


# The Association between Thyroid-Stimulating Hormone and Long-Term Outcomes in Patients with ST Segment Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention

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**Objective:** Thyroid hormones are closely related to the cardiovascular system. Our study aimed to explore the impact of admission thyroid-stimulating hormone (TSH) levels on long-term outcomes in patients with acute ST segment elevation myocardial infarction (STEMI) by detailed stratifications of TSH.

**Methods:** Consecutive STEMI patients admitted to our hospital were divided into four groups: Group 1 (TSH <0.35 mIU/L), Group 2 (TSH 0.35–1.0 mIU/L), Group 3 (TSH 1.0–3.5 mIU/L), and Group 4 (TSH >3.5 mIU/L). The primary endpoint was all-cause mortality during follow-up, and the median follow-up was 2.5 years. Cox proportional hazard regression models were performed to identify the prognostic value of TSH.

**Results:** A total of 1186 patients were included. Group 4 was presented with higher systolic and diastolic blood pressure (all  $P < 0.001$ ), and Group 1 had more patients complicated by heart failure (Killip class >I,  $P = 0.014$ ). During follow-up, 138 deaths occurred. Patients in Group 4 had the worst long-term outcomes ( $P < 0.001$ ). The cumulative survival in Group 4 was remarkably lower (Log rank  $P < 0.001$ ), whereas the other three groups were comparable (Log rank  $P = 0.365$ ). Through Cox regression analysis, only TSH >3.5 mIU/L was identified as an independent risk factor for long-term mortality after STEMI.

**Conclusion:** Only TSH elevation beyond the normal range was associated with worse long-term prognosis in STEMI patients, while high-normal TSH or reduced TSH did not alter long-term prognosis of STEMI patients. TSH >3.5 mIU/L was an independent risk factor for long-term mortality in STEMI.

**Keywords:** acute myocardial infarction, thyroid hormone, thyroid-stimulating hormone, STEMI, TSH

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## Introduction

Thyroid hormones (TH) are closely related to the cardiovascular system. TH receptors are present in the myocardium and vascular tissue, and alterations in TH concentration may adversely affect cardiovascular physiology.<sup>1,2</sup> Hyperthyroidism is associated with systolic hypertension, shortness of breath during minimal exertion and atrial fibrillation, while hypothyroidism can lead to diastolic hypertension and dyslipidemia.<sup>3,4</sup>

The thyroid-stimulating hormone (TSH) is synthesized and released from the pituitary gland. Regulated by serum triiodothyronine (T3) and thyroxine (T4) through the classic feedback loop mechanism, the TSH is an appropriate marker for thyroid dysfunction screening.<sup>4,5</sup> Some recent studies have explored the relationship between TSH levels and the outcomes in cardiovascular diseases.<sup>6–10</sup> The status of elevated TSH but normal T3 and T4, also known as subclinical hypothyroidism, has been proved to be associated with worse prognosis in patients with MI.<sup>6,7</sup> However, these studies usually simply divided patients into two groups of high TSH and normal TSH, and the impact of reduced TSH or high-normal TSH on the outcomes in acute MI patients remains unclear, especially under the background that subtle fluctuation of T3 or T4 are amplified by changes in TSH.<sup>11</sup> Therefore, our study aimed to explore the impact of TSH on long-term outcomes in patients with acute MI by more detailed groupings of TSH.

## Methods

### Study Population

This is a retrospective study that aimed to evaluate the association between TSH concentration and long-term mortality in ST segment elevation myocardial infarction (STEMI). Consecutive STEMI patients treated by primary percutaneous coronary intervention (PCI) in our hospital from December 2014 to December 2018 were enrolled. The diagnosis of STEMI was established on chest pain or equivalent syndromes for more than 30 minutes in combination with consistent electrocardiogram (ECG) changes and increased serum troponin I (TnI). Included in this study were adult patients with a diagnosis of STEMI and treated by primary PCI within 12 hours after admission. Excluded from this study were patients with incomplete data of TSH, patients with clear previous thyroid diseases and those taking TH therapy or antithyroid drugs, and patients lost to follow-up. Patients with previous cardiac events were not specifically excluded from this study. The study was registered at [chictr.org.cn](http://chictr.org.cn) (ChiCTR1900028516), and protocols were approved by the ethics committee of The First Affiliated Hospital of Chongqing Medical University (No. 2019-148) and complied with the declaration of Helsinki. All subjects were provided with written informed consent.

### Study Protocols

Baseline characteristics including age, gender, body mass index (BMI), medical histories, clinical presentations and laboratory data were collected through electronic medical

record system. TH, including TSH, free T3 (FT3) and free T4 (FT4) were measured within 24 hours after admission and were analyzed by the chemiluminescence immunoassay (Unicel™ DXI 800, Beckman Coulter, USA). The reference ranges for TSH, FT3 and FT4 of our laboratory were 0.35–3.5 mIU/L, 2.14–4.21 pg/mL and 0.59–1.25 ng/dL, respectively. To determine the association between TSH and long-term mortality in STEMI, patients were assigned into four groups as follows: Group 1 (TSH <0.35 mIU/L), Group 2 (TSH 0.35–1.0 mIU/L), Group 3 (TSH 1.0–3.5 mIU/L), and Group 4 (TSH >3.5 mIU/L). The cut-offs of TSH used for groupings were based on the fact that 0.35–3.5 mIU/L was the normal reference range of TSH of our laboratory and 1.0 mIU/L was the median value in patients with normal TSH. During the acute coronary angiography, the culprit vessels were treated according to the guidelines of PCI for STEMI.<sup>12,13</sup> After intervention, patients were sent to coronary care unit for ECG monitoring and further management. The medications during hospitalization went as far as possible to comply with contemporary clinical guidelines.<sup>12,13</sup>

### Follow-Up

The primary endpoint of this study is all-cause mortality during long-term follow-up. The secondary endpoints include heart failure, malignant arrhythmias, bleeding and mortality during hospitalization. Heart failure refers to symptoms and signs requiring the administration of diuretics. Malignant arrhythmias refer to second-degree and third-degree atrioventricular block, ventricular tachycardia and ventricular fibrillation. Bleeding refers to major bleeding that requires hemostatic agents, endoscopic intervention or surgery. All patients were regularly contacted every 6 months through telephone reviews or office visits. The median (interquartile range) of follow-up was 2.5 (1.6–3.6) years.

### Statistical Analysis

Continuous variables were expressed as mean  $\pm$  standard deviation (SD) and compared using one-way analysis of variance or Bonferroni correction. Categorical variables were presented as frequency (percentage) and compared using Pearson chi-square test or Fisher's exact test, as appropriate. Kaplan–Meier curves were adopted to demonstrate all-cause mortality during follow-up. Comparisons among groups were achieved by Log rank test. To identify whether TSH elevation constitutes a risk factor for long-term mortality in STEMI, multivariate Cox proportional

hazard regression models were developed. The models were adjusted for age, sex, BMI, comorbidities, admission vital signs and laboratory data. The adjusted hazard ratios (HRs) with their respective 95% confidence intervals (CIs) for each group were calculated. All statistical analyses were carried out using the SPSS statistical software version 25.0 (SPSS Inc., Chicago, Illinois). Statistical significance was defined as a two-sided P value <0.05.

## Results

### Baseline Demographics of the Patients

Between December 2014 and December 2018, a total of 1422 consecutive patients with STEMI were admitted to our hospital and treated by primary PCI, among which thyroid profiles were available in 1288 patients. In these 1288 patients, 91 were lost to follow-up, and 11 were excluded with a clear previous diagnosis of thyroid diseases or taking TH therapy or antithyroid drugs. Finally, 1186 patients were included in the study. They were assigned into four groups as described above. The baseline characteristics of the study population are listed in Table 1. The four groups had a comparable BMI, proportion of male and smokers, while with the elevation of TSH, the mean age of each group was observed to increase (P =

0.001). Group 4 had more hypertension (P = 0.009) and renal insufficiency (P = 0.001), but other comorbidities including diabetes, dyslipidemia, previous MI or stroke did not differ among groups (all P > 0.05). With regard to clinical presentation, patients in Group 4 were presented with higher systolic blood pressure (P < 0.001) and diastolic blood pressure (P < 0.001), and Group 1 had more complicated by heart failure (Killip class >I, P = 0.014) or cardiogenic shock (P = 0.011).

### ECG and Coronary Features of the Patients

Table 2 displays the comparison localization of myocardial infarction (MI) identified by ECGs and coronary features of the four groups. Although without statistical significance among the four groups, anterior infarction was more frequently seen in Group 4 (47.0% in Group 1, 51.7% in Group 2, 57.0% in Group 3 and 59.1% in Group 4, P = 0.104), and Group 1 had more inferior infarction (56.1% in Group 1, 52.5% in Group 2, 46.0% in Group 3 and 45.5% in Group 4, P = 0.077). As for the culprit vessel, there was no significant difference between groups (P = 0.057). Group 4 had higher proportion of post-thrombolysis in myocardial infarction flow grade < III,

**Table 1** Baseline Characteristics of the Study Population

	Group 1 (n = 132)	Group 2 (n = 497)	Group 3 (n = 491)	Group 4 (n = 66)	P value
	(TSH <0.35 mIU/L)	(TSH 0.35–1.0 mIU/L)	(TSH 1.0–3.5 mIU/L)	(TSH >3.5 mIU/L)	
<b>Demographics</b>					
Age, years	61.57 ± 12.16	63.12 ± 12.04	63.83 ± 12.51	69.03 ± 13.32	0.001
Male, %	106 (80.3)	404 (81.3)	389 (79.2)	44 (66.7)	0.052
BMI, kg/m <sup>2</sup>	23.31 ± 4.67	23.89 ± 3.81	24.22 ± 4.14	24.05 ± 3.73	0.132
Smoker, %	94 (71.2)	348 (70.0)	321 (65.5)	38 (57.6)	0.106
<b>Medical history, %</b>					
Hypertension	59 (44.7)	242 (48.7)	271 (55.2)	43 (65.2)	0.009
Diabetes mellitus	25 (18.9)	100 (20.1)	113 (23.0)	20 (30.3)	0.195
Dyslipidemia	13 (9.8)	50 (10.1)	59 (12.0)	5 (7.6)	0.601
Previous MI	8 (6.1)	23 (4.6)	17 (3.5)	0 (0)	0.145
Previous stroke	4 (3.0)	28 (5.6)	38 (7.7)	6 (9.1)	0.139
Renal insufficiency	2 (1.5)	16 (3.2)	9 (1.8)	8 (12.1)	0.001
<b>Clinical presentation</b>					
SBP, mmHg	119.73 ± 26.22	121.42 ± 23.60	128.78 ± 25.50	133.08 ± 30.05	<0.001
DBP, mmHg	74.25 ± 15.86	75.10 ± 15.44	78.93 ± 15.75	82.45 ± 20.28	<0.001
Heart rate, bpm	81.31 ± 21.62	82.92 ± 18.84	81.77 ± 16.64	86.55 ± 19.21	0.187
Killip class >I, %	46 (34.8)	136 (27.4)	109 (22.2)	21 (31.8)	0.014
Cardiac arrest, %	9 (6.8)	37 (7.4)	14 (2.9)	4 (6.1)	0.007
Cardiogenic shock, %	19 (14.4)	46 (9.3)	29 (5.9)	4 (6.1)	0.011

**Abbreviations:** BMI, body mass index; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 2** Electrocardiogram and Coronary Features of the Study Population

	Group 1 (n = 132)	Group 2 (n = 497)	Group 3 (n = 491)	Group 4 (n = 66)	P value
	(TSH <0.35 mIU/L)	(TSH 0.35–1.0 mIU/L)	(TSH 1.0–3.5 mIU/L)	(TSH >3.5 mIU/L)	
Location of MI, %					
Anterior MI	62 (47.0)	257 (51.7)	280 (57.0)	39 (59.1)	0.104
Inferior MI	74 (56.1)	261 (52.5)	226 (46.0)	30 (45.5)	0.077
Culprit vessel, %					0.057
LM	2 (1.5)	2 (0.4)	1 (0.2)	1 (1.5)	
LAD	59 (44.7)	238 (47.9)	266 (54.2)	34 (51.5)	
LCX	18 (13.6)	44 (8.9)	55 (11.2)	4 (6.1)	
RCA	53 (40.2)	213 (42.9)	169 (34.4)	27 (40.9)	
Triple-vessel disease, %	24 (18.2)	87 (17.5)	79 (16.1)	16 (24.2)	0.423
Post-TIMI < III, %	6 (4.5)	26 (5.2)	20 (4.1)	8 (12.1)	0.046
Thrombus aspiration, %	8 (6.5)	43 (8.7)	33 (6.7)	4 (6.1)	0.675
GP IIb/IIIa inhibitors, %	60 (48.8)	231 (46.5)	200 (40.7)	23 (34.8)	0.082
Stenting, %	114 (86.4)	431 (86.7)	425 (86.6)	51 (77.3)	0.209

**Abbreviations:** MI, myocardial infarction; LM, left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction flow grade.

indicating potentially worse coronary lesion (4.5% in Group 1, 5.2% in Group 2, 4.1% in Group 3 and 12.1% in Group 4,  $P = 0.046$ ). The proportion of triple-vessel disease, thrombus aspiration during PCI, administration of GP IIb/IIIa inhibitors and stenting were similar (all  $P > 0.05$ ).

### Laboratory Findings of the Patients

Table 3 shows the laboratory findings of all groups. The value of TnI did not differ among the four groups ( $P = 0.084$ ) but was significantly higher when Group 4 was compared with the combination of Group 1–3 ( $10.15 \pm 11.23$  ng/mL in Group 1–3,  $7.26 \pm 9.34$  ng/mL in Group 4,

**Table 3** Laboratory Findings of the Study Population

	Group 1 (n = 132)	Group 2 (n = 497)	Group 3 (n = 491)	Group 4 (n = 66)	P value
	(TSH <0.35 mIU/L)	(TSH 0.35–1.0 mIU/L)	(TSH 1.0–3.5 mIU/L)	(TSH >3.5 mIU/L)	
Laboratory findings					
Troponin I, ng/mL	10.97 ± 11.98	10.56 ± 11.48	9.51 ± 10.74	7.26 ± 9.34	0.084
BNP >100pg/mL, %	53/98 (54.1)	163/370 (44.1)	195/351 (55.6)	29/44 (65.9)	0.002
WBC, $\times 10^9/L$	12.48 ± 3.89	11.84 ± 4.07	10.96 ± 3.76	10.57 ± 3.82	<0.001
Hemoglobin, g/L	140.23 ± 18.85	138.72 ± 19.08	137.34 ± 20.15	134.15 ± 18.26	0.138
Creatinine, $\mu\text{mol/L}$	89.80 ± 86.50	83.28 ± 38.11	84.16 ± 58.87	93.67 ± 63.19	0.367
TC, mmol/L	4.38 ± 0.92	4.38 ± 1.11	4.51 ± 1.10	4.60 ± 0.95	0.135
LDL-C, mmol/L	2.81 ± 0.88	2.82 ± 0.97	2.90 ± 0.94	3.06 ± 0.84	0.168
HDL-C, mmol/L	1.11 ± 0.31	1.12 ± 0.33	1.10 ± 0.31	1.13 ± 0.30	0.683
TSH, uIU/mL	0.24 ± 0.09	0.66 ± 0.19	1.70 ± 0.57	6.80 ± 5.37	<0.001
FT3, pg/mL	3.16 ± 1.80	2.85 ± 0.48	2.90 ± 0.47	2.83 ± 0.46	<0.001
FT4, ng/dL	1.01 ± 0.58	0.91 ± 0.18	0.91 ± 0.18	0.84 ± 0.19	<0.001
LVEF, %	54.54 ± 7.78	55.20 ± 7.47	55.24 ± 7.12	55.50 ± 8.24	0.786
LVEF <50%, %	25/125 (20.0)	87/458 (19.0)	76/446 (17.0)	12/62 (19.4)	0.828
LVEDD, mm	48.97 ± 5.09	49.06 ± 5.34	49.23 ± 5.61	49.03 ± 5.83	0.949

**Abbreviations:** BNP, brain natriuretic peptide; WBC, white blood cell; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension.

**Table 4** Medications During Hospitalization and After Discharge of All Groups

	Group 1 (n = 132)	Group 1 (n = 497)	Group 2 (n = 491)	Group 3 (n = 66)	P value
	(TSH <0.35 mIU/L)	(TSH 0.35–1.0 mIU/L)	(TSH 1.0–3.5 mIU/L)	(TSH >3.5 mIU/L)	
Medications during hospitalization, %					
Aspirin	125 (94.7)	477 (96.0)	475 (96.7)	60 (90.0)	0.138
Clopidogrel	38 (40.3)	148 (29.8)	152 (31.0)	24 (36.4)	0.700
Ticagrelor	97 (73.5)	354 (71.2)	345 (70.3)	42 (63.6)	0.536
Statins	128 (97.0)	493 (99.2)	487 (99.2)	64 (97.0)	0.054
ACEI/ARB	54 (40.9)	175 (35.2)	206 (42.0)	29 (43.9)	0.130
β-Blocker	77 (58.3)	263 (52.9)	292 (59.5)	42 (63.6)	0.119
PPI	111 (84.1)	415 (83.5)	393 (80.0)	55 (83.3)	0.478
Medications after discharge, %					
Aspirin	115/129 (89.1)	416/469 (88.7)	419/471 (89.0)	52/63 (82.5)	0.505
Clopidogrel	48 (37.2)	192 (40.9)	196 (41.6)	34 (54.0)	0.167
Ticagrelor	79 (61.2)	278 (59.3)	270 (57.3)	28 (44.4)	0.128
Statins	127 (98.4)	465 (99.1)	464 (98.5)	62 (98.4)	0.693
ACEI/ARB	86 (66.7)	298 (63.5)	321 (68.2)	44 (69.8)	0.446
β-Blocker	100 (77.5)	385 (82.1)	374 (79.4)	54 (85.7)	0.403
PPI	94 (72.9)	348 (74.2)	337 (71.5)	39 (61.9)	0.222

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; PPI, proton pump inhibitors.

P = 0.001). Group 4 had more patients with brain natriuretic peptide (BNP) >100pg/mL (P = 0.002), and lower white blood cell counts, FT3 and FT4 (all P < 0.001). The serum creatinine, lipid profiles and left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension were similar (all P > 0.05).

## The Medications During Hospitalization

The medications during hospitalization and after discharge of the four groups are presented in Table 4. Interestingly, there was no significant difference in the administration of medications when patients were divided into groups according to TSH levels (all P > 0.05).

## Comparison of Clinical Outcomes According to TSH

The major adverse events during hospitalization and long-term all-cause mortality of the four groups are displayed in Figure 1. Group 4 had the highest incidence of malignant arrhythmias, followed by Group 1 (10.6% in Group 1, 8.7% in Group 2, 4.1% in Group 3 and 12.1% in Group 4, P = 0.002), while the incidence of heart failure, bleeding and in-hospital mortality did not differ (all P > 0.05). During a median 2.5 (1.6–3.6) years follow-up, 138 deaths occurred. Patients with TSH >3.5 mIU/L had the worst long-term outcomes, and 20 deaths (30.3%) were recorded (P < 0.001). The Kaplan–Meier curve in Figure 2A revealed that the

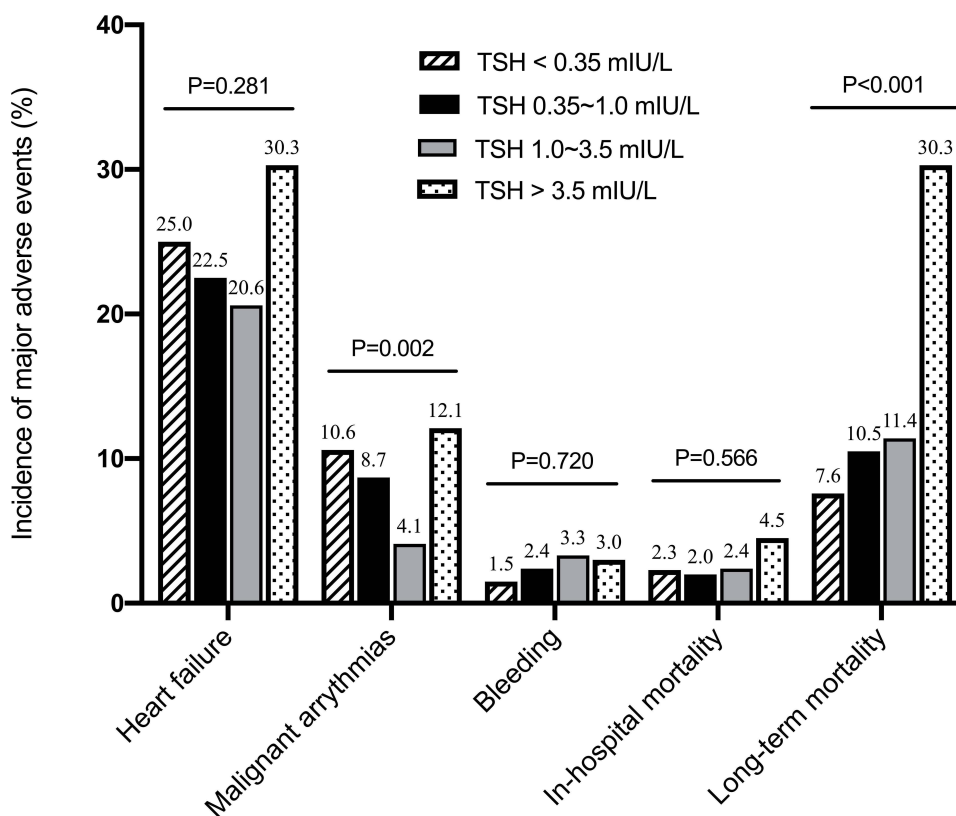
cumulative survival in Group 4 was remarkably lower (Log rank P < 0.001), whereas the cumulative survival was comparable in the other three groups (Log rank P = 0.365). When patients were divided into two groups of TSH ≤3.5 mIU/L and TSH >3.5 mIU/L, the cumulative survival of patients with TSH >3.5 mIU/L was significantly lower than that of TSH ≤ 3.5 mIU/L (Log rank P < 0.001), as shown in Figure 2B.

## Multivariable Cox Regression Models for Long-Term Mortality Prediction

Multiple multivariate Cox regression models were developed to demonstrate the impact of TSH value in different levels on the long-term all-cause mortality in STEMI, as listed in Table 5. It was observed that only TSH elevation beyond the normal range (>3.5 mIU/L) was an independent risk factor for long-term mortality in all four models. In addition, TSH elevation within the normal range (0.35–3.5 mIU/L) or TSH lower than the normal range (<0.35 mIU/L) was not associated with increased risk of death.

## Discussion

The major findings of our study were as follows. The serum TSH concentration was associated with long-term prognosis in STEMI patients treated by PCI. However, only TSH elevation beyond the normal range was associated with worse long-term prognosis, while TSH



**Figure 1** The major adverse events during hospitalization and long-term all-cause mortality of the four groups.

elevation within the normal range or TSH reduction did not alter long-term mortality of STEMI patients. An admission TSH level  $>3.5$  mIU/L was an independent risk factor for long-term mortality in STEMI patients treated by PCI.

## Overt Thyroid Dysfunctions and CAD

The associations between overt thyroid dysfunction and coronary artery disease (CAD) have been explored.<sup>3,4</sup> In a large cohort that consisted 59,021 hyperthyroid patients, Kim has demonstrated that hyperthyroidism was associated with increased risk of MI independent of cardiovascular risk factors.<sup>14</sup> Overt hypothyroidism was proved to accompany by marked atherosclerotic risk factors, including hypercholesterolemia, diastolic hypertension and increased carotid intima-media thickness.<sup>1,15</sup> In patients with acute MI, it was found that hypothyroidism was associated with more severe coronary atherosclerosis.<sup>16</sup>

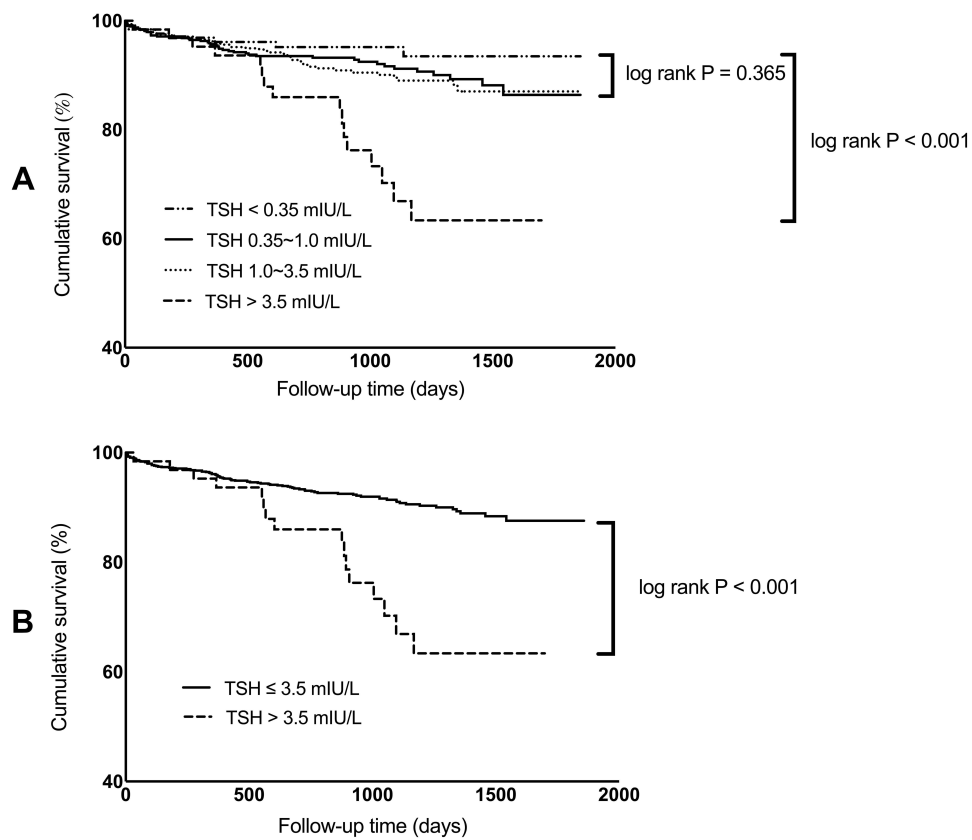
## Subclinical Hypothyroidism and CAD

The prognostic role of subclinical hypothyroidism, defined as elevated TSH but normal T3 and T4, in CAD has also been investigated recently. Seo reported TSH

$>5.5$  mIU/L to be an independent predictor for worse 3.5-years mortality in acute MI patients.<sup>7</sup> Soeiro also demonstrated that acute coronary syndrome patients with TSH  $>4$  mIU/L experienced more major adverse cardiac events during hospitalization.<sup>6</sup> However, in both studies, the prognostic impact of TSH reduction was not analyzed, and whether slightly elevated TSH but within the normal range constitutes a risk factor for worse clinical outcomes is also worth explored, since previous studies suggested that only mild fluctuation of TSH were associated with adverse outcomes in clinical practice.<sup>2</sup> Therefore, this study attempted to investigate this question by dividing patients into more groups according to TSH and obtained the findings above.

## Different TSH Levels and Cardiovascular Outcomes

A previous pooled study of 10 cohorts has found that decreased TSH is linked to increased risks of CAD mortality and incident AF, with risks being highest when TSH  $<0.10$  mIU/L.<sup>17</sup> Another population-based study showed that low serum TSH was an independent risk factor for



**Figure 2 (A)** The cumulative survival in Group 4 was remarkably lower (Log rank  $P < 0.001$ ), whereas the cumulative survival was comparable in the other three groups (Log rank  $P = 0.365$ ). **(B)** When patients were divided into two groups, the cumulative survival of patients with  $TSH > 3.5\text{ mIU/L}$  was significantly lower than that of  $TSH \leq 3.5\text{ mIU/L}$  (Log rank  $P < 0.001$ ).

increased plasma levels of fibrinogen, which in turn have been associated with elevated risk of cardiovascular events.<sup>18</sup> These results may lead to the conclusion that decreased TSH in general population was associated with increased mortality; however, it was found in our study

that a low admission TSH in the population of STEMI was not associated with worse long-term outcomes.

$TSH > 3.5\text{ mIU/L}$  was identified as an independent risk factor for long-term mortality after STEMI, which was in line with previous two studies.<sup>6,7</sup> A meta-analysis

**Table 5** Multivariate Cox Proportional Hazard Models of TSH in Different Levels for All-Cause Mortality in STEMI

TSH, mIU/L	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
<0.35	1.45 (0.74–2.85)	0.283	0.76 (0.39–1.50)	0.432	0.79 (0.40–1.56)	0.499	0.63 (0.32–1.24)	0.182	0.55 (0.24–1.23)	0.145
0.35–1.0	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
1.0–3.5	1.13 (0.77–1.64)	0.537	1.07 (0.73–1.56)	0.725	1.04 (0.70–1.52)	0.859	1.24 (0.84–1.83)	0.278	0.85 (0.53–1.35)	0.489
>3.5	3.03 (1.81–5.08)	<0.001	2.25 (1.33–3.80)	0.002	2.29 (1.36–3.89)	0.002	2.67 (1.57–4.55)	<0.001	2.06 (1.09–3.90)	0.027

**Notes:** Model 1: Adjusted for age and sex. Model 2: Model 1 + BMI, hypertension, diabetes, dyslipidemia, previous MI and previous stroke. Model 3: Model 2 + systolic blood pressure, heart rate, cardiac arrest and cardiogenic shock. Model 4: Model 3 + troponin I, LDL-C, creatinine and BNP >100pg/mL.  
**Abbreviations:** BMI, body mass index; MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol; BNP, brain natriuretic peptide.

involving 675 patients younger than 60 years reported that patients with elevated TSH had significantly worse parameters of left ventricular diastolic function compared with healthy controls.<sup>19</sup> Vascular impairments, such as increased systemic vascular resistance and altered vascular compliance have also been reported in patients with elevated TSH.<sup>20</sup> Another study that included 11 cohorts found that elevated TSH is associated with increased risk of CAD events and mortality, particularly in those with TSH >10 mIU/L.<sup>21</sup> These results, together with our findings, suggest that TSH elevation beyond the reference range is a solid marker for unfavorably outcome in acute MI.

The impact of elevation within the normal range of TSH in the setting of acute MI has not been investigated previously. In some recent studies, researchers found that participants with high-normal TSH levels were associated with less favorable lipid profiles.<sup>22,23</sup> Li revealed that TSH within the reference range is positively associated with the risk of CAD; individuals with 2.5–5.5 mIU/L of TSH had a 4-fold risk of CAD compared with those with 0.3–0.9 mIU/L.<sup>24</sup> In our study, it was firstly concluded that TSH elevation within the normal range did not portend prognosis in STEMI. We hypothesize that such slight TSH elevation after STEMI may only serve as a reaction to the state of stress and does not have pathological impact like chronic high-normal TSH status.

## Implications

There are some clinical implications of this study. First, TSH elevation correlates with patients' prognosis after STEMI. During future clinical practice, a TSH >3.5 mIU/L may add to current risk scores of STEMI. Second, the findings may guide further studies on the topic whether interventions are needed in patients whose TH are altered after acute MI. The replacement therapy of TH should adapt to patients' age, clinical presentation and co-existing morbidities.<sup>25</sup> It is noteworthy that the mean age of the subjects under this study was in the 60s, while TH replacement in these elderly deserves to be treated with caution. To date, two pilot studies have attempted to assess the effect of TH replacement therapy in MI patients.<sup>26,27</sup> Pingitore found that in patients with low T3 after STEMI, the administration of T3 was safe and able to improve left ventricular function.<sup>26</sup> However, Jabbar demonstrated that treatment with levothyroxine in patients with subclinical hypothyroidism and acute MI did not significantly improve LVEF after 52 weeks.<sup>27</sup> It should

be noted that both studies included very limited number of patients; therefore, more larger studies are needed to address this question.

## Limitations

Our study has several limitations. First, the TSH of a small proportion of patients were not acquired in our study. Most of such patients were likely to have unfavorable outcomes within a short interval before the TSH could be obtained. In these patients, the TSH level were supposed to be high. Thus, the association between TSH and the mortality may still be underestimated. Second, it was unknown whether the alteration of TSH had existed before STEMI or occurred after STEMI. A comparison of TSH before and after STEMI may be more meaningful. Also, considering the main objective of the study and the limited number of patients enrolled, further stratifications of patients by FT3 or FT4 were not achieved, otherwise the results would be more valuable. Finally, due to the single-center and retrospective design of the study, some selection and information bias could not be ruled out. The causal relationship between TSH and outcomes of patients could also not be drawn. More prospective randomized controlled trials are needed to assess the prognostic impact of different levels of TSH in STEMI patients.

## Conclusions

Only TSH elevation beyond the normal range was associated with worse long-term prognosis in STEMI patients, while high-normal TSH or reduced TSH did not alter long-term prognosis of STEMI patients. TSH >3.5 mIU/L was an independent risk factor for long-term mortality in STEMI patients treated by primary PCI.

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## Disclosure

All authors have no potential conflicts of interest to disclose.



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