

The Prognostic Value of Thyroid-Stimulating Hormone in Patients with Coronary Artery Disease and Depression

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Purpose: Patients with the comorbidity of coronary artery disease (CAD) and depression are very common and always have poor prognosis. The relationship between thyroid-stimulating hormone (TSH) levels and major cardiovascular event (MACE) in these patients is still unknown. We aimed to explore this association.

Patients and Methods: We enrolled 203 CAD patients proven by coronary angiography (CAG). In the meanwhile, they were all assessed to have depression symptom by professional psycho-cardiologists. After an average follow-up of 23.7 months, patients were divided into two groups (high TSH group with TSH $\geq 1.395\mu\text{IU/mL}$ and low TSH group with TSH $< 1.395\mu\text{IU/mL}$) according to the cut-off value of baseline TSH. The impact of two different TSH groups for adverse events in CAD patients with depression was evaluated.

Results: The average age of these patients was 64.9 years old. The two TSH groups had no significant difference in the comparison of other baseline data. Area under the receiver operating characteristic (ROC) curves (AUC) analysis indicated the well-discriminatory power of TSH levels for the occurrence of MACE (AUC = 0.61, 95% CI: 0.52–0.70, $P = 0.03$). In the KM survival analysis, high TSH group had a higher risk of MACE ($P = 0.029$). After multi-factor adjustment, there still existed a higher risk of MACE in high TSH group (HR = 2.05, 95% CI: 1.08–3.88, $P = 0.028$).

Conclusion: In patients with the comorbidity of CAD and depression, higher TSH levels are associated with the occurrence of MACE. More researches need to be conducted to prove this association and explore whether the drug-related TSH reduction can decrease the occurrence of adverse events in the future.

Keywords: thyroid-stimulating hormone, TSH, coronary artery disease, CAD, depression, MACE

Introduction

Coronary artery disease (CAD), one of the major forms of cardiovascular diseases (CVDs), is usually defined as ischemic symptoms associated with the evidence of 50% or more blockage in at least one major coronary artery by coronary angiographic (CAG), previous hospitalization for a myocardial infarction (MI), or angina.¹ CVDs were the primary cause of mortality in non-communicable diseases and accounted for about one-third of all deaths worldwide (17.5 million deaths) in 2012 according to the World Health Organization Reports.² CAD and depression are two huge challenges that global public health needs to face, especially in the developed and developing countries.^{1,3} In China, the prevalence of depression in CAD patients from the community ranged from 34.6% to 45.8% and hospitalized patients with the comorbidity of depression and CAD even reached 51%.⁴

Previous studies have proved the upper part of the reference range of thyroid-stimulating hormone (TSH) levels was associated with endothelial dysfunction,⁵ systolic and diastolic blood pressure,⁶ arterial stiffness⁷ and coronary

atherosclerosis,⁸ less favourable lipid levels⁹ and myocardial infarction.¹⁰ Other evidence also showed that a higher level of TSH was closely related to the occurrence, severity of CAD and poor prognosis in CAD patients.^{8,11–14} TSH is also believed to have associations with depression, but some debates exist. In some studies, the conclusion is that TSH has a negative correlation with depression.^{15–19} Some researches support the view that they are positively related.^{17,20}

CAD patients with the comorbidity of depression always have a poor prognosis.²¹ Hypothalamic-pituitary-thyroid axis, as an important part of neuroendocrine system, is a vital mechanism of the comorbidity of CAD and depression.²² TSH is the most sensitive marker of thyroid function²³ and is associated with both CAD and depression. The association between TSH and prognostic value in CAD patients with depression is unknown. Our study aimed to explore the predictive power of TSH levels for the major cardiovascular event (MACE) in these patients.

Patients and Methods

Study Population

Our study enrolled 705 patients who have undergone CAG surgery in the Cardiology Department of Guangdong Provincial People's Hospital from October 2017 to January 2018. Patients with the missing TSH and follow-up data, thyroid disease, usage of drugs affecting TSH recently or other cardiac severe comorbidities were excluded. And we also excluded those who were assessed without depression or did not complete the Patient Health Questionnaire-9 (PHQ-9). A total of 203 patients who were proved at least one epicardial coronary artery stenosis $\geq 50\%$ through CAG and with mild depression or above were included in our final analysis.

Our study is a prospective observational study aimed to investigate the predicting effect of patients' baseline TSH to poor prognosis. The Medical Ethics Committee of Guangdong Provincial People's Hospital had reviewed and approved our proposal (No. GDREC2017203H). This study was conducted in accordance with the Declaration of Helsinki. We have obtained written informed consents from every participant.

Depression Assessment

PHQ-9²⁴ is a widely used instrument to screen depression, and its validity in Chinese CAD patients has been verified.²⁵ Patients with a PHQ-9 score ≥ 5 were defined as having depression symptoms. A higher score means more severe depression. Our professional psycho-cardiologists assessed the depression status for all patients one day before the CAG through the PHQ-9 scale.

Diagnostic Criteria of Other Variables

Body mass index (BMI) was calculated via weight divided by height. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg for twice at different times, or currently receiving antihypertensive therapy. Diabetes specifically refers to type 2 diabetes and was diagnosed with blood glucose ≥ 7.0 mmol/L, random blood glucose ≥ 11.1 mmol/L, 2h blood glucose ≥ 11.1 mmol/L after glucose load or under the hypoglycemic treatment.

The severity of coronary artery stenosis was dependent on the number of three main vessels with stenosis $\geq 50\%$ as shown by CAG, while patients with a stenosis of left main coronary artery $\geq 30\%$ would be defined as the highest severity level. Education background was divided into four levels according to the years of receiving education. There were four levels including less than 6 years, 7–9 years, 10–12 years and more than 12 years, respectively. We used the Cockcroft-Gault formula to calculate the creatinine clearance (CCR) through the serum creatinine tested at admission.²⁶

Biochemical Examination

The nurses extracted patients' venous blood samples in the early morning, thyroid function including TSH, Free Triiodothyronine (FT3), Free Tetraiodothyronine (FT4) were measured through direct chemical lighting method (US Siemens company). The reference range of TSH is 0.56–5.91 μ U/mL. Other indicators include blood lipids, Hs-CRP, which were measured by a fully automated luminescent immunoassay.

Follow-Up and Endpoint Events

All patients were followed up by trained cardiovascular physicians by telephone or in-person at 1 year, and 2 years after discharges. The average follow-up time was 23.7 ± 6.3 months. MACE was considered as the endpoint of our follow-up. MACE included death due to cardiovascular events, non-fatal stroke, non-fatal myocardial infarction, non-fatal heart failure, and revascularization. Patients for whom we could not obtain accurate terminal events through follow-up were excluded.

TSH Groups and Statistical Analysis

At the data analysis stage, all 203 CAD patients with depression were separated into two groups according to the condition of baseline TSH and MACEs. Receiver operating characteristic (ROC) curves showed the most discriminating cutoff point values of TSH to predict the occurrences of MACE. Then, we got the cutoff point value of TSH was 1.395 $\mu\text{IU/mL}$, and patients were divided into two groups according to this threshold value (high TSH group with $\text{TSH} \geq 1.395$ and low TSH group with $\text{TSH} < 1.395$).

Measurement data in accordance with normal distribution was described as mean $\pm$ SD, the non-normal distribution of metrology was expressed in the form of median (interquartile range), and counting data was represented as number and percentage. The data were analyzed by the chi-squared statistic tests, Fisher's exact tests, independent sample *t*-tests, the one-way analysis of variance test, or the Kruskal–Wallis test when appropriate. Cox proportional hazards regression models and Kaplan–Meier (KM) survival analysis were used to evaluate the differences of MACE between the two TSH groups.

The baseline data were first compared. Due to the limitation of small sample size and in order not to omit variables that might affect the outcome, the criteria of being included in the univariate Cox regression analysis was relaxed to with a baseline difference level of less than 0.25 (gender, blood glucose, HDLC, CCR, BUN, FT4, Hs-CRP, LVEF, type of CAD were included). In univariate Cox regression analysis, variables with a significance level of 0.05 (only gender with a *p*-value = 0.029) were regarded as correction variables for multivariate Cox regression. Other variables considered to be most closely related to MACE, such as age and severity of coronary artery stenosis, were also included in the multivariate Cox regression. Data were analyzed using SPSS version 25.

Results

Baseline Characteristics

A total of 203 patients who were proved at least one epicardial coronary artery stenosis $\geq 50\%$ through CAG and with mild depression or above were included in our final analysis. There are 72 stable angina pectoris, 92 patients with unstable angina, and 39 acute MI patients in our population. Of all 203 CAD patients with depression, 138 (68%) were male, 65 (32%) were female. The average age of the patients was 64.9 y. 126 (62.1%) and 83 (40.9%) were diagnosed with hypertension and diabetes, respectively. Table 1 shows the baseline demographic laboratory tests as well as social and medical history in two TSH groups. The two groups had no significant difference in the comparison of the baseline.

TSH for Predicting the Outcomes

All the patients were followed up for an average of about 24 months (ranged from several days to 29 months). There were 42 MACEs happened in our study. Area under the ROC curves (AUC) analysis indicated the well-discriminatory power of TSH levels for the presence of MACE (AUC = 0.61, 95% CI: 0.52–0.70, *P* = 0.03, Figure 1). In the KM survival analysis, high TSH group had a higher risk of MACE (*P* = 0.029, Figure 2). After adjusting for all potential confounders including age, gender, and severity of coronary artery stenosis, there still existed a higher risk of MACE in high TSH group (HR = 2.05, 95% CI: 1.08–3.88, *P* = 0.028, Figure 3, Table 2).

Discussion

The prevalence of depression is high in patients with CAD.²² These patients with the comorbidity of depression and CAD still easily experienced MACE even after percutaneous coronary intervention (PCI) treatment. To our knowledge, this is the first study to explore the predictive value of TSH in patients with the comorbidity of depression and CAD. We

Table 1 Baseline Characteristics Among Participants Grouped by TSH

Characteristics	Overall	Low TSH Group (n = 104)	High TSH Group (n = 99)	P-value
Demographic				
Age, year	64.9±10.5	64.7±10.9	65.1±10.1	0.79
BMI, kg/m ²	24.2±3.6	24.1±3.6	24.4±3.6	0.51
Male, n(%)	138(68)	74(71.2)	64(64.6)	0.32
Laboratory test				
Blood glucose, mg/dL	5.7(4.7, 7.6)	6(4.9, 8.1)	5.5(4.6, 7.4)	0.17
TC, mg/dl	4.3(3.6, 5)	4.3(3.6, 4.8)	4.2(3.5, 5.1)	0.86
HDLc, mg/dl	0.9(0.8, 1.1)	1(0.8, 1.2)	0.9(0.8, 1.1)	0.13
LDLC, mg/dl	2.8(2.3, 3.3)	2.8(2.3, 3.2)	2.8(2.2, 3.4)	0.55
TG, mg/dl	1.4(1, 2)	1.4(1, 2)	1.3(1, 2)	0.6
CK, U/L	81(61, 123.5)	79(60, 120)	82(62, 130)	0.57
CKMB, U/L	10.7(8.3, 13)	10.9(8.3, 13.1)	10.4(8.2, 13)	0.61
CCR, mL/min/1.73 m ²	56.8(44.2, 74.7)	57.7(45.9, 75.8)	52.6(42.9, 73.3)	0.22
BUN, mmol/L	6.3(5.1, 7.6)	6.1(5.2, 7.7)	6.3(5.1, 7.6)	0.46
HbA1c, %	6.3(5.8, 7.4)	6.3(5.8, 7.4)	6.4(5.8, 7.4)	0.96
FT3, pmol/L	4.7(4.2, 5.2)	4.7(4.2, 5.2)	4.7(4.2, 5.2)	0.75
FT4, pmol/L	11.6(10.1, 13.3)	11.8(10.4, 13.6)	11.4(10, 13)	0.067
Hs-CRP, mg/L	3.2(0.94, 9.5)	2.6(0.8, 8.5)	4.1(1, 11)	0.2
LVEF, %	61(49.5, 64.5)	62(50.8, 65)	60(46, 64)	0.23
Social and medical history				
Marriage, n(%)	184(90.6)	93(89.4)	91(91.9)	0.54
Education, n(%)				0.88
Less than 6 years	75(36.9)	41(39.4)	34(34.3)	
7–9 years	50(24.6)	25(24)	25(25.3)	
10–12 years	39(19.2)	21(20.2)	18(18.2)	
More than 12 years	36(17.7)	17(16.3)	19(19.2)	
PHQ-9	7(5, 10)	7(5, 10)	7(6, 11)	0.77
Severity of coronary artery stenosis, n(%)				0.46
1	45(22.2)	24(23.1)	21(21.2)	
2	39(19.2)	23(22.1)	16(16.2)	
3	119(58.6)	57(54.8)	62(62.6)	
Hypertension, n(%)	126(62.1)	66(63.5)	60(60.6)	0.68
Myocardial infarction, n(%)	39(19.3)	15(14.4)	24(24.2)	0.076
Diabetes, n(%)	83(40.9)	42(40.4)	41(41.4)	0.88

found that MACE was more likely to occur in patients with higher TSH (TSH ≥ 1.395) with or without adjustment for multifactorial variables.

Association Among TSH, CAD and Depression

Several studies have explored the effect of TSH to CAD patients, they found higher TSH had diagnostic and prognostic significance of CAD and was associated with the severity of CAD.^{11–13} Previous studies have shown that TSH will calcify coronary artery by combining TSH receptor on vascular smooth muscle cells.^{27,28} Yoneda et al found the injection of TSH in conduit arteries could significantly impair endothelial vasodilation,²⁹ which might aggravate the symptoms of CAD patients and affect their prognosis.

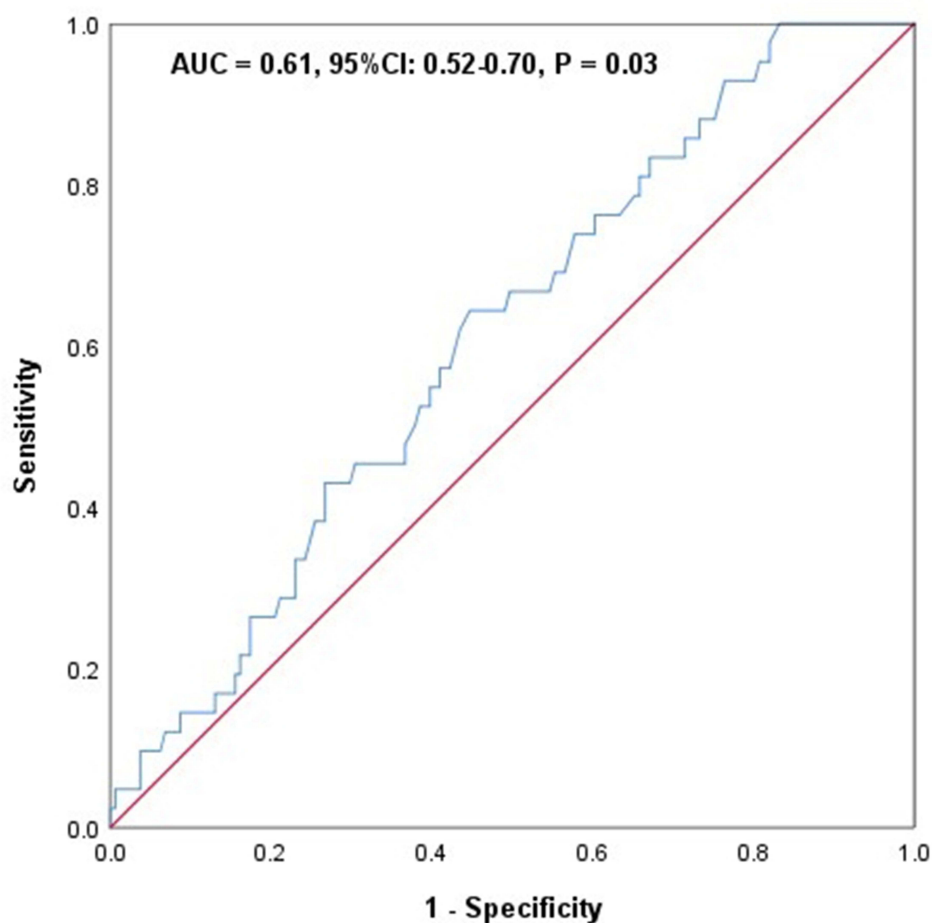


Figure 1 ROC curves showed discriminatory power of TSH levels on MACE.

Serum TSH was also proved to increase inflammatory molecules and inhibit nitric oxide production.^{12,30} The increased inflammatory reaction will accelerate the atherosclerosis process and inhibit endothelial cell functions, such as migration and angiogenesis.^{29,31} What is more, chronic low-grade inflammation was believed to be one important pathogenesis of depression.³² In our study, patients with high TSH levels had a higher hypersensitive-c-reactive-protein (Hs-CRP) but did not reach a statistical significance (Median value 4.1 vs 2.6 mg/L).

As we all know, serum lipid is one of the recognized risk factors of CAD, TSH levels were found positively associated with serum lipid concentrations.⁹ What is more, in a national study with a large sample in Korean, a significant association was observed between the high level of HDL-C, triglyceride and depression.³³ TSH was also proved positively related to HDLC in depression patients.³⁴ TSH may cause poor prognosis by indirectly affecting the blood lipids in patients with coronary heart disease and depression.

TSH can also stimulate the production of cytokines interleukin 6 (IL-6) secretion by adipocytes and tumour necrosis factor- α (TNF- α) secretion by bone marrow cells, these cytokines were associated with the damage of endothelium-dependent vasodilation and oxidative stress.³⁵ Cytokines are strongly associated with depression. He et al found the concentration of cytokines such as IL-6 and vascular endothelial growth factor (VEGF) increased in mice with depression and these cytokines may become predictive biomarkers for novel diagnostic as well as therapeutic of depression.³⁶

In the study of Yang et al, higher levels of TSH were independently related to the presence of CAD only among participants ≤ 65 years old.¹⁴ There is still no suitable explanation to age-related differences on CAD, while the age of TSH groups in our study has no statistical difference. FT4 is a prohormone that cannot be transported by myocytes and

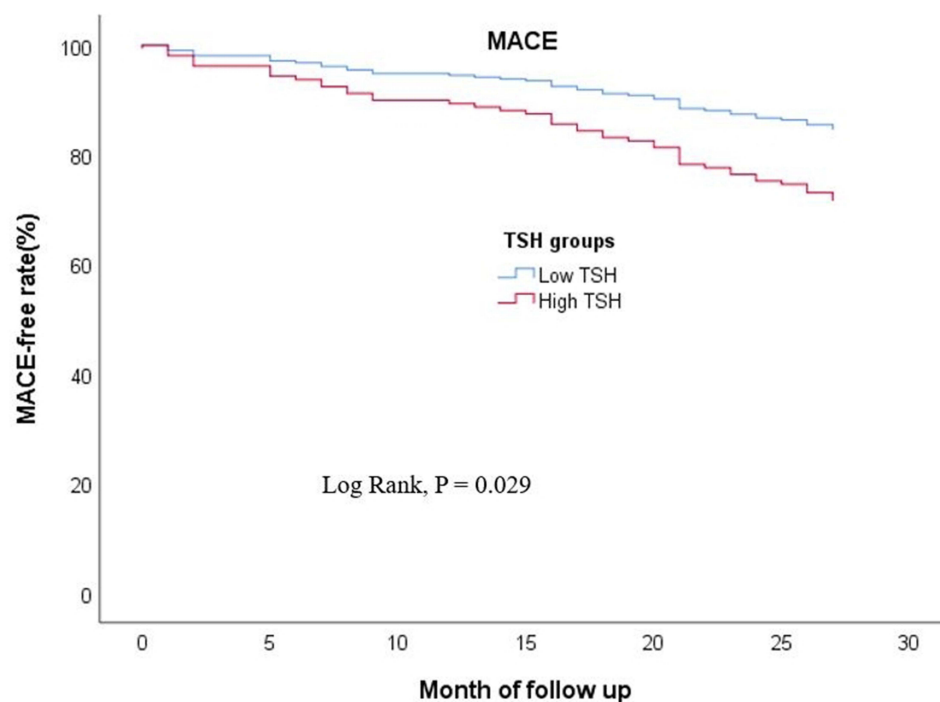


Figure 2 Kaplan–Meier curve for MACE events grouped by TSH level in CAD patients with depression.

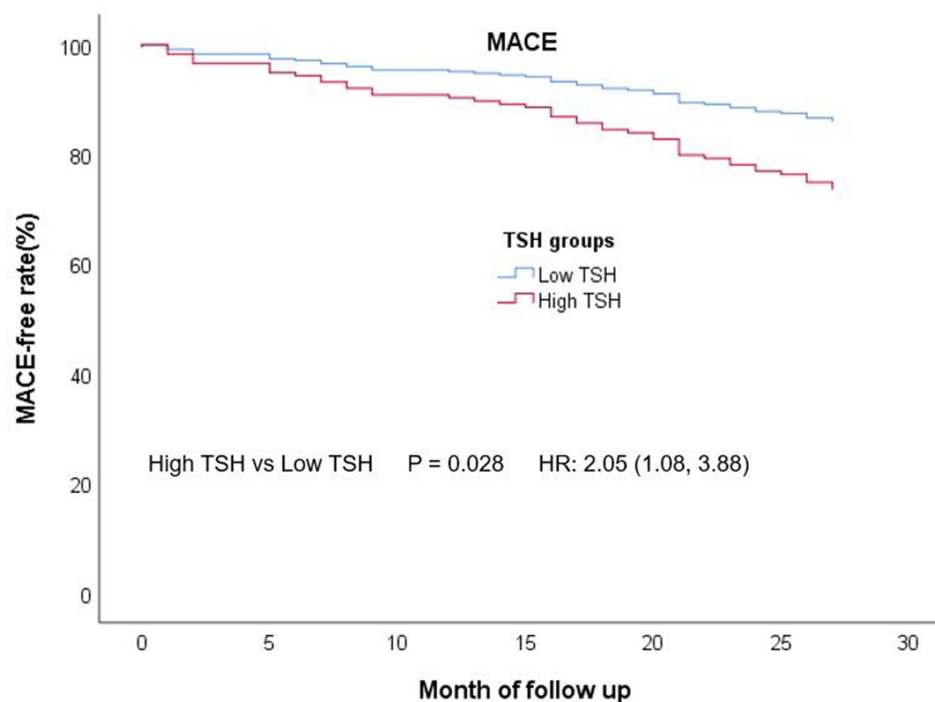


Figure 3 Cox regression curve for MACE events grouped by TSH level in CAD patients with depression after adjusting for age, sex, and the severity of coronary artery stenosis.

Table 2 Unadjusted and Adjusted Predictive Value of TSH Levels for MACE Events in CAD Patients with Depression

Variables	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
TSH level	1.99(1.06, 3.73)	0.033	2.05(1.08, 3.88)	0.028
Age	1.01(0.98, 1.04)	0.65	0.99(0.96, 1.02)	0.62
Gender	0.51(0.28, 0.93)	0.029	0.47(0.25, 0.89)	0.02
Severity of coronary artery stenosis		0.14		0.088
1	Reference		Reference	
2	3.11(0.99, 9.78)	0.052	3.61(1.12, 11.59)	0.031
3	2.68(0.94, 7.67)	0.066	2.98(1.03, 8.63)	0.045

Notes: The severity of coronary artery stenosis was depended on the number of three main vessels with stenosis $\geq 50\%$ as shown by CAG, while patients with a stenosis of left main coronary artery $\geq 30\%$ would be defined as the highest severity level.

Abbreviations: CAD, coronary artery disease; TSH, thyroid-stimulating hormone; MACE, major cardiovascular event; CAG, coronary angiography; ROC, receivers operating characteristic; AUC, area under the curve; MI, myocardial infarction; CVD, cardiovascular diseases; PHQ-9, Patient Health Questionnaire-9; BMI, body mass index; CCR, creatinine clearance; FT3, free triiodothyronine; FT4, free tetraiodothyronine; LDLC, low density lipoprotein cholesterol; HDLC, high density lipoprotein cholesterol; PCI, percutaneous coronary intervention; Hs-CRP, hypersensitive-c-reactive-protein; IL-6, interleukin 6; TNF- α , tumor necrosis factor- α ; VEGF, vascular endothelial growth factor.

has no relationship to adaptive response to myocardial ischemia in CAD patients.^{29,37} In our study, it may be limited by the small sample size that the level of FT4 has a significant difference at baseline. In statistical analysis, FT4 did not contribute to MACE in univariate Cox regression, which might also indicate that the difference in FT4 was accidental.

The association between thyroid function and psychiatric disorders, particularly mood disorders, has long been recognized and described more than 200 years ago.³⁸ Lee et al found the highest TSH tertile group was 1.92 times more likely to have depressive symptoms in Korea.¹⁷ A retrospective cohort study that included 13,017 subjects described the same conclusion that the highest tertile TSH level owed higher risk of depressive symptom.²⁰ Higher TSH reduces the efficacy of antidepressant therapy by affecting brain-derived neurotrophic factor levels in depressed patients.²³ Some studies indicated that TSH was negatively correlated with depression, and low TSH values might be considered either a compensating physiological response to stress or a pathological element in a co-existing depression.^{15,39} Joffe and Levitt's study showed the low-normal TSH group was significantly more depressed and had higher suicidal tendencies than the high-normal group.⁴⁰ The real effect of TSH in depression is not very sure and needs larger as well as higher quality research to prove in different sex, age, races and regions.

Strengths and Limitations

The strength of our study is that we continuously enroll patients with angiography-proven CAD in three months. This approach significantly decreases the potential errors in the diagnosis of the disease. All included patients have finished the depression scales under the guidance of professional doctors. This is the first study to explore the relationship of TSH in CAD patients with depression. It has important implications for improving the prognosis of part of the special patients with CAD. Due to the sample quantity and the limit of the endpoint events, we did not analyze the patients with MI or angina pectoris individually. There are still some limitations in our study. At first, our research was conducted in a single center from a southern central hospital, which cannot represent patients in the entire China or other regions. Secondly, the small sample size might lead to inaccurate conclusions. Thirdly, since the subsequent TSH data is not obtained, the impact of TSH changes on poor prognosis cannot be evaluated. Finally, the influence of high TSH to MACE might be underestimated because patients who experienced emergency PCI surgery and always had a bad prognosis were not included.

Conclusion

In patients with the comorbidity of CAD and depression, higher TSH levels are associated with the occurrence of MACE. More researches need to be conducted to prove this association and explore whether the drug-related TSH reduction can decrease the occurrence of adverse events in the future.

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Disclosure

All the authors declare that they don't have any conflict of interest in the study.

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