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Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention

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Abstract

Background: *Thyroid hormones profoundly influence the cardiovascular system, but the effects of mild thyroid dysfunction on the clinical outcome of acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) are not well defined. This study aimed to determine the effect of mild thyroid dysfunction on 12-month prognosis in ACS patients undergoing PCI.*

Methods: *In this prospective cohort study with a 12-month follow-up, 1560 individuals were divided into four groups based on thyroid hormone levels upon admission: euthyroidism (used as a reference group), subclinical hypothyroidism, subclinical hyperthyroidism, and low triiodothyronine syndrome (low T3 syndrome). The outcomes measured were all-cause mortality, cardiac mortality, nonfatal reinfarction, and unplanned repeat revascularization.*

Results: *In this study, the prevalence of mild thyroid dysfunction was 10.8%. Multivariate analysis showed that low T3 syndrome, but not subclinical hypothyroidism or subclinical hyperthyroidism, was associated with a higher rate of all-cause (HR 2.553, 95% CI 1.093–5.964, p = 0.030) and cardiac mortality (HR 2.594, 95% CI 1.026–6.559, p = 0.034), compared with the euthyroidism group.*

Conclusions: *Mild thyroid dysfunction was frequent in patients with ACS undergoing PCI. Low T3 syndrome was the predominant feature and was associated with 12-month adverse outcomes in these patients.* (Cardiol J 2020; 27, 3: 262–271)

Key words: mild thyroid dysfunction, clinical outcome, acute coronary syndrome, percutaneous coronary intervention

Introduction

Patients with acute coronary syndrome (ACS) frequently have a poor prognosis, and ACS is a major health and economic burden [1–4]. Although the use of percutaneous coronary intervention (PCI) and new antiplatelet drugs have greatly improved the prognosis [5], patients with ACS still suffer high rates of mortality (up to 5%) and heart failure (up to 20%) [6]. Thyroid hormones act on multiple systems within the body, and the cardiovascular system is the foremost target [7]. The cardiovascular system may be adversely affected even if thyroid hormone levels only change slightly [7]. In patients with ACS, a decrease in serum triiodothyronine (T3), as well as the impaired conversion of thyroxine (T4) into T3, have been reported [8, 9]. Thyroid hormone related indicators are also predictors for thrombus burden [10], severity of coronary artery lesions [11, 12], cardiac function [13, 14] and myocardial injury size [8, 9, 15] in ACS patients. However, the screening and treatment of mild thyroid dysfunction is still controversial [16–20] and not recommended for ACS patients [1–4]. However, mild thyroid dysfunction, including subclinical hypothyroidism, subclinical hyperthyroidism, and euthyroid sick syndrome, is frequently present in patients with ACS [21–23]. Additionally, mild thyroid dysfunction can also be

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predicative of an increased risk of mortality in heterogeneous patients with various cardiac diseases [21]. However, few studies have focused on the association between mild thyroid dysfunction and adverse prognoses in patients with coronary heart disease [22, 23]. In this study, the aim was to assess the prevalence of mild thyroid dysfunction and the association of mild thyroid dysfunction with 12-month prognosis in ACS patients undergoing PCI.

Methods

Study design and setting

This study was based on a prospective cohort, the P-PUSH study, which has been previously described [24]. In brief, from January 1, 2015 to July 31, 2016, 1768 patients with ACS were hospitalized and underwent PCI at a large hospital in Northeast China (Shengjing Hospital of China Medical University, Shenyang, China). Clinical and procedural data were obtained by the investigators using electronic medical records, interventional imaging data (Picture Archiving and Communications Systems [PACS] technology), and operation records. GRACE scores were determined as defined previously [1–4]. Prospective clinical follow-up after discharge was performed regularly in all cases by direct hospital visits and telephone interviews with the patient's general practitioner/cardiologist, the patient, or the patient's family. All events were adjudicated and classified by two cardiologists. The exclusion criteria of this study were as follows: 1) primary hypothyroidism or hyperthyroidism (36 cases); 2) concomitant treatment with synthetic thyroid hormones, antithyroid drugs, corticosteroids, dopamine, dobutamine, or amiodarone (19 cases); 3) loss of follow-up (68 cases); 4) no thyroid data (20 cases); and 5) atypical thyroid status (65 cases), including high T4 syndrome (12 cases), low T3-low T4 syndrome (20 cases), and other abnormalities (33 cases). 1560 patients were ultimately included in this study (Fig. 1). This study complies with the Declaration of Helsinki, and the Shengjing Hospital of China Medical University Research Ethics Committee which approved the research protocol. Written informed consent was formally obtained from all participants.

Participants and procedures

Acute coronary syndrome was classified according to current guidelines [1–4]. Briefly, unstable angina is defined as chest discomfort or anginal equivalent, ST-segment depression, transitory ST-segment elevation or prominent T-wave inversion, and negative cardiac biomarkers (CK-MB, T/I troponin). Non-ST-segment elevation myocardial infarction (MI) is defined as chest discomfort or anginal equivalent, ST-segment depression, transitory ST-segment elevation or prominent T-wave inversion, and positive cardiac biomarkers (CK-MB, T/I troponin). ST-segment elevation MI (STEMI) is defined as chest pain and significant ST-segment elevation (≥ 0.1 mV in at least two standard leads or ≥ 0.2 mV in at least two contiguous precordial leads) or new left bundle branch block. PCI was performed in accordance with current guidelines, with aspiration thrombectomy and glycoprotein IIb/IIIa inhibitor administration performed at the discretion of the operators [1–4]. The operators also prescribed periprocedural and postprocedural anti-platelet regimens and other cardiovascular medications according to the guidelines [1–4].

Thyroid hormone sampling

In all cases, venous blood samples were drawn upon admission in standard tubes at room temperature, rapidly centrifuged and measured for thyroid-stimulating hormone (TSH), free T3 (fT3) and free T4 (fT4) by a completely automated immunoassay analyzer (i2000, Abbott, USA) in the core laboratory of Shengjing Hospital. The reference intervals for the laboratory were as follows: TSH: 0.3–4.8 uIu/mL; fT3: 2.63–5.71 pmol/L; fT4: 9.01–19.05 pmol/L. Based on thyroid hormone values, patients were categorized into four groups: (1) euthyroidism, with all circulating levels of TSH, fT3, and fT4 in the reference range; (2) subclinical hypothyroidism (SHypo), with TSH levels between 4.8 and 10 uIu/mL and fT3 and fT4 in the reference range; (3) subclinical hyperthyroidism (SHyper), with TSH levels less than 0.3 mIU/L and fT3 and fT4 in the reference range; and (4) low T3 syndrome, with fT3 levels less than 2.63 mIU/L and TSH and fT4 levels in the reference range [7].

Clinical endpoints

The clinical endpoints of this study were all-cause mortality, cardiac mortality, nonfatal reinfarction, and unplanned repeat revascularization, including any unplanned repeat PCI or surgical bypass of target or non-target vessels. All endpoints are defined by the standardized definitions [25].

Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files (**Suppl. Appendix**).

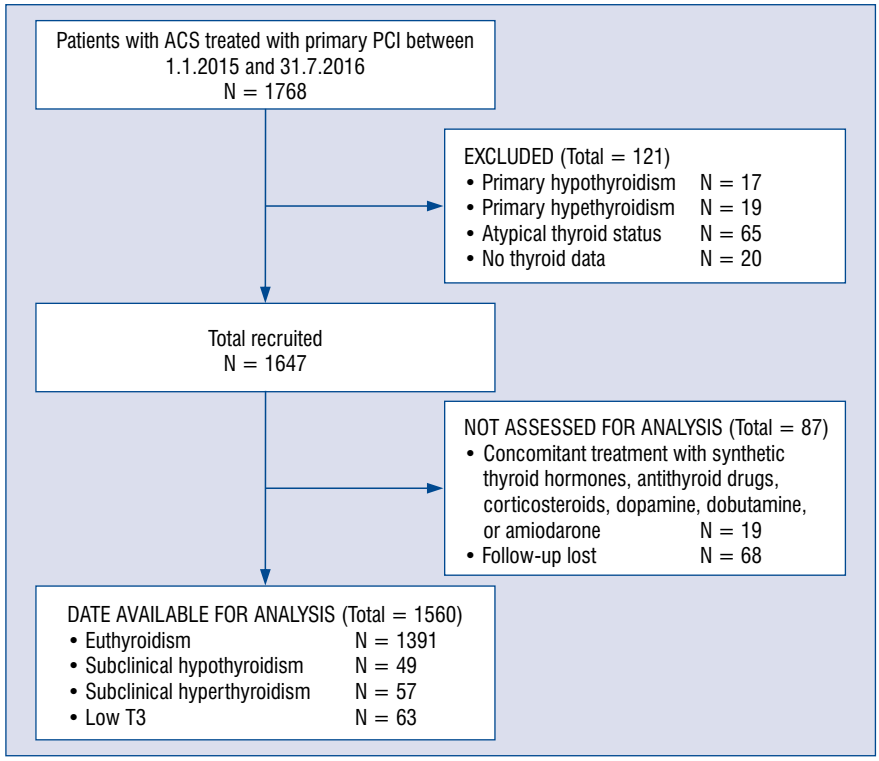

Figure 1. Flow diagram of participant selection; ACS — acute coronary syndrome; PCI — percutaneous coronary intervention.

Statistical analysis

Quantitative variables with normal distribution are represented as mean ± standard deviation (SD) and compared by variance analysis. Quantitative variables without normal distribution are represented as median (interquartile range [IQR]) and compared with a Kruskal-Wallis H test. Categorical variables are presented as counts and proportions (%) and were compared with the χ^2 test. Cox proportional hazards regression modeling by forward stepwise procedure was used to analyze the effect of variables on event-free survival. The euthyroidism group was considered the reference group. Variables included in the model were chosen by separate univariate analyses (**Suppl. Appendix S1 and S2**); those with p value of < 0.05 were included in the final model (see Table 3). Age, gender, current smoking, prior heart failure (HF), heart rate on admission, left ventricular ejection fraction (LVEF), MI on admission, creatinine, left main coronary artery disease, number of stents, drug-eluting stent, and angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARBs) were included in the Cox regression multivariable analysis of all-cause mortality (**Suppl. Appendix S1**). Age, gender, prior HF, heart rate on admission, LVEF, MI on admission, creatinine, left main coronary artery disease, drug-eluting stent and ACEI/ARBs were included in the Cox regression multivariable analysis of cardiac mortality (**Suppl. Appendix S2**). Results were reported as hazard ratios (HRs) with associated 95% confidence intervals (CIs). The cumulative event rate was estimated from Kaplan-Meier curves and compared using the log-rank test. All tests were two-sided, and statistical significance was defined as $p < 0.05$. All statistical analyses were performed with SPSS version 19 (SPSS Inc., Chicago, Illinois, USA).

Results

Participants and baseline characteristics

Figure 1 represents the flowchart for patient selection. The final study cohort included 1560 ACS patients undergoing PCI, including 169 patients with mild thyroid dysfunction (10.8%), and were divided into four groups: 1) euthyroidism group, 1391 (89.2%) patients; 2) SHypo group, 49 (3.1%) patients; 3) SHyper group, 57 (3.7%) patients; and 4) low T3 syndrome group, 63 (4.0%) patients. Clinical characteristics are shown in Table 1. The SHypo and low T3 syndrome groups had significantly higher percentages of females (51.0% and 49.2%, respectively) compared to the euthyroidism (27.7%) and SHyper (21.1%) groups. The low T3 syndrome group had a tendency towards older age and higher troponin-I levels on admission and lower

Table 1. Baseline patient characteristics.

Variable	All (n = 1560)	Euthyroidism (n = 1391)	Subclinical hypothyroidism (n = 49)	Subclinical hyperthyroidism (n = 57)	Low T3 (n = 63)	P
Clinical characteristics						
Age	61.8 ± 11.1	61.5 ± 11.1	63.9 ± 9.5	62.3 ± 13.3	65.6 ± 9.7*	0.018
Female	453 (29.0%)	385 (27.7%)	25 (51.0%)	12 (21.1%)	31 (49.2%)*	< 0.001
Diabetes mellitus	486 (31.2%)	417 (30.0%)	19 (38.8%)	23 (40.4%)	27 (31.2%)	0.057
Hypertension	905 (58.0%)	801 (57.6%)	31 (63.3%)	30 (52.6%)	43 (68.3%)	0.256
Dyslipidemia	1121 (71.9%)	1016 (73.0%)	30 (61.2%)	34 (59.6%)	41 (65.1%)*	0.025
Current smoking	711 (45.6%)	640 (46.0%)	16 (32.7%)	29 (50.9%)	26 (41.3%)	0.210
History of MI	169 (10.8%)	146 (10.5%)	6 (12.2%)	9 (15.8%)	8 (12.7%)	0.585
Prior PCI	149 (9.6%)	131 (9.4%)	6 (12.2%)	7 (12.3%)	5 (7.9%)	0.772
Prior HF	74 (4.7%)	59 (4.2%)	4 (8.2%)	4 (7.0%)	7 (11.1%)*	0.039
MI on admission	1055 (67.7%)	918 (66.0%)	29 (59.2%)	51 (89.5%)	57 (90.5%)*	< 0.001
Cardiogenic shock	18 (1.2%)	10 (0.7%)	1 (2.0%)	2 (3.5%)	5 (7.9%)	< 0.001
SBP on admission [mmHg]	136.1 ± 22.7	136.7 ± 22.6	138.3 ± 22.3	127.7 ± 23.5	129.3 ± 23.4*	0.001
HR on admission [bpm]	75.4 ± 14.3	75.2 ± 14.1	74.3 ± 10.6	77.4 ± 14.7	77.9 ± 18.6	0.510
LVEF [%]	58.3 ± 8.7	58.5 ± 8.6	60.5 ± 8.0	55.9 ± 10.2	55.7 ± 8.5	0.002
Laboratory characteristics						
Creatinine [μmol/L], median (Q1, Q3)	71 (61, 85)	71 (61, 84)	70 (62, 94)	66 (58, 88)	75 (58, 113)	0.358
Troponin-I on admission [ng/mL], median (Q1, Q3)	0.67 (0.01, 21.00)	0.65 (0.01, 18.18)	0.27 (0.01, 12.02)	16.00 (0.67, 82.00)	25.20 (2.10, 66.60)*	< 0.001
TSH [μIU/mL], median (Q1, Q3)	1.41 (0.83, 2.26)	1.41 (0.88, 2.16)	6.00 (5.23, 6.82)	0.22 (0.13, 0.27)	1.40 (0.61, 2.37)	< 0.001
fT_3 [pmol/L], median (Q1, Q3)	3.93 (3.47, 4.34)	3.95 (3.55, 4.36)	4.04 (3.41, 4.41)	3.97 (3.37, 4.34)	2.36 (2.05, 2.52)	< 0.001
fT_4 [pmol/L], median (Q1, Q3)	12.92 (11.77, 14.29)	12.98 (11.82, 14.32)	12.14 (10.79, 13.08)	13.49 (12.33, 15.14)	12.32 (10.54, 13.74)	< 0.001
PCI characteristics						
Left main disease	145 (9.3%)	119 (8.6%)	8 (16.3%)	7 (12.3%)	11 (17.5%)*	0.025
Three-vessel disease	369 (23.7%)	331 (23.8%)	9 (18.4%)	14 (24.6%)	15 (23.8%)	0.849
Number of stents, median (Q1, Q3)	2 (1, 2)	2 (1, 2)	2 (1, 2)	1 (1, 2)	2 (1, 2)	0.910
Drug-eluting stent	1504 (96.4%)	1342 (96.5%)	47 (95.9%)	53 (93.0%)	62 (98.4%)	0.437
Medications at discharge						
ASA	1550 (99.4%)	1383 (99.4%)	49 (100.0%)	57 (100.0%)	61 (96.8%)	0.068
Clopidogrel	1417 (90.8%)	1266 (91.0%)	44 (89.8%)	52 (91.2%)	55 (87.3%)	0.784
Ticagrelor	119 (7.6%)	103 (7.4%)	5 (10.2%)	4 (7.0%)	7 (11.1%)	0.643
Statin	1534 (98.3%)	1373 (98.7%)	49 (100.0%)	54 (94.7%)	58 (92.1%)	< 0.001
ACEI/ARBs	808 (51.8%)	734 (52.8%)	19 (38.8%)	29 (50.9%)	26 (41.3%)	0.083
Beta-blockers	782 (50.1%)	705 (50.7%)	17 (34.7%)	32 (56.1%)	28 (44.4%)	0.091

ASA — acetylsalicylic acid; ACEI/ARBs — angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; HF — heart failure; HR — heart rate; LVEF — left ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention; SBP — systolic blood pressure

Table 2. Frequency of clinical outcomes by thyroid status.

	All (n = 1560)	Euthyroidism (n = 1391)	Subclinical hypothyroidism (n = 49)	Subclinical hyperthyroidism (n = 57)	Low T3 (n = 63)	P
All-cause mortality	59 (3.8%)	47 (3.4%)	1 (2.0%)	4 (7.0%)	7 (11.1%)	0.007
Cardiac mortality	48 (3.1%)	37 (2.7%)	1 (2.0%)	4 (7.0%)	6 (9.5%)	0.005
Nonfatal reinfarction	22 (1.4%)	18 (1.3%)	1 (2.0%)	1 (1.8%)	2 (3.2%)	0.629
Unplanned repeat revascularization	60 (3.8%)	50 (3.6%)	4 (8.2%)	5 (8.8%)	1 (1.6%)	0.062

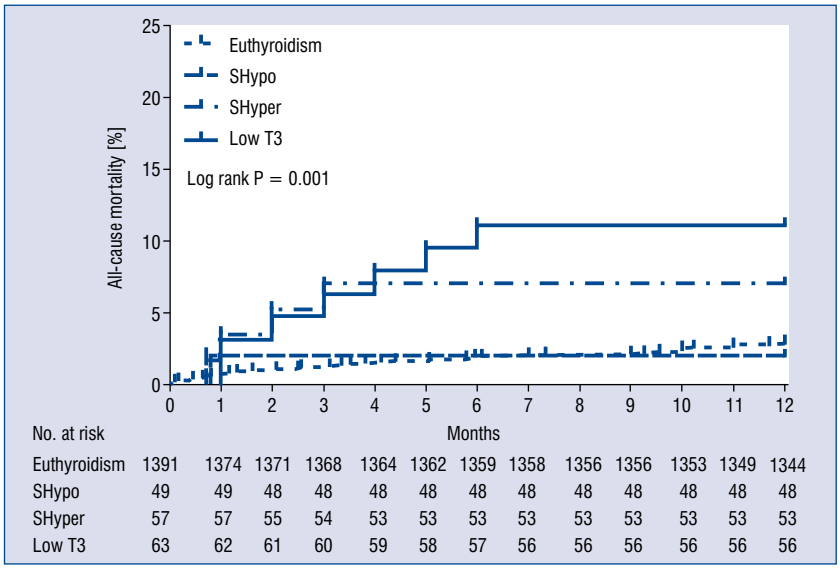

Figure 2. Kaplan-Meier cumulative event curves for all-cause mortality by thyroid status; SHypo — subclinical hypothyroidism; SHyper — subclinical hyperthyroidism.

LVEF and rate of statin use at discharge. The percentage of prior HF, MI on admission, cardiogenic shock and left main coronary artery disease were also significantly higher in the low T3 syndrome group. Individuals in the SHyper group were more likely to have dyslipidemia. There was a significant trend of lower systolic blood pressure upon admission in SHyper group (Table 1).

Clinical endpoints by thyroid status

The clinical endpoints are shown in Table 2. During the 12-month follow-up period, there was a significant trend of higher all-cause mortality and cardiac mortality in the low T3 syndrome group.

The cumulative event curves for all-cause mortality can be seen in Figure 2. Log-rank tests indicated significant differences among the four groups ($p = 0.001$). Furthermore, as shown in Table 3, a significantly increased risk of all-cause mortality was found in the low T3 syndrome group, but not in the SHypo or SHyper groups, compared with the euthyroidism group (HR 3.496, 95% CI 1.579–7.729, $p = 0.002$). After adjusting for covariates, the low T3 syndrome group still displayed a significantly higher all-cause mortality, compared with the euthyroidism group (HR 2.553, 95% CI 1.093–5.964, $p = 0.030$) (Table 3).

Using Kaplan-Meier analysis (Fig. 3), it was found that there were significant differences in cardiac mortality among the four groups ($p < 0.001$). Univariate analysis also revealed that the low T3 syndrome group, but not the SHypo or SHyper groups, had a higher rate of cardiac mortality, compared with the euthyroidism group (HR 3.781, 95% CI 1.596–8.959, $p = 0.003$) (Table 3). This was confirmed again by Cox regression multivariable analysis (HR 2.594, 95% CI 1.026–6.559, $p = = 0.034$) (Table 3). There were no significant differences in nonfatal reinfarction or unplanned repeat revascularization among the four groups (Table 3).

Table 3. Hazard ratios for all-cause and cardiac mortality by thyroid status.

	Univariate analysis		Multivariate analysis[a]	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
All-cause mortality				
Euthyroidism	**1 [Reference]**		**1 [Reference][a]**	
Subclinical hypothyroidism	0.603 (0.083–4.367)	0.616	0.557 (0.077–4.043)	0.563
Subclinical hyperthyroidism	2.165 (0.780–6.009)	0.138	1.970 (0.706–5.494)	0.195
Low T3	3.493 (1.579–7.729)	0.002	2.553 (1.093–5.964)	0.030
Cardiac mortality				
Euthyroidism	**1 [Reference]**		**1 [Reference][b]**	
Subclinical hypothyroidism	0.767 (0.105–5.589)	0.793	0.696 (0.095–5.087)	0.721
Subclinical hyperthyroidism	2.749 (0.980–7.714)	0.055	2.431 (0.860–6.874)	0.094
Low T3	3.781 (1.596–8.959)	0.003	2.594 (1.026–6.559)	0.034
Nonfatal reinfarction				
Euthyroidism	**1 [Reference]**			
Subclinical hypothyroidism	1.589 (0.212–11.900)	0.652		
Subclinical hyperthyroidism	1.368 (0.183–10.244)	0.761		
Low T3	2.478 (0.575–10.681)	0.223		
Unplanned repeat revascularization				
Euthyroidism	**1 [Reference]**			
Subclinical hypothyroidism	2.342 (0.846–6.485)	0.101		
Subclinical hyperthyroidism	2.047 (0.739–5.668)	0.168		
Low T3	0.435 (0.060–3.147)	0.409		

[a]Adjusted for age, gender, current smoking, prior HF, HR on admission, LVEF, myocardial infarction on admission, cardiogenic shock, creatinine, left main disease, number of stents, drug-eluting stent, and ACEI/ARBs
[b]Adjusted for age, gender, prior HF, HR on admission, LVEF, myocardial infarction on admission, cardiogenic shock, creatinine, left main disease, drug-eluting stent, and ACEI/ARBs
Abbreviations — see Table 1

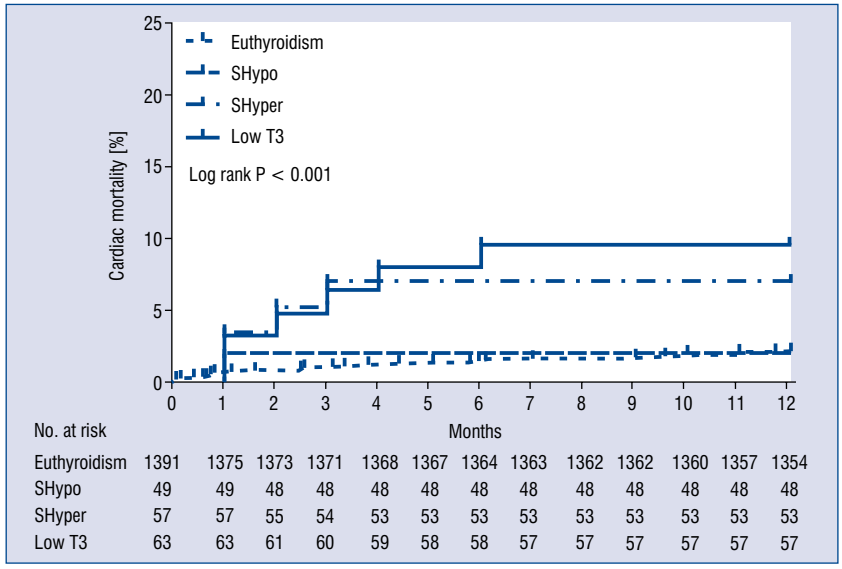

Figure 3. Kaplan-Meier cumulative event curves for cardiac mortality by thyroid status; SHypo — subclinical hypothyroidism; SHyper — subclinical hyperthyroidism.

Discussion

The present study examined the association between mild thyroid dysfunction and 12-month prognosis in ACS patients undergoing PCI, and demonstrated that: 1) the prevalence of mild thyroid dysfunction was as high as 10.8% in patients with ACS undergoing PCI; 2) low T3 syndrome, but not subclinical hypothyroidism or subclinical hyperthyroidism, was associated with a higher rate of all-cause and cardiac mortality; and 3) there was no association between mild thyroid dysfunction and nonfatal reinfarction or unplanned repeat revascularization in ACS patients undergoing PCI.

Mild thyroid dysfunction is frequently present in patients with various cardiac diseases [21]. Further, plasma thyroid hormone levels may also change in ACS patients [8, 9]. Iervasi et al. [21] found that the prevalence of thyroid dysfunction was up to 40% in cardiac patients undergoing coronary angiography. Another study showed a 15% prevalence of mild thyroid dysfunction in patients with STEMI who underwent PCI [23]. In this study, there was a 10.8% prevalence of mild thyroid dysfunction in patients with ACS undergoing PCI. However, the current guidelines do not recommend the routine assessment of thyroid function in ACS patients [1–4]. The prevalence of mild thyroid dysfunction in the present study was far lower than that reported by Iervasi et al. [21]. This is mainly due to differing definitions of thyroid dysfunction. Iervasi et al. [21] used a broader scope of definition: euthyroid patients with normal values of TSH, fT3, and fT4; low T3 syndrome patients with fT3 < 2.0 pg/mL; hypothyroid patients with TSH > 3.8 uIU/mL; and hyperthyroid patients with TSH < 0.3 uIU/mL.

Thyroid hormones extensively affect the physiological and pathological processes of the cardiovascular system [7] and are associated with coronary atherosclerosis [11, 12], thrombus burden [10], cardiomyocyte injury [8, 9, 15], and cardiac function recovery [13, 14]. For the first time, in a total of 573 consecutive heterogeneous cardiac patients undergoing thyroid function evaluation, Iervasi et al. [21] reported that subclinical hypothyroidism and subclinical hyperthyroidism were associated with an increased risk of cardiac mortality. In contrast, patients with STEMI undergoing PCI, had no significant differences in adverse prognoses between subclinical hypothyroidism or subclinical hyperthyroidism and euthyroidism [23]. In addition, the present study found that neither subclinical hypothyroidism or subclinical hyperthyroidism were associated with a higher rate of all-cause or cardiac mortality, nor were they associated with a higher rate of nonfatal reinfarction or unplanned repeat revascularization in ACS patients undergoing PCI. The reason for different conclusions may be that the latter two studies only included ischemic heart disease patients undergoing PCI, but not heterogeneous patients with various cardiac diseases. Also, PCI could greatly improve the prognosis of ischemic heart disease [1–4].

Low T3 syndrome was found to be a strong prognostic predictor of death in patients with cardiac disease [21, 26–28]. It then was verified by other research that low T3 syndrome was associated with adverse outcomes in patients after experiencing ACS [29]. However, only 27.7% patients in that study received PCI, which can greatly improve the prognosis of ischemic heart disease and is now widely available for ACS patients [1–4]. For the first time, we studied the association between low T3 syndrome and the prognosis of ACS patients undergoing PCI. The present study found that low T3 syndrome was associated with a higher rate of all-cause and cardiac mortality in ACS patients undergoing PCI. Mechanistic correlates of these findings have been demonstrated. T3, which is the most important bioactive thyroid hormone for cardiomyocytes, is mostly produced by a process of deiodination of T4 [7]. It can affect cardiomyocytes via genomic and nongenomic actions [7]. T3 regulates transcription by binding hormone receptors (TRs) in the nucleus, which then bind to thyroid hormone response elements (TREs) present in regulatory regions of target genes. Nongenomic actions of T3 include thyroid hormone signaling, changes in thyroid hormone levels, and changes in thyroid hormone receptors. Previous studies have confirmed that the thyroid hormone receptor TRα1 can limit myocardial injury and post-ischemic cardiac remodeling through T3 binding, and it regulates genes related to contractile proteins, pacemaker activity and conduction, cell growth, differentiation and metabolism [30–32]. Also, thyroid hormones could affect cardiac apoptosis through the suppression of ischemia reperfusion-induced activation of the pro-apoptotic p38 mitogen-activated protein kinase (MAPK) and upregulation of cardio-protective molecules such as heat shock protein 27 (HSP27) and heat shock protein 70 (HSP70), which are also involved in ischemic preconditioning [30–32]. T3 may also regulate plasma membrane ion currents, activate survival pathways, and decrease oxidative stress in mitochondria [7]. Therefore, heart rate, cardiac contractility, vascular smooth muscle, and

endothelial function will be modulated [7]. When T3 is low, negative effects on the cardiovascular system, such as delayed diastolic filling, decreased cardiac contractility, and increased vascular resistance will occur [7]. Thyroid hormones also indirectly effect myocytes by activating the inflammatory immune response through genomic and nongenomic mechanisms [33]. Clinical studies also confirmed that low T3 was associated with larger thrombus burden [10], higher severity of coronary artery lesions [11, 12], worse cardiac function [13, 14] and larger myocardial injury size [8, 9, 15] in ACS patients.

Taken together, in ACS patients, decreased levels of T3 have a severe pathological effect, rather than acting as an adaptive response to minimize catabolism [34]. Considering the results of this study and the others mentioned, it is worthwhile to monitor thyroid hormone levels in patients with ACS. Doing so will help to identify patients at high risk of adverse events and mortality. Also, of interest is the potential of thyroid hormones as a therapeutic target for improving the prognosis of ACS since patients still suffer adverse outcomes [6]. In fact, experimental evidence from animal models has shown that T3 therapy could limit infarct extension, protect against reperfusion injury, improve cardiac structure and function, decrease the incidence of tachyarrhythmias, and reduce adverse left ventricular remodeling [7]. Furthermore, a previous study found that thyroid replacement therapy was beneficial in preventing coronary disease progression and other cardiovascular events in patients with hypothyroidism undergoing PCI [35]. However, the efficacy and safety of T3 therapy has not yet been confirmed in randomized, controlled clinical trials in patients with ACS and low T3 syndrome undergoing PCI. Moreover, there are still several problems related to thyroid hormone replacement, such as the type of thyroid hormone used (T3 or T4), medication route (parenteral or oral), the timing related to onset of ACS, the duration of medication use, and complications associated with overtreatment, including atrial fibrillation and bone fracture. Adequately powered randomized studies need to be performed to obtain meaningful conclusions before thyroid hormone replacement can become a routine clinical treatment for ACS patients, such as the ThyrAMI trial (Trial registration: ISRCTN; trial number: ISRCTN52505169) and the TRUST trial (Specific Program Cooperation — Theme Health, Proposal No: 278148-2, NCT01660126) [36, 37].

Limitations of the study

This study had several limitations. First, this study was prospective and observational, so potential confounders and selection bias could not be completely eliminated. Second, when patients suffer from ACS, the secretion of thyroid hormone will fluctuate in the early phase of the disease [7]. Particularly, the level of T3 will drop in the first 2–3 days after the ischemic event. However, in this study, thyroid function tests were only performed at admission and not repeated later, as recommended by the guidelines [16–19]. Thus, transient forms of thyroid dysfunction could be excluded and low T3 syndrome was likely underestimated. Third, studies have indicated that iodinated contrast media may influence thyroid function [22, 38, 39]. In this study, the thyroid function of some patients was tested after the use of iodinated contrast media because they needed emergency PCI. Finally, the raw number of events in this study was quite small during the follow-up period, which may be a limitation in the overall interpretation of the study results.

Conclusions

Mild thyroid dysfunction was frequent in patients with ACS undergoing PCI, and low T3 syndrome was the predominant feature. Low T3 syndrome, but not subclinical hypothyroidism or subclinical hyperthyroidism, was associated with a higher rate of all-cause and cardiac mortality.

Acknowledgements

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Conflict of interest: None declared

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