated with ISR.

Conclusion Anemia is closely associated with ISR after PCI, patients with lower hemoglobin have a higher risk of ISR.

Introduction

Percutaneous coronary intervention (PCI) has become an effectively and widely used treatment for patients with coronary artery disease (CAD) since 1979[1]. Despite on-going improvement of drug-eluting stent (DES), in-stent restenosis (ISR) remains one of the major complications of PCI, which accounts for approximately 5%[2, 3]. The factors involved in the development of ISR are multiple, including inflammatory response, patient-specific and procedure-related risk factors[4].

Anemia is found to be associated with a greater rate of cardiovascular events[5, 6]. The prevalence of anemia is comparatively high in patients with CAD. Previous studies have demonstrated that anemia is related to a higher risk of death, major adverse cardiovascular events (MACE), myocardial infarction (MI), and bleeding after PCI[7–10].

Although studies have shown that anemia is associated with fatal adverse events post PCI, data is lacking regarding the relation between anemia and ISR. In this study, we explored whether anemia was associated with ISR and could be used as an independent predictor of ISR after PCI in patients with CAD.

Materials And Methods

Patients and study design

This was a retrospective observational cohort study carried out at the First Hospital of Jiaxing. Our study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee at the First Hospital of Jiaxing, Jiaxing, China. A total of 538 CAD patients were treated with second-generation DES between January 2017 and September 2019 and performed followed-up angiography 9–12 months after the initial PCI in our hospital were enrolled, and written informed consent was obtained from all patients. Patients with major adverse cardiac events(death, stroke, repeated PCI) after PCI, severe infection, malignancy, severe chronic kidney disease(estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m²),severe anemia (hemoglobin levels < 6 g/dL), active liver disease, and coagulation disorders were excluded.

The initial assessments of the patients included a medical history, pharmacotherapy, angiographic characteristics and blood biochemistry tests for a complete blood cell count, low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG). Anemia was defined as a baseline hemoglobin(Hb) levels < 12 g/dL.

PCI procedures and follow-up evaluations

PCI was performed as described earlier, and DES were implanted in all patients according to the current guidelines. All patients received dual antiplatelet therapy before and after the procedures. The follow-up angiography was performed 9–12 months after the initial PCI. The evaluation of restenosis was carried out using the conventional QCA technique. ISR was defined as a luminal narrowing with more than 50% diameter stenosis of a stented coronary segment or within a 5mm segment proximal or distal to the stent[11].

Statistical analysis

All statistical analyses were carried out using IBM SPSS 22.0. Data for continuous variables are expressed as mean ± SD and categorical variables as percentages. Continuous variables were analyzed by *t*-test and categorical variables by χ^2 -test. A one-way ANOVA analysis was used to determine differences among different categories of Hb. A two tailed P value less than 0.05 was considered statistically significant. Binary logistic regression analysis was performed to assess the risk factors of ISR. Odds ratio (OR) and 95% confidence interval (CI) were calculated. To analyze the influence of covariates on the relation between anemia and ISR, we carried out multivariate logistic regression analysis. Only those variables with statistical significance set at P less than 0.05 at univariate analysis together with age and gender were included in a multivariate logistic regression model to determine the independent predictors of ISR[12]. Moreover, we also performed a receiver operating characteristics (ROC) curve analysis to describe the accuracy of Hb for prediction of ISR.

Results

General characteristics of the patients with and without ISR

Among the 538 subjects included in the study, 28 patients (5.2%) suffered ISR, and 20 patients underwent repeat revascularization with the assistance of intravascular ultrasound (IVUS), the baseline characteristics are summarized in Table 1. Overall, patients were 62.2 ± 10.2 years of age (range 29–87 years) and 71.4% were male. Compared with non-ISR group, patients with ISR more frequently had a higher LDL-c level and lower Hb level. The rate of co-morbidities, including diabetes, anemia, chronic kidney disease (CKD) was significantly higher in ISR group (P values 0.015, ≤ 0.001 , 0.008, respectively). Angiographic findings showed that the prevalence of multiple stenting, smaller diameters stent implanted, bifurcation and calcification was significantly higher in patients with ISR (P values 0.012, 0.007, 0.010, 0.045, respectively).

Table 1
Baseline and procedural characteristics

Variable	ISR (n = 28)	Non-ISR (n = 510)	P Value
Male, n(%)	18 (64.3)	366 (71.7)	0.394
Age(years)	62.5 ± 12.3	62.2 ± 10.1	0.102
Current smoker, n (%)	12 (42.9)	221 (43.3)	0.961
BMI (kg/m2)	23.7 ± 3.3	24.5 ± 2.8	0.411
Hypertension, n(%)	17 (60.7)	330 (61.3)	0.667
Diabetes mellitus, n(%)	11 (39.3)	102 (20.0)	0.015
LDL-c (mmol/L)	3.1 ± 1.6	2.6 ± 0.9	0.002
TG(mmol/L)	1.5 ± 0.6	1.6 ± 0.9	0.187
Hb(g/dL)	115.4 ± 20.1	134.9 ± 21.3	0.001
LVEF (%)	57.5 ± 7.9	60.0 ± 6.6	0.051
Anemia (%)	15 (53.5)	97(19.0)	0.001
CKD (%)	8 (28.6)	59 (11.6)	0.008
ACS (%)	15 (53.6)	280 (54.9)	0.890
Multiple stenting, n(%)	14	142	0.012
Stent length (mm)	28.8 ± 6.1	29.6 ± 5.4	0.457
Stent diameter (mm)	2.9 ± 0.4	3.2 ± 0.5	0.007
Multivessel coronary disease (%)	6 (21.4)	96 (18.8)	0.732
LMCA, n(%)	2 (7.1)	10 (2.0)	0.071
LAD, n(%)	7 (25.0)	75 (14.7)	0.140
LCX, n(%)	18 (64.2)	230 (45.1)	0.053
RCA, n(%)	7 (25.0)	202 (39.6)	0.123
Bifurcation lesion, n(%)	13 (46.4)	125 (24.5)	0.010
Calcification, n(%)	4 (14.3)	23 (4.5)	0.045
Statins, n(%)	26 (92.9)	483 (94.7)	0.673

Abbreviation: ISR, In-stent restenosis; BMI, Body mass index; CKD, Chronic kidney disease; Hb, hemoglobin; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; LMCA, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery

Variable	ISR (n = 28)	Non-ISR (n = 510)	P Value
Aspirin, n(%)	28 (100)	502 (98.4)	0.504
Clopidogrel, n(%)	15 (53.6)	253 (49.6)	0.683
Ticagrelor, n(%)	10 (35.7)	227 (44.5)	0.361
Abbreviation: ISR, In-stent restenosis; BMI, Body mass index; CKD, Chronic kidney disease; Hb, hemoglobin; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; LMCA, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery			

Relationship between baseline Hb and the occurrence of ISR

We divided the patients into three groups according to the baseline of Hb level before the initial PCI (Moderate anemia: <9 g/dL; Mild anemia: ≥ 9 and <12 g/dL; and nonanemia group: ≥ 12 g/dL) to explore the relationship between the baseline Hb and the ISR at follow-up. The clinical and angiographic characteristics were compared among different Hb groups (Table 2). Anemia was present in 20.8% of all patient. We found that the patients with lower Hb were more likely to develop ISR (Moderate anemia: 26.3; Mild anemia: 8.6; and nonanemia :3.5; $P < 0.001$). Patients with anemia were more likely had CKD and discontinue the use of aspirin.

Table 2
Clinical characteristics of different hemoglobin categories

Variable	Moderate anemia(n = 19)	Mild anemia (n = 93)	Nonanemia(n = 426)	P
Hb(g/dL)	83.3 ± 5.1	104.9 ± 6.2	142.5 ± 14.4	≤0.001
Male(n)	16 (84.2)	63 (67.7)	305 (71.6)	0.344
Age(years)	66.0 ± 12.8	63.3 ± 10.4	61.8 ± 10.0	0.106
Current smoker (%)	9 (47.4)	40 (43.0)	184 (43.2)	0.936
BMI (kg/m ²)	24.6 ± 2.6	24.4 ± 2.9	24.5 ± 2.8	0.922
Hypertension(%)	13 (68.4)	63 (67.7)	271 (63.6)	0.706
Diabetes mellitus (%)	5 (26.3)	25 (26.9)	83 (19.5)	0.241
LDL-c(mmol/L)	2.6 ± 1.1	2.5 ± 0.9	2.6 ± 0.9	0.805
TG(mmol/L)	1.7 ± 0.9	1.5 ± 0.8	1.6 ± 0.9	0.531
LVEF(%)	56.8 ± 6.3	60.2 ± 6.3	59.9 ± 6.8	0.113
CKD (%)	9 (47.4)	13 (14.0)	45 (10.6)	≤0.001
ACS (%)	11 (57.9)	51 (54.8)	233 (54.7)	0.963
Multiple stenting(%)	3 (15.8)	31 (33.3)	122 (28.6)	0.290
Stent length(mm)	28.3 ± 4.9	29.4 ± 5.1	29.6 ± 5.6	0.557
Stent diameter(mm)	3.0 ± 0.5	3.1 ± 0.4	3.2 ± 0.4	0.207
Multivessel coronary disease(%)	3 (15.8)	12 (12.9)	87 (20.4)	0.231
LMCA(%)	0	0	12 (2.8)	0.200
LAD(%)	2 (10.5)	8 (8.6)	72 (16.9)	0.111
LCX(%)	8 (42.1)	47 (50.5)	193 (45.3)	0.618
RCA(%)	10 (52.6)	37 (39.8)	162 (38.0)	0.434
Bifurcation lesion(%)	3(15.8)	23(24.7)	112(26.3)	0.578
Calcification (%)	0	7 (7.5)	20 (4.7)	0.314
Statins (%)	19 (100)	88 (94.6)	402 (94.4)	0.569

Abbreviation: Hb, hemoglobin; BMI, Body mass index; CKD, Chronic kidney disease; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; LMCA, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; ISR, In-stent restenosis;

Variable	Moderate anemia(n = 19)	Mild anemia (n = 93)	Nonanemia(n = 426)	P
Aspirin(%)	17 (89.5)	90 (96.7)	423 (99.3)	0.001
Clopidogrel (%)	8 (42.1)	48 (51.6)	212 (49.8)	0.752
Ticagrelor(%)	7 (36.8)	40 (43.0)	190 (44.6)	0.782
ISR(%)	5 (26.3)	8 (8.6)	15 (3.5)	0.001
Abbreviation: Hb, hemoglobin; BMI, Body mass index; CKD, Chronic kidney disease; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; LMCA, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; ISR, In-stent restenosis;				

Predictors of ISR at follow-up

Binary logistic regression analysis was used to assess predictors of ISR at follow-up. All variables that were potentially correlated and clinically important were included in the univariate logistic model (Table 3). We found that diabetes, anemia, CKD, higher LDL-c were the significant predictors of the ISR (P value 0.018, 0.001, 0.011, 0.003 respectively). Additional, multiple stenting, smaller stent diameter, bifurcation lesion and calcification were also significantly associated with ISR (P value 0.015, 0.009, 0.012, 0.030, respectively). Then we applied multivariate logistic regression analysis that included all the significant univariate predictors found in Table 3 together with age and gender to determine the independent predictors of ISR. As a result, anemia was found to be an independent risk factor for ISR after adjustment for other confounding factors (OR:2.786, 95% CI: 1.091–7.115; P = 0.032) (Table 4). Besides, LDL-c (OR, 1.682; 95% CI, 1.145 to 2.469; P = 0.008), diabetes (OR, 3.582; 95% CI, 1.406 to 9.125; P = 0.007), CKD (OR, 2.841; 95% CI, 1.006 to 8.027; P = 0.049), multiple stenting (OR, 2.823; 95% CI, 1.184 to 6.731; P = 0.019), stent diameter (OR, 2.778; 95% CI, 1.069 to 7.194; P = 0.036) and bifurcation lesion (OR, 2.459; 95% CI, 1.020 to 5.926; P = 0.045) also were independent predictors of ISR at follow-up. ROC curve analysis of the diagnostic accuracy of the Hb for ISR showed an area under the curve (AUC) of 0.758 (95% CI, 0.675 to 0.840; P < 0.001) (Fig. 1).

Table 3
Univariable logistic regression analysis for the prediction of ISR

Variable	OR	95%CI	P Value
Gender	0.708	0.319–1.571	0.396
Age	1.003	0.967–1.042	0.858
Current smoker	1.020	0.473–2.199	0.961
BMI	0.908	0.788–1.046	0.179
Hypertension	1.186	0.544–2.587	0.668
Diabetes mellitus	2.588	1.176–5.696	0.018
LDL-c	1.651	1.187–2.296	0.003
TG	0.813	0.489–1.353	0.426
LVEF	0.958	0.916–1.001	0.057
Anemia	4.283	1.949–9.410	0.001
CKD	3.058	1.289–7.252	0.011
ACS	0.948	0.442–2.033	0.890
Multiple stenting	2.592	1.205–5.573	0.015
Stent length(mm)	0.974	0.908–1.044	0.456
Stent diameter(mm)	3.413	1.361–8.547	0.009
Multivessel coronary disease	1.176	0.464–2.980	0.732
LMCA	3.846	0.801–18.460	0.092
LAD	1.933	0.794–4.707	0.146
LCX	2.191	0.992–4.840	0.052
RCA	0.508	0.212–1.218	0.129
Bifurcation lesion	2.669	1.236–5.763	0.012
Calcification	3.529	1.131–11.014	0.030
Statins	0.727	0.164–3.223	0.674
Aspirin	NA	NA	NA

Abbreviation: ISR, In-stent restenosis; BMI, Body mass index; CKD, Chronic kidney disease; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; LMCA, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery

Variable	OR	95%CI	P Vaule
Clopidogrel	0.853	0.397–1.828	0.683
Ticagrelor	0.693	0.314–1.530	0.364
Abbreviation: ISR, In-stent restenosis; BMI, Body mass index; CKD, Chronic kidney disease; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; LMCA, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery			

Table 4
Independent predictors of ISR by multivariable logistic regression analysis

Variable	OR	95%CI	P Vaule
Gender	0.599	0.239–1.501	0.274
Age	1.002	0.961–1.045	0.919
Diabetes mellitus	3.582	1.406–9.125	0.007
LDL-c	1.682	1.145–2.469	0.008
Anemia	2.786	1.091–7.115	0.032
CKD	2.841	1.006–8.027	0.049
Multiple stenting	2.823	1.184–6.731	0.019
Stent diameter(mm)	2.778	1.069–7.194	0.036
Bifurcation lesion	2.459	1.020–5.926	0.045
Calcification	3.356	0.896–12.572	0.072

Discussion

In the present study, we found that anemia was strongly associated with the occurrence of ISR and might be used as an independent predictor of ISR at follow-up. Although it is widely recognized that preprocedural anemia is associated with poor outcomes after PCI in patients with CAD, data about the impact of anemia on ISR at follow-up is insufficient.

Catakoglu et al. [13]demonstrated that anemia is an important risk factor for predicting nonfatal coronary events after PCI, which included ST-segment elevation MI, non ST-segment elevation MI, target-vessel revascularization (TVR) and target- lesion revascularization (TLR). While Geng et al. [12]found no statistic significant relation between low hemoglobin and ISR. In our research, after adjustment for

confounding factors, a strong relation between anemia and ISR was revealed, indicating that anemic patients were more likely develop ISR after PCI.

The mechanisms of ISR in patients who have anemia and undergo PCI are not wellknown and probably multifactorial. The presence of anemia may lead to decreased supply of oxygen, and hypoxia has been identified with vascular cell proliferation and angiogenesis[14], which are necessary for the development, maintenance, and expansion of the neointimal lesions present in restenosis[15–17]. In addition, compensatory consequences of hypoxia, such as a hyperdynamic state with increased cardiac output, left ventricular hypertrophy and progressive cardiac enlargement, and, a proatherogenic role also contribute to the restenosis[18]. Moreover, anemia was found independently correlated with high platelet reactivity in patients with DES PCI[19], which have been shown contribute to the development of restenosis[20, 21].

Our data also showed that higher LDL-c, multiple stenting, bifurcation lesion and smaller stent diameter are associated with ISR after PCI, which is supported by previous studies[22–24]. Smoking is known to be a risk factor for CAD, but our data showed no significant relation between smoking and ISR. Interestingly, some studies supported that smoking is associated with a lower rate of restenosis, although still controversial[25]. Diabetes mellitus was considered as the most-consistent clinical parameter that increase the risk of restenosis[26, 27], which is accordance with our data. Several studies have explored the impact of CKD on ISR after PCI, end-stage renal disease might increase the risk for restenosis[28], while mild or moderate CKD had no impact on the incidence of ISR post-PCI[29], which is inconsistent with our results. In our study, patients with CKD are more likely combined with anemia, which may explain the different outcome.

In the present study, there're several limitations. First, it was retrospective in nature. Second, the sample size was relatively small and the follow-up period was relatively short. Third, our findings were based on a single measurement of preprocedural Hb level, the Hb during the follow-up were not evaluated. Large prospective trials are needed to confirm whether anemia can act as an independent predictor of ISR.

Conclusion

Patients with baseline anemia before PCI have a higher incidence of ISR after PCI compared with nonanemic counterparts. Anemia can be used as a predictor of ISR. Our results have important clinical implications and assessment of Hb level is crucial during periprocedural.

List Of Abbreviations

Hb, hemoglobin; BMI, Body mass index; CKD, Chronic kidney disease; LVEF, Left ventricular ejection fraction; ACS, Acute coronary syndrome; LDL-c, Low-density lipoprotein cholesterol; TG, triglycerides; ISR, In-stent restenosis;

Declarations

Ethics approval and informed consent

The study followed the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Hospital of Jiaxing (No. LS-2020-124). All participated in the study signed their consent after being fully informed of the purpose of research.

Consent for publication

Not applicable

Availability of data and materials

The data and material are available in the hospital information system (HIS) of our hospital.

Competing interests

The authors declare no competing interests.

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Authors' contribution

Huilin Hu: Conceptualization, Methodology; Shijun Wang: Formal analysis; Guanmin Tang: Supervision; Changlin Zhai: Investigation; Liang Shen: Conceptualization, Writing- Review and Editing

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Figures

Figure 1

The ROC curve analysis of Hb for predicting ISR. ISR, in-stent restenosis; Hb, hemoglobin; ROC, receiver operating characteristic.