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Original Research

Analysis of Risk Factors for Major Adverse Cardiovascular Events in Patients with Coronary Stent Restenosis after Revascularization

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Abstract

Background: To investigate the risk factors for myocardial infarction, recurrent in-stent restenosis (ISR) and target vessel revascularization (TVR) in patients with coronary ISR within 4 years after revascularization. **Methods**: A total of 1884 patients who were hospitalized at Fuwai Hospital for ISR and successfully treated with coronary intervention between January 2017 and December 2018 were included to determine whether there were myocardial infarction, recurrent ISR, TVR and other major adverse cardiovascular events (MACEs) within 4 years after intervention. The patients were divided into the MACE group (215 patients) and the non-MACE group (1669 patients). The clinical data of patients in the two groups were compared, and the risk factors for postoperative MACEs in the ISR patients were obtained by multivariate logistic regression analysis. The receiver operating characteristic (ROC) curve was used to determine the optimal prediction threshold for postoperative MACEs in ISR patients. The difference in survival curves between the two groups was compared using Kaplan–Meier survival analysis. **Results**: The albumin (43.42 $\pm$ 4.77 vs. 44.17 $\pm$ 4.46, $p = 0.021$), direct bilirubin (2.5 (2, 3.5) vs. 2.8 (2.07, 3.73), $p = 0.036$) and free triiodothyronine (FT3) (2.85 $\pm$ 0.43 vs. 2.92 $\pm$ 0.42, $p = 0.019$) levels in the MACE group were significantly lower than those in the non-MACE group, and there was a significant negative correlation between albumin and FT3 and MACEs. The results of univariate and multivariate logistic regression analyses revealed that FT3 was an independent predictor of postoperative MACEs in ISR patients (Odds Ratio (OR) = 0.626, 95% CI: 0.429–0.913, $p = 0.015$). The ROC curve analysis determined that an FT3 value of 2.785 pmol/L was the optimal prediction threshold. According to the threshold, ISR patients were divided into the FT3 $<$2.785 group and the FT3 $\geq$2.785 group. The Kaplan–Meier analysis revealed that the postoperative recurrence rate of MACEs of the FT3 $<$2.785 group was substantially greater than that of the FT3 $\geq$2.785 group (Hazard Ratio (HR) = 0.76, 95% CI: 0.58–0.994, $p = 0.044$). **Conclusions**: FT3 can be used as an independent predictor of postoperative myocardial infarction, recurrent ISR and TVR in ISR patients. When FT3 is $<$2.785 pmol/L, the incidence of postoperative myocardial infarction, recurrent ISR and TVR in ISR patients increases significantly.

Keywords: coronary in-stent restenosis (ISR); myocardial infarction; target vessel revascularization; triiodothyronine (FT3)

1. Introduction

The prevalence of in stent restenosis (ISR) after bare-metal stent implantation is approximately 16% to 44%, but with the widespread use of drug-eluting stents, the incidence of ISR decreases to 5% to 15% [1]. However, the number of patients receiving coronary stent implantation is increasing yearly. In 2021, the total number of coronary interventional procedures in mainland China exceeded 1.16 million, with an average of 1.48 stents or drug-coated balloons per patient [2]. As a result, the total number of patients with ISR remains negligible. Some studies have suggested that the pathogenesis of ISR is due to the damage to blood vessels that is caused by stent implantation, which triggers a series of local and systemic chain reactions. The final result of these reactions determines whether the vascular endothelium forms a smooth and thin intima or stent restenosis occurs [3]. This pathological process includes the activation of endothelial cells after injury, platelet degranulation and aggregation [4,5], the release of growth factors and cytokines, the proliferation and migration of smooth muscle cells (SMCs), an increase in extracellular matrix synthesis [3], bone marrow endothelial progenitor cells [6–8], and inflammatory responses.

After receiving revascularization therapy, some of these patients still had short-term or long-term major adverse cardiovascular events (MACEs), such as myocardial infarction, recurrent ISR (reISR) and target vessel revascularization (TVR). This not only imposes a huge financial burden on patients and their families but also imposes a severe psychological burden. Currently, there are few studies of MACEs in patients with ISR after revascularization, and there are no accepted predictors. The aim of this study was

Table 1. Baseline characteristics of the study participants.

	MACEs group (n = 215)	Non-MACEs group (n =1669)	*p* values
Gender (male, %)	162 (75.3%)	1332 (79.8%)	0.129
Age	60 (54, 67)	62 (55, 68)	0.081
BMI	25.35 (23.92, 27.76)	25.95 (23.94, 28.08)	0.999
History of smoking	131 (60.9%)	1055 (63.2%)	0.548
History of hypertension (%)	145 (67.8%)	1126 (67.6%)	1.000
History of diabetes mellitus (%)	92 (42.8%)	735 (44.0%)	0770
Hyperlipidemia (%)	200 (93%)	1562 (93.6%)	0.768
History of stroke (%)	27 (12.6%)	206 (12.3%)	0.912
CKD history (%)	3 (1.4%)	27 (1.6%)	1.000
Out-patient medication			
Aspirin	207 (97.6%)	1626 (98.1%)	0.594
Adenosine diphosphate (ADP) inhibitor			0.006
Clopidogrel	137 (63.7%)	1218 (73%)	
Ticagrelor	78 (36.3%)	451 (27%)	
Beta receptor blocker	169 (78.6%)	1322 (79.2%)	0.858
Angiotensin converting enzyme inhibitor /Angiotensin receptor blocker	117 (54.4%)	922 (55.2%)	0.827
statin	215 (100%)	1669 (100%)	1.000
Number of ISR vessels			0.194
1	189 (87.9%)	1518 (91.0%)	
2	23 (10.7%)	134 (8.0%)	
3	3 (1.4%)	17 (1.0%)	
ISR location			0.471
Left anterior descending (LAD)	95 (44.2%)	785 (47%)	
Left circumflex artery (LCX)	27 (12.6%)	222 (13.3%)	
Right coronary artery (RCA)	73 (34%)	561 (33.6%)	
LAD + LCX	10 (4.7%)	46 (2.8%)	
LAD + RCA	5 (2.3%)	28 (1.7%)	
LCX + RCA	4 (1.9%)	12 (0.7%)	
LAD + LCX + RCA	0 (0%)	2 (0.1%)	
Treatment			0.325
Drug Eluting Stent (DES)	114 (53%)	970 (58.1%)	
Drug Coated Balloon (DCB)	101 (47%)	699 (41.9%)	
Left ventricular ejection fraction	62% (60%, 66%)	62% (60%, 65%)	0.549
Big endothelin	0.22 (0.16, 0.31)	0.24 (0.18, 0.34)	0.109
Preoperative brain natriuretic peptide	116.6 (45.7, 195.8)	104.2 (49.8, 244)	0.508
Glycosylated hemoglobin	6.54 ± 1.21	6.54 ± 1.18	0.562
Albumin	43.42 ± 4.77	44.17 ± 4.46	0.021
Glutamic-pyruvic transaminase (ALT)	23 (14, 35)	23 (17, 34)	0.400
Glutamic oxalacetic transaminase (AST)	23 (17, 26)	23 (19, 28)	0.405
Total bilirubin	12.03 (8.92, 15.4)	12.97 (10.33, 16.29)	0.423
Direct bilirubin	2.5 (2, 3.5)	2.8 (2.07, 3.73)	0.036
Creatinine	73.66 (66.68, 87.09)	83.54 (72.77, 94.03)	0.060
eGFR	94.752(76.82, 117.49)	86.03 (69.95, 103.41)	0.092
Urea nitrogen	5.31 (4.1, 6.3)	5.4 (4.4, 6.5)	0.623
Uric acid	284.61 (242.17, 367.82)	350.2 (294.6, 407.11)	0.057
Triglyceride	1.31 (1.09, 2.48)	1.45 (1.09, 1.96)	0.897
Total cholesterol	3.71 (3.16, 4.69)	3.69 (3.21, 4.39)	0.874
High density lipoprotein cholesterol (HDL-c)	1.14 (0.96, 1.39)	1.06 (0.9, 1.23)	0.666

Table 1. Continued.

	MACEs group (n = 215)	Non-MACEs group (n =1669)	*p* values
Low density lipoprotein cholesterol (LDL-C)	2 (1.63, 2.95)	2.12 (1.71, 2.74)	0.735
lipoprotein(a) (Lpa)	107.2 (46.6, 306)	199 (69.52, 469.39)	0.235
Apolipoprotein A1 (ApoA1)	1.32 (1.19, 1.66)	1.32 (1.18, 1.5)	0.890
Apolipoprotein B (ApoB)	0.68 (0.59, 0.92)	0.71 (0.59, 0.85)	0.977
Highly sensitive C-reactive protein (hsCRP)	1.27 (0.48, 2.52)	1.33 (0.6, 2.85)	0.527
Erythrocyte Sedimentation Rate	7 (3, 12)	7 (3, 12)	0.689
FT3	2.85 ± 0.43	2.92 ± 0.42	0.019
FT4	1.15 ± 0.17	1.15 ± 0.17	0.648
Triiodothyronine (T3)	1.04 ± 0.19	1.07 ± 0.20	0.052
Thyroxin (T4)	7.80 ± 1.82	7.84 ± 1.64	0.437
TSH	1.7 (0.97, 2.69)	1.7 (1.1, 2.55)	0.594
White blood cell	6.74 ± 1.79	6.58 ± 1.63	0.300
Neutrophil	4.35 ± 1.47	4.20 ± 1.30	0.272
Percentage of neutrophils	63.92 ± 8.20	63.38 ± 8.04	0.535
haemoglobin	142.93 ± 17.83	145.46 ± 15.68	0.060
Platelet	224.08 ± 71.26	221.18 ± 58.82	0.591

CKD, Chronic Kidney Disease; MACEs, major adverse cardiovascular events; BMI, body mass index; ISR, in stent restenosis; reISR, recurrent ISR; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine; FT4, free thyroxin; TSH, thyroid stimulating hormone.

to investigate predictors of myocardial infarction, recurrent ISR and TVR in patients with ISR following revascularization intervention.

2. Subjects and Methods

2.1 Study Population

A retrospective analysis was conducted that included 1884 patients, 1494 males and 390 females, who were admitted to Fuwai Hospital for ISR and successfully received coronary intervention between January 2017 and December 2018. According to the presence or absence of myocardial infarction, recurrent ISR and target vessel revascularization during the follow-up, the patients were divided into a MACE group (n = 215) and a non-MACE group (n = 1669). The median follow-up duration was 35 months.

Each individual signed an informed consent form. The Fuwai Hospital's ethical committee approved this study.

The inclusion criteria were as follows: (1) individuals whose ISR was verified by coronary angiography (ISR was defined as the loss of $\geq$50% of the coronary lumen in the area of a previously stented lesion, and stenosis within 5 mm of the edge of the stent by coronary angiography was also defined as ISR); and (2) successful revascularization.

The exclusion criteria as follows: (1) patients who had bare metal stents implanted; (2) patients with stent implantation in bypass vessels; and (3) patients with severe heart, liver, renal insufficiency, abnormal thyroid function, anemia, infection or tumor.

2.2 Data Collection

(1) Age, sex, height, weight, previous medical history (hypertension, diabetes, hyperlipidemia, stroke history, chronic renal insufficiency history) and other data were collected. (2) Operation information, including ISR location, number and intervention treatment (stent reimplantation or drug-coated balloon use) were collected. (3) Fasting venous blood was collected from all patients in the morning before operation, and tests for routine blood, liver and kidney functions, electrolytes, fasting blood glucose, blood lipids and thyroid function (chemiluminescent immunoassay, reference range: thyroid stimulating hormone (TSH): 0.56–5.91 μIU/mL, free triiodothyronine (FT3): 3.53–7.37 pmol/L, free thyroxin (FT4): 7.98–16.02 pmol/L), N-terminal pro brain natriuretic peptide (NT-proBNP), and other related tests were performed. The ventricular ejection fraction was determined by echocardiography, and the estimated glomerularfiltrationrate (eGFR) values were calculated using the Cockcroft-Gault formula. (4) The patients were followed up for MACEs, including occurrence time, and outpatient drug use.

2.3 Statistical Analysis

SPSS 25.0 (IBM Corp., Armonk, IL, USA) and R version 4.4.0 (R Core Team, 2013, Vienna, Austria) were used for statistical analyses of the data. Continuous variables are expressed as the mean ± standard deviation (normal distribution) and median (nonnormal distribution). Two independent sample *t* tests (normal distribution) or nonpara-

Table 2. Spearmans correlation analysis.

Variable	Index of correlation	*p*
FT3	0.054	0.019
Direct bilirubin	0.037	0.109
Albumin protein	0.053	0.021

FT3, free triiodothyronine.

metric tests were used to compare the two groups (nonnormal distribution). For comparisons between the two groups, the chi-square test was employed to describe count data as a frequency (example) and rate (%). The correlation between other variables and MACEs was described using Spearman's correlation analysis. Univariate and multivariate logistic regression analyses (backward LR) were used to determine independent predictors of MACEs in ISR patients. Receiver operating characteristic (ROC) curve analysis was performed using R version 4.4.0 to determine the optimal threshold as well as the sensitivity and specificity of the threshold. Based on the ideal threshold, patients were separated into two groups, and survival differences between the two groups were examined using Kaplan–Meier survival analysis. $p < 0.05$ indicated a statistically significant difference.

3. Results

3.1 Study Participants and Baseline Characteristics

There were no differences in age, sex, body mass index (BMI), history of hypertension, hyperlipidemia, stroke, diabetes, history of chronic renal insufficiency, ISR reference vessel size, ISR events, or therapy between the two groups. The percentage of patients receiving ticagrelor as an outpatient treatment in the MACE group was considerably greater than that in the non-MACE group (78 (36.3%) vs. 451 (27%), $p = 0.006$). Albumin (43.42 $\pm$ 4.77 vs. 44.17 $\pm$ 4.46, $p = 0.021$), direct bilirubin (2.5 (2, 3.5) vs. 2.8 (2.07, 3.73), $p = 0.036$) and FT3 (2.85 $\pm$ 0.43 vs. 2.92 $\pm$ 0.42, $p = 0.019$) levels in the MACE group were significantly lower than those in the non-MACE group, and there was no significant difference in other indicators between the two groups (Table 1).

3.2 Analysis of Correlation

Albumin ($r = -0.053$, $p = 0.021$) and FT3 ($r = -0.054$, $p = 0.019$) were substantially adversely linked with MACEs, according to Spearman correlation analysis. There was no significant correlation between direct bilirubin and MACEs ($r = -0.037$, $p = 0.109$) (Table 2).

3.3 Univariate and Multivariate Logistic Regression Analysis

The correlation indicators described above were included in a univariate logistic regression analysis, which showed that both albumin and FT3 were predictors of MACEs. Multivariate logistic regression analysis showed that FT3 was an independent predictor of postoperative MACEs in ISR patients (Odds Ratio (OR) = 0.626, 95% CI [0.429–0.913], $p = 0.015$) (Table 3).

Table 3. Univariate and multivariate logistic regression analysis.

Variable	Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*
FT3	0.627 (0.43–0.915)	0.616	0.626 (0.429–0.913)	0.015
Albumin	0.964 (0.934–0.994)	0.021	0.972 (0.941–1.004)	0.085

FT3, free triiodothyronine; OR, odds ratio.

3.4 Analysis of Receiver Operating Characteristic (ROC) Curve and Kaplan–Meier Survival Analysis

The ROC curve of MACEs was analyzed for FT3, and the optimal threshold for FT3 was determined using the Youden index. When FT3 <2.785 pmol/L, the sensitivity was 52.6%, the specificity was 42.8%, and the area under the curve was 54.7% ($p = 0.025$).

Patients were divided into the FT3 $\geq$2.785 group and the FT3 <2.785 group according to the ROC-derived threshold. The findings of the Kaplan–Meier survival analysis revealed that the incidence of MACEs was considerably lower in the FT3 $\geq$2.785 group than in the FT3 <2.785 group (Hazard Ratio (HR) = 0.76, 95% CI [0.88–0.994], $p = 0.044$) (Fig. 1).

4. Discussion

The main findings of this study were as follows: (1) FT3 was an independent predictor of myocardial infarction, recurrent ISR and TVR in ISR patients after revascularization; and (2) when FT3 was <2.785 pmol/L, the risk ratio of patients with MACE increased significantly.

Angiographic ISR was defined as the loss of $\geq$50% of the coronary lumen in the area of a previously stented lesion, and stenosis within 5 mm of the edge of the stent as determined by coronary angiography was also defined as ISR [9]. The etiologies of ISR include mechanical and biological factors, where the biological factors include neoplasia, normal hyperplasia, plaque rupture and oxidative stress reactions, among others [10]. In addition, calcified nodules in stents and stent edge effects are also involved in the pathological progression of ISR [10]. It has been shown that drug-eluting stent ISR is primarily characterized by novel intimal atherosclerosis [11]. The results of this study also indicate that although there was no significant difference in low-density lipoprotein cholesterol (LDL-C) levels between the two groups, the average LDL-C level in both groups was higher than 1.8 mmol/L. These findings indicate that LDL-C is an essential factor in the occurrence of ISR after the first percutaneous coronary intervention (PCI).

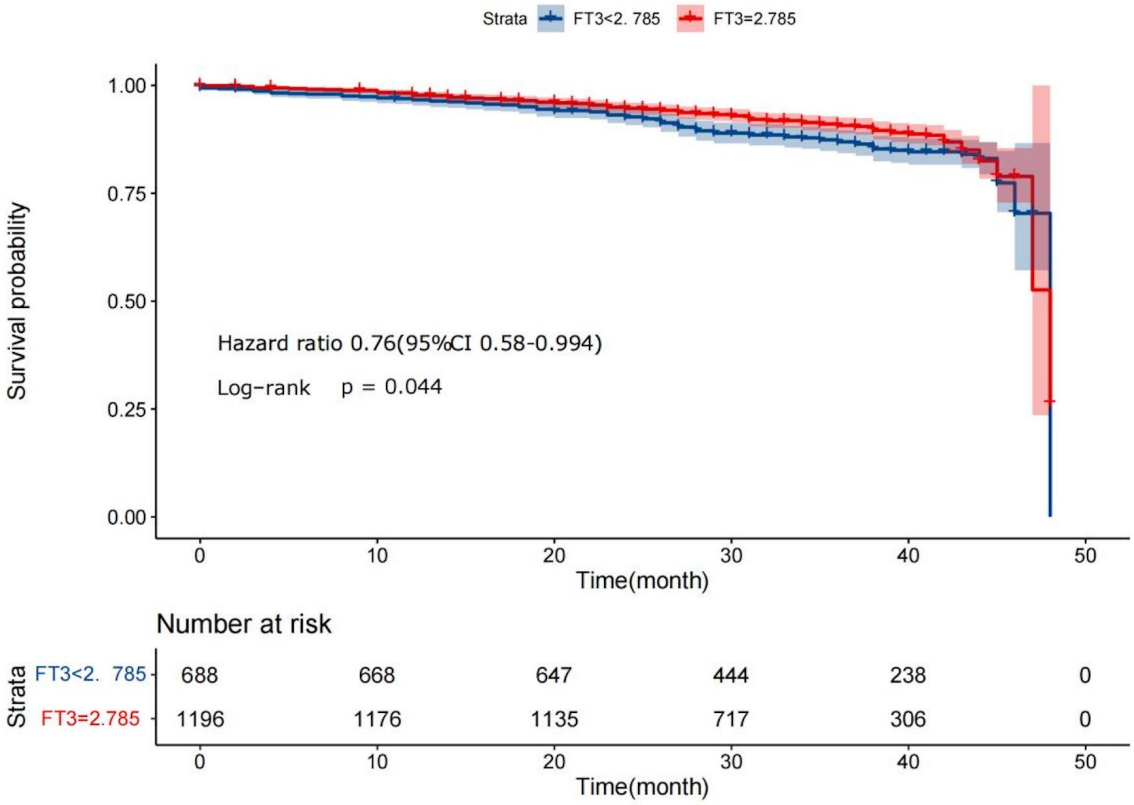

Fig. 1. Kaplan–Meier survival analysis on FT3 <2.785 group and ≥2.785 group. FT3, free triiodothyronine.

4.1 The Relationship between Thyroid Function and Coronary Atherosclerosis

Thyroxine, including tetraiodothyronine (T4) and triiodothyronine (T3), is an influential endocrine hormone that maintains the normal growth and development of the human body, the function of various organs, and the balance of calcium [12]. T4 is its main storage form and is transformed into biologically active T3 by type I and type II deiodinases [12]. In recent years, it has been shown that T3 not only functions as an endocrine hormone but is also widely involved in the regulation of lipid metabolism [13], endothelial function [14], angiogenesis [15,16], blood pressure, and myocardial contractility [12], all of which are closely linked to the formation and development of atherosclerosis. In recent years, a number of studies have found a correlation between thyroid hormone and acute coronary syndrome (ACS), and low FT3 is an independent risk factor for coronary artery severity and MACE after PCI [17–22]. Studies have also explored the relationship between thyroxine and ISR [23]. Canpolat *et al.* [23] reported that elevated plasma FT4 levels were an independent risk factor for ISR after BMS implantation, but few studies have investigated the relationship between FT3 and ISR. In this study, it was found that low FT3 was an independent risk factor for myocardial infarction, recurrent ISR, and TVR in patients with ISR after revascularization, and its mechanism may involve the following aspects.

4.2 Effect of Thyroxine on Lipid Metabolism

Patients with hypothyroidism often have abnormal lipid profiles. Tian *et al.* [24] found that TSH activated the cAMP/PKA/CREB signaling pathway by binding to TSH receptors on the surface of the rat liver cell membrane. This directly upregulates the expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) and promotes cholesterol synthesis. Bakker *et al.* [13] found that T3 can upregulate the expression of LDL-C receptor genes on the surface of the liver cell membrane, increasing the synthesis of LDL-C receptors and thus accelerating the clearance of LDL-C from the circulation. However, Bonde *et al.* [25] observed that proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in hyperthyroid patients were approximately 22% lower than those in the normal population and that FT3 levels were significantly negatively correlated with plasma total cholesterol, very low density lipoprotein cholesterol (VLDL-C), and LDL-C. It was hypothesized that FT3 can reduce plasma LDL-C levels by upregulating the expression of the LDL-C receptor gene and lowering the concentration of PCSK9 in hepatocytes. The event group had considerably lower FT3 levels than the non-MACE group in this study, but there was no significant difference in lipid profiles between the two groups. This result could be related to the diminished effect of FT3 on lipid levels in both groups due to statin use.

4.3 Effect of Thyroxine on Vascular Endothelial Cells and Smooth Muscle Function

T3 is also involved in the regulation of vascular endothelial cell function. When Carrillo-Sepúlveda *et al*. [14] studied the effect of thyroxine on the thoracic aorta of rats, it was found that T3 activated nitric oxide (NO) synthase in endothelial cells and smooth muscle cells via the phosphatidylinositol 3-kinase/protein (PI3K/Akt) signaling pathway, resulting in NO production that triggered a rapid diastolic response in the smooth muscle of the vessel. This regulatory function is weakened when T3 levels decrease.

T3 also inhibits vascular calcification. Sato *et al*. [26] reported that T3 affected the expression of genes associated with calcification in rat smooth muscle cells of the aorta. In *in vitro* studies using cultured human coronary smooth muscle cells, physiological concentrations of FT3 (15 pmol/L) increased the mRNA levels of matrix Gla protein (*MGP*), which is considered to be a potent inhibitor of vascular calcification *in vivo*. These results suggest that physiological concentrations of thyroid hormone can directly promote the expression of the *MGP* gene in smooth muscle cells via thyroid hormone nuclear receptors, thereby preventing vascular calcification *in vivo*. Ittermann *et al*. [27] noted that thyroid hormone reduction modifies the smooth muscle structure of the arteries and causes thickening of the vessel walls and decreased compliance, which further aggravates atherosclerosis.

Vascular endothelial cells are damaged by the implantation of coronary stents, and physiological contractions and diastolic function of the vessel walls are inhibited. When the plasma FT3 concentration is reduced, NO secretion by endothelial cells is further suppressed, and the inhibition of vascular calcification is weakened.

4.4 T3 is Involved in the Regulation of the Oxidative Stress Response

Oxidative stress plays a crucial role in myocardial ischemia–reperfusion (I/R) injury. Studies [28,29] have shown that T3 can increase the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-px) in myocardial cells, reduce the production of reactive oxygen species (ROS), and protect against myocardial I/R injury. In the ischemia–reperfusion injury model, T3 supplementation significantly reduces I/R-induced ROS production and mitochondrial superoxide concentrations, thus acting as a myocardial protective feature.

In addition, the proportion of patients treated with ticagrelor as outpatients was higher in the MACE group than in the non-MACE group in this study. This finding may be due to the fact that follow-up physicians switched to ticagrelor instead of clopidogrel because of MACE events occurs.

4.5 Other Factors that may Cause ISR after PCI

Although there was no significant difference in MACE incidence between diabetic and non-diabetic patients in this study, a number of previous studies have found a higher rate of ISR in diabetic patients after PCI [30–34]. Study [30] has shown that insulin resistance and elevated cytokine levels are associated with a higher incidence of ISR after PCI even in patients with normal glucose tolerance. Elevated inflammatory markers (interleukin 6; interleukin 1; tumor necrosis factor alpha; C-reactive protein, etc.) and impaired endothelial function can be detected in pre-diabetic patients with coronary heart disease, resulting in abnormally elevated levels of this cytokine after PCI [31]. Overactive inflammatory pathways that cause clotting can also cause restenosis in coronary stents and a poorer prognosis [32,33]. Currently, it is believed that sodium-glucose cotransporter 2 (SGLT2)-inhibitors can improve clinical outcomes in patients after PCI [34]. However, the relationship between SGLT2-inhibitors and cardiovascular outcomes in PCI patients was not widely recognized at the time this study was initiated 10 years ago and the proportion of diabetics using SGLT2-inhibitors in this study was extremely low. The effect of SGLT2-inhibitors on interventional therapy in ISR-CTO patients with diabetes mellitus was not analyzed.

5. Limitations

This study has certain limitations. First, the study was a single-center retrospective cohort study, and most of the patients included in the ISR study had their first interventions completed at different hospitals in China. Therefore, detailed stent information (diameter and length) could not be collected for the patients' first intervention, making it impossible to complete an effective comparison of relevant stent information. Second, due to the retrospective study design, some indicators related to ISR (such as the matrix metalloproteinase family and secretory frizzled-related proteins) were not included, and the study indicators were limited. Additional, intravascular imaging was also lacking in this study; therefore, some mechanic factors, such as stent underexpansion, could not be assessed. Finally, due to the design of the observational study, it was not possible to investigate whether treatment with thyroxine improved outcomes in ISR patients with reduced FT3 levels. This is expected to be addressed in future prospective clinical studies of such patients.

6. Conclusions

Low FT3 is a predictor of myocardial infarction, recurrent ISR and TVR in patients with ISR after revascularization. When the FT3 level is decreased (FT3 $<$2.785 pmol/L), the risk of postoperative MACE recurrence in ISR patients is significantly increased.

Availability of Data and Materials

Datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

WXY contributed to the study design and quality control. ZXY and TJW contributed to acquisition, analysis and interpretation of data, both of them contributated to drafting and revising the manuscript. YD contributed to the clinical collection and analysis of data, and follow up. LL, JSY, JGC, XX and LYH contributed to patients inclusion, operation and interpretation of data. JEW contributed to analysis and interpretation of data. SBQ has performed the analysis and explaination in discussion. All the authors critically revised the manuscript and gave final approval and agreed to be accountable for all aspects of the work, ensuring both its integrity and accuracy. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Yuncheng Central Hospital of Shanxi Province (NO. YXKT2022028). All subjects gave their written informed consent before they participated in the study.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Xi Y, Chen J, Bi Y, Xie S, Liao T, Zhang Y, *et al*. Long-term clinical safety and efficacy of drug-coated balloon in the treatment of in-stent restenosis: a meta-analysis and systematic review. Catheterization and Cardiovascular Interventions. 2020; 96: E129–E141.

[2] LittleAxe. Data on interventional treatment of coronary heart disease in mainland China in 2021 were released. 2022. Available at: https://www.cn-healthcare.com/articlewm/20220727/content-1407434.html (Accessed: 27 July 2022).

[3] Gori T. Restenosis after Coronary Stent Implantation: Cellular Mechanisms and Potential of Endothelial Progenitor Cells (A Short Guide for the Interventional Cardiologist). Cells. 2022; 11: 2094.

[4] Becker RC, Sexton T, Smyth SS. Translational Implications of Platelets as Vascular first Responders. Circulation Research. 2018; 122: 506–522.

[5] Hytönen J, Leppänen O, Braesen JH, Schunck WH, Mueller D, Jung F, *et al*. Activation of Peroxisome Proliferator-Activated Receptor-δ as Novel Therapeutic Strategy to Prevent In-Stent Restenosis and Stent Thrombosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016; 36: 1534–1548.

[6] Chambers SEJ, Pathak V, Pedrini E, Soret L, Gendron N, Guerin CL, *et al*. Current Concepts on Endothelial Stem Cells Definition, Location, and Markers. Stem Cells Translational Medicine. 2021; 10: S54–S61.

[7] Fadini GP, Mehta A, Dhindsa DS, Bonora BM, Sreejit G, Nagareddy P, *et al*. Circulating stem cells and cardiovascular outcomes: from basic science to the clinic. European Heart Journal. 2020; 41: 4271–4282.

[8] Braune S, Latour RA, Reinthaler M, Landmesser U, Lendlein A, Jung F. In Vitro Thrombogenicity Testing of Biomaterials. Advanced Healthcare Materials. 2019; 8: e1900527.

[9] Murat SN, Yarlioglues M, Celik IE, Kurtul A, Duran M, Kilic A, *et al*. The Relationship between Lymphocyte-to-Monocyte Ratio and Bare-Metal Stent in-Stent Restenosis in Patients with Stable Coronary Artery Disease. Clinical and Applied Thrombosis/Hemostasis. 2017; 23: 235–240.

[10] Shlofmitz E, Iantorno M, Waksman R. Restenosis of Drug-Eluting Stents: A New Classification System Based on Disease Mechanism to Guide Treatment and State-of-the-Art Review. Circulation: Cardiovascular Interventions. 2019;12: e007023.

[11] Hong SJ, Lee SY, Hong MK. Clinical Implication of Optical Coherence Tomography-Based Neoatherosclerosis. Journal of Korean Medical Science. 2017; 32: 1056–1061.

[12] Ahmadi N, Ahmadi F, Sadiqi M, Ziemnicka K, Minczykowski A. Thyroid gland dysfunction and its effect on the cardiovascular system: a comprehensive review of the literature. Endokrynologia Polska. 2020; 71: 466–478.

[13] Bakker O, Hudig F, Meijssen S, Wiersinga WM. Effects of Triiodothyronine and Amiodarone on the Promoter of the Human LDL Receptor Gene. Biochemical and Biophysical Research Communications. 1998; 249: 517–521.

[14] Carrillo-Sepúlveda MA, Ceravolo GS, Fortes ZB, Carvalho MH, Tostes RC, Laurindo FR, *et al*. Thyroid hormone stimulates no production via activation of the PI3K/Akt pathway in vascular myocytes. Cardiovascular Research. 2010; 85: 560–570.

[15] Bhargava M, Lei J, Ingbar DH. Nongenomic actions of L-thyroxine and 3,5,3'-triiodo-L-thyronine. Focus on "L-Thyroxine vs. 3,5,3'-triiodo-L-thyronine and cell proliferation: activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase". American Journal of Physiology-Cell Physiology. 2009; 296: C977–C979.

[16] Lourbopoulos AI, Mourouzis IS, Trikas AG, Tseti IK, Pantos CI. Effects of Thyroid Hormone on Tissue Hypoxia: Relevance to Sepsis Therapy. Journal of Clinical Medicine. 2021; 10: 5855.

[17] Cao Q, Jiao Y, Yu T, Sun Z. Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention. Cardiology Journal. 2020; 27: 262–271.

[18] Seo SM, Koh YS, Park HJ, Kim DB, Her SH, Lee JM, *et al*. Thyroid stimulating hormone elevation as a predictor of long-term mortality in patients with acute myocardial infarction. Clinical Cardiology. 2018; 41: 1367–1373.

[19] Su W, Zhao XQ, Wang M, Chen H, Li HW. Low T3 syndrome improves risk prediction of in-hospital cardiovascular death in patients with acute myocardial infarction. Journal of Cardiology. 2018; 72: 215–219.

[20] Viswanathan G, Balasubramaniam K, Hardy R, Marshall S, Zaman A, Razvi S. Blood Thrombogenicity is Independently Associated with Serum TSH Levels in Post–Non-ST Elevation Acute Coronary Syndrome. The Journal of Clinical Endocrinology and Metabolism. 2014; 99: E1050–E1054.

[21] Yu N, Wang L, Zeng Y, Zhao Y, Chen S, Pan H, *et al*. The Association of Thyroid Hormones with Coronary Atherosclerotic Severity in Euthyroid Patients. Hormone and Metabolic Research. 2022; 54: 12–19.

[22] Zhang M, Sara JDS, Matsuzawa Y, Gharib H, Bell MR, Gulati R, *et al*. Clinical outcomes of patients with hypothyroidism undergoing percutaneous coronary intervention. European Heart Journal. 2016; 37: 2055–2065.

[23] Canpolat U, Turak O, Özcan F, Öksüz F, Mendi MA, Yayla Ç,

et al. Impact of free thyroxine levels and other clinical factors on bare metal stent restenosis. Archives of Endocrinology and Metabolism. 2017; 61: 130–136.

[24] Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, *et al*. A novel role for thyroid-stimulating hormone: up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. Hepatology. 2010; 52: 1401–1409.

[25] Bonde Y, Breuer O, Lütjohann D, Sjöberg S, Angelin B, Rudling M. Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in humans. Journal of Lipid Research. 2014; 55: 2408–2415.

[26] Sato Y, Nakamura R, Satoh M, Fujishita K, Mori S, Ishida S, *et al*. Thyroid Hormone Targets Matrix Gla Protein Gene Associated with Vascular Smooth Muscle Calcification. Circulation Research. 2005; 97: 550–557.

[27] Ittermann T, Lorbeer R, Dörr M, Schneider T, Quadrat A, Heßelbarth L, *et al*. High levels of thyroid-stimulating hormone are associated with aortic wall thickness in the general population. European Radiology. 2016; 26: 4490–4496.

[28] Forini F, Ucciferri N, Kusmic C, Nicolini G, Cecchettini A, Rocchiccioli S, *et al*. Low T3 State Is Correlated with Cardiac Mitochondrial Impairments after Ischemia Reperfusion Injury: Evidence from a Proteomic Approach. International Journal of Molecular Sciences. 2015; 16: 26687–26705.

[29] Barreiro Arcos ML. Role of thyroid hormones-induced oxidative stress on cardiovascular physiology. Biochimica et Biophysica Acta: General Subjects. 2022; 1866: 130239.

[30] Sasso FC, Pafundi PC, Marfella R, Calabrò P, Piscione F, Furbatto F, *et al*. Adiponectin and insulin resistance are related to restenosis and overall new PCI in subjects with normal glucose tolerance: the prospective AIRE Study. Cardiovascular Diabetology. 2019; 18: 24.

[31] Sardu C, Paolisso P, Sacra C, Mauro C, Minicucci F, Portoghese M, *et al*. Effects of Metformin Therapy on Coronary Endothelial Dysfunction in Patients with Prediabetes with Stable Angina and Nonobstructive Coronary Artery Stenosis: the CODYCE Multicenter Prospective Study. Diabetes Care. 2019; 42: 1946–1955.

[32] Sardu C, D'Onofrio N, Torella M, Portoghese M, Loreni F, Mureddu S, *et al*. Pericoronary fat inflammation and Major Adverse Cardiac Events (MACE) in prediabetic patients with acute myocardial infarction: effects of metformin. Cardiovascular Diabetology. 2019; 18: 126.

[33] Sardu C, D'Onofrio N, Mauro C, Balestrieri ML, Marfella R. Thrombus Aspiration in Hyperglycemic Patients with High Inflammation Levels in Coronary Thrombus. Journal of the American College of Cardiology. 2019; 73: 530–531.

[34] Paolisso P, Bergamaschi L, Santulli G, Gallinoro E, Cesaro A, Gragnano F, *et al*. Infarct size, inflammatory burden, and admission hyperglycemia in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: a multicenter international registry. Cardiovascular Diabetology. 2022; 21: 77.