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CLINICAL INVESTIGATIONS

Thyroid stimulating hormone elevation as a predictor of long-term mortality in patients with acute myocardial infarction

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Background: Hypothyroidism has been known to be associated with hyperlipidemia, endothelial dysfunction and atherosclerosis. Elevation of thyroid-stimulation hormone (TSH) is a gold standard to detect these conditions. However, no large studies have investigated the association between TSH elevation and long-term clinical outcomes in patients with acute myocardial infarction (AMI).

Hypothesis: Hypothyroidism is associated with higher mortality in patients with AMI.

Methods: A total of 4748 AMI patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents were consecutively enrolled. We analyzed 1977 patients whose thyroid function data available after the exclusion of hyperthyroidism and possible central hypothyroidism. Patients were divided into two groups; euthyroid group (n = 1846) with normal TSH and normal free thyroxine (FT4); hypothyroidism group (n = 131) with elevated TSH and normal or low FT4. The two groups were subsequently compared with their all-cause and cardiac mortalities.

Results: Median follow-up duration was 3.5 years. Hypothyroidism group were older, included in more females, and had higher incidences of atrial fibrillation, stroke, and renal dysfunction. Elevated TSH was associated with significantly higher all-cause mortality (26.0% vs 11.7%, $P < 0.0001$) and cardiac mortality (9.2% vs 4.6%, $P = 0.014$). The multivariate Cox proportional hazards model identified that TSH elevation was a significant predictor of all-cause mortality (adjusted hazard ratio 1.560, 95% confidence interval 1.017 to 2.392, $P = 0.041$).

Conclusions: Our data suggest that AMI patients with TSH elevation had worse clinical outcome. Moreover, TSH elevation was a predictor of all-cause mortality in patients with AMI.

KEYWORDS

acute myocardial infarction, hypothyroidism, thyroid stimulation hormone

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1 | INTRODUCTION

Alteration of thyroid function may adversely affect the heart and cardiovascular system, which has a direct effect on the cardiovascular disease and is caused by a complex relationship with risk factors for the cardiovascular disease.[1,2] Hyperthyroidism is associated with systolic hypertension, atrial fibrillation, and hypercoagulability, while hypothyroidism can lead to hyperlipidemia and vascular inflammation.[3–7]

In several clinical studies, subclinical hypothyroidism (SH), defined by elevated thyroid-stimulating hormone (TSH) levels and normal serum free thyroxine (FT4) levels, has also been associated with dyslipidemia, hypertension, impaired renal function, accelerated atherosclerosis and coronary artery disease.[8–10]

Although there is a study of thyroid hormonal change in the early period of acute myocardial infarction (AMI) and thyroid hormone has been recently reported to play an important role during cardiac remodeling after AMI,[11,12] research on the clinical outcome of AMI according to thyroid function is lacking. Accordingly, we sought to examine the association between hypothyroidism and clinical outcomes in patients who treated with drug-eluting stent (DES) implantation for AMI.

2 | METHODS

2.1 | Study population and COREA-AMI registry

The convergent REgistry of cAtholic and chonnAm university for AMI) (COREA-AMI) is a retrospective multicenter registry of demographic, clinical, and procedural data, and has long-term clinical outcome of all AMI patients underwent percutaneous coronary intervention (PCI) with the use of DES from nine major cardiovascular centers in Korea between January 2004 and December 2009. All participated hospitals are located throughout the country, and they all have performed high-volume PCI more than 500 cases per year. There was no industry involvement in the design, conduct, or analysis of the study. The study protocol was approved by institutional review boards at each participating institution. This registry was registered on ClinicalTrial.gov (study ID: NCT02385682).

For the present study, 2693 out of total 4748 registered patients were able to identify TSH and FT4 level. Of these, patients except hyperthyroidism, subclinical hyperthyroidism, and possible central hypothyroidism were divided into normal and elevated TSH groups. The two groups were subsequently compared with respect to their all-cause and cardiac mortalities.

2.2 | Assessment and definition of thyroid function

Blood samples were obtained at the time of their arrival in the hospital prior to PCI and were used to perform the standard battery of hematological and biochemical tests. The serum TSH and FT4 levels were measured by enzyme immunoassay using a commercially available kit (ADVIA Centaur XP (Seimens, Washington, DC, USA). The reference ranges of TSH and FT4 were 0.35 to 5.50 mIU/L and 0.93 to 1.70 ng/dL, respectively.

Overt hypothyroidism (OH) was defined as a documented history of OH in the patients' clinical record or elevated TSH (>5.50 mIU/L) and low FT4 (<0.93 ng/dL) levels. SH was defined as a documented history of SH in the patients' clinical record or elevated TSH and normal FT4 levels. Euthyroidism (ET) was defined as no documented history of hypothyroidism in the patients' clinical record and/or normal TSH and FT4 levels. In this study, hypothyroidism refers to the combination of SH and OH.

2.3 | Percutaneous coronary intervention procedure and medical treatment

Before the PCI, all patients received loading doses of dual-antiplatelet agents including aspirin with 250 to 500 mg and clopidogrel with 600 mg. Newer antiplatelet agents, such as prasugrel, ticagrelor were not available during the period in which this study was conducted. The procedure was performed through femoral or radial artery after administration of unfractionated heparin (100 U/kg). During the procedure, patients received unfractionated heparin to maintain an activated clotting time between 250 and 300 seconds. A glycoprotein IIb/IIIa inhibitor was administered at the discretion of a physician. The choice of stent, pre-stenting balloon dilatation, post-stenting adjuvant balloon inflation, and the use of glycoprotein IIb/IIIa inhibitors was at each physician's discretion. After the procedure, antiplatelet therapy consists of using 100 mg of aspirin and 75 mg of clopidogrel for 1 year and then using only one.

2.4 | Study definitions and clinical follow-up

The records of cardiovascular risk factors, past history, and laboratory findings were mainly dependent on patients' medical record. All-cause mortality was considered to be cardiac deaths after the exclusion of noncardiac mortality. Cardiac mortality was caused by myocardial infarction, heart failure, and arrhythmia including sudden cardiac death.

The clinical, angiographic, procedural or operative, and outcome data were collected in the dedicated PCI and surgical databases by independent research personnels. All the outcomes of interest were confirmed by source document and they were centrally adjudicated

by a local events committee of the Cardiovascular Center of Seoul St. Mary's Hospital, Seoul, Korea, whose members were unaware of patients' status. For validation of complete follow-up data, information on censored survival data was obtained through 31 July 2013 from a telephone interview with the corresponding patients and also from the National Population Registry of the Korea National Statistical Office with the use of unique personal identification number.

2.5 | Statistical analysis

Continuous variables were expressed as mean ± SD and compared with the Student's *t* test or the Mann-Whitney *U* test. Discrete variables were expressed as percentages and compared with the χ^2 test or Fisher's exact test. A multivariable Cox regression analysis (after confirming the appropriateness of the proportional hazards assumption) was carried out to identify independent predictors for all-cause and cardiac mortalities. Variables which were evaluated in the multivariable Cox regression analysis included using those with a statistical *P* value less than <0.05 in the baseline characteristics (Table 1) and also those without statistical significance, but with prognostic impact demonstrated in previous studies. The effect of each variable in developing models was assessed using the Wald test and described as hazard ratios (HR) with 95% confidence intervals (CI). The cumulative survival was estimated by the Kaplan-Meier survival curves, and compared using the log-rank tests. All analyses were two-tailed, with clinical significance defined as values of $P < 0.05$. All statistical analyses were done with Statistical Analysis Software package (SAS version 9.1, SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Characteristics of the study populations

The study flowchart was briefly presented in Figure 1. Among 4748 patients registered, we selected 1977 subjects could be analyzed serum TSH and FT4 levels. All patients were divided into two groups according to TSH level; a normal TSH group (n = 1846) and an elevated TSH group (n = 131) composed of SH (n = 106) and OH (n = 25).

Baseline demographic, clinical, laboratory, angiographic, and procedural characteristics between the two groups are shown in Tables 1. Elevated TSH group were older, and had more female gender, higher prevalence of AF (atrial fibrillation), and old stroke. These patients with elevated TSH were more likely to have lower estimated glomerular filtration rate (eGFR) and high-sensitivity C-reactive protein (hs-CRP), and higher presentation of non-ST-segment elevation myocardial infarction (NSTEMI). Lipid profiles, hemodynamic status, peak cardiac enzyme, and angiographic findings were not different between the two groups.

3.2 | Clinical outcomes for the study populations

The median duration of follow-up period was 1281 days. Complete follow-up data for clinical outcomes were obtained in 100% of the overall cohort for the duration of this study.

In the elevated TSH group, all-cause mortality occurred in a total of 34 (26.0%) while in the normal TSH group, 216 (11.7%) during long-term follow-up. The incidence of cardiac mortality and in-hospital mortality were significantly higher in patients with elevated TSH. Based on analysis of the study population, the elevated TSH showed significant association with all-cause mortality (unadjusted HR 2.44, 95% CI 1.70 to 3.50, $P < 0.001$) (Table 2). However, there were no differences between two groups in terms of nonfatal stroke, nonfatal myocardial infarction, and revascularization.

Because the study population was relatively small and difference of sample size between the two groups was large, multivariate Cox regression was performed in several models (Table 3). The elevated TSH group had a significant association with all-cause mortality in model 1 through 5, but not in model 6 with left ventricular ejection fraction (LVEF) added.

The Kaplan-Meier survival curves (Figure 2) showed that elevated TSH showed significantly worse outcomes than normal TSH as determined by the log-rank test; all-cause mortality and cardiac mortality (P = <0.001 and P = 0.014, respectively). This survival curve shows that the survival difference becomes even bigger depending on the time.

In Supporting Information Tables S1 and S2, the elevated TSH group was divided by SH and OH and compared with normal TSH. OH and SH had more incidence rates of all-cause mortality than ET. SH compared to ET had significant value only in model 1 when adjusted Cox regression was carried out. However, OH had significant values in all six models.

3.3 | Subgroup analysis

We calculated the unadjusted HR for all-cause mortality in various subgroups (Supporting InformationFigure S1). The incidence of the all-cause mortality was higher in the elevated TSH group than in the normal TSH group in all subgroups, although statistical significance was not found in patients with young age, NSTEMI presentation, eGFR ≥ 60 mL/min/1.73 m^2, and LVEF <40%. There were no significant interactions between the TSH level and all-cause mortality among the subgroups.

4 | DISCUSSION

The present study demonstrated that TSH elevation was associated with an increase in all-cause mortality compared to normal TSH in patients with AMI and may be a risk factor for all-cause mortality after adjusting various factors. In particular, OH is a significant independent prognostic factor for all-cause mortality even after all other confounding factors, including risk factors of coronary artery disease, laboratory finding, angiographic finding, and LVEF, have been taken into account. To our knowledge, this study is the first data which show the clinical impact of thyroid function in patients with AMI.

In a meta-analysis of 55 cohort studies, hypothyroidism is associated with higher risks of cardiac mortality and all-cause mortality compared with ET in both the general public and cardiac patients.[13] Recent study demonstrated that hypothyroidism was an independent

TABLE 1 Baseline patient demographic, clinical, angiographic, and procedural data according to TSH level

Variables	Normal TSH (n = 1846)	Elevated TSH (n = 131)	*P* value
Demographics			
Age (year)	61.4 ± 12.8	67.8 ± 11.1	<0.001
Age ≥ 65 years	934 (50.6)	100 (76.3)	<0.001
Female gender	471 (22.5)	59 (45.0)	<0.001
Risk factors			
BMI (kg/m^2)	24.3 ± 3.2	23.8 ± 3.2	0.101
Diabetes mellitus	628 (34.0)	45 (34.4)	0.938
Hypertension	935 (50.7)	74 (56.5)	0.196
Atrial fibrillation	71 (3.9)	17 (13.0)	<0.001
Current smoking	781 (42.3)	50 (38.2)	0.354
Family history of CAD	119 (6.4)	3 (2.3)	0.056
Prior history of stroke	117 (6.3)	16 (12.2)	0.009
Prior history of myocardial infarction	40 (3.8)	8 (6.1)	0.188
Prior history of PCI	60 (3.3)	7 (5.3)	0.206
Prior history of CABG	30 (1.6)	3 (2.3)	0.478
Hemodynamic status			
Initial systolic blood pressure (mmHg)	129.1 ± 30.5	126.5 ± 30.4	0.350
Initial diastolic blood pressure (mmHg)	78.4 ± 18.8	77.1 ± 19.1	0.470
Initial heart rate	76.6 ± 20.1	78.3 ± 21.2	0.337
Killip classes II-IV	342 (18.5)	27 (20.6)	0.558
Primary diagnosis at admission			0.001
STEMI	1175 (63.7)	65 (49.6)	
NSTEMI	671 (36.3)	66 (50.4)	
Discharge medication			
Statin	1708/1802 (94.8)	113/123 (91.9)	0.167
Beta-blocker	1301/1802 (72.2)	89/123 (72.4)	0.977
ACEI/ARB	1372/1802 (76.1)	98/123 (79.7)	0.372
Laboratory data			
LVEF (%)	53.3 ± 11.0	51.6 ± 11.4	0.103
LVEF <40%	191/1781 (10.7)	20/121 (16.5)	0.049
FT4	1.19 ± 0.20	1.08 ± 0.29	<0.001
TSH	1.28 ± 0.88	11.52 ± 33.42	0.001
Glucose (mg/dL)	170.1 ± 79.2	175.2 ± 81.5	0.511
Creatinine (mg/dL)	1.15 ± 0.88	1.19 ±0.66	0.468
eGFR, mL/min/1.73 m^2	76.6 ± 26.4	68.7 ± 27.8	0.001
eGFR <60 mL/min/1.73 m^2	400 (21.7)	53 (40.5)	<0.001
Hs-CRP (mg/L)	2.20 ± 4.04	1.72 ± 2.70	<0.001
CK-MB (ng/mL)	114.8 ± 144.4	96.0 ± 142.1	0.150
Troponin-I (ng/mL)	26.8 ± 42.7	21.1 ± 33.2	0.563
Total cholesterol (mg/dL)	180.9 ± 40.3	181.1 ± 32.8	0.960
Triglycerides (mg/dL)	123.5 ± 88.6	133.5 ± 123.0	0.239
HDL cholesterol (mg/dL)	41.6 ± 10.1	41.4 ± 11.6	0.848
LDL cholesterol (mg/dL)	114.8 ± 35.0	112.6 ± 37.0	0.529
Angiographic and procedural data			
Glycoprotein IIb-IIIa inhibitor	93 (5.0)	8 (6.1)	0.591
IABP	47 (2.5)	3 (2.3)	1.000
ECMO	2 (0.1)	0 (0)	1.000
Culprit vessel, n (%)			0.605
Left main	47 (2.5)	4 (3.1)	
Left anterior descending artery	894 (48.4)	68 (51.9)	
Left circumflex artery	291 (15.8)	20 (15.3)	

TABLE 1 (Continued)

Variables	Normal TSH (n = 1846)	Elevated TSH (n = 131)	*P* value
Right coronary artery	614 (33.3)	39 (29.8)	
Involved vessels, n (%)			0.114
One vessel	833 (45.1)	64 (48.9)	
Two vessels	593 (32.1)	31 (23.7)	
Three vessels	420 (22.8)	36 (27.5)	
Pre-PCI TIMI flow grade 0, n (%)	741 (43.2)	49 (42.2)	0.839
Post-PCI TIMI flow grade III, n (%)	1583 (88.8)	107 (84.3)	0.118

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK-MB, creatine kinase-MB fraction; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; FT4, free thyroxine; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; IABP, intra-aortic balloon pulsation; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI,ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TSH, thyroid-stimulating hormone.
Data are presented as the mean ± standard deviation or n (%).

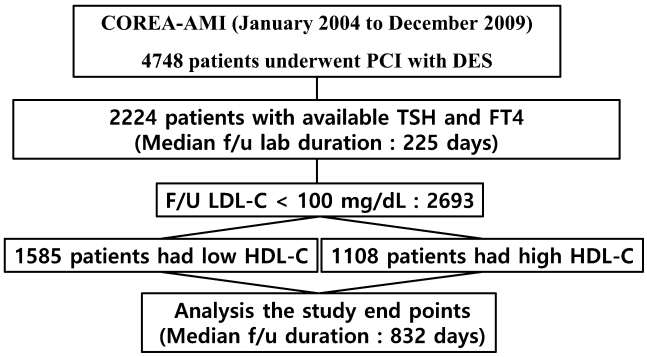

FIGURE 1 Study flow chart. COREA-AMI, Convergent REgistry of cAtholic and chonnAm university for acute myocardial infarction; DES, drug-eluting stent; FT4, free thyroxine; TSH, thyroid-stimulating hormone

predictor of cardiovascular and cerebral events in patients who received PCI; moreover, it highlighted that adequate thyroid replacement treatment could prevent cardiovascular events.[14] Another study analyzed that SH is associated with worse clinical events including cardiac mortality and repeat revascularization among the majority of patients with acute coronary syndrome who receive PCI.[15] In the present study, OH was significantly associated with mortality and SH was numerically associated with mortality even in AMI patients alike other studies. And mortality was more frequently occurred in OH compared with SH.

There is a small study that reported that improvements in thyroid hormone were associated with improved cardiac function after AMI. In this study, the thyroid hormone tends to decrease in acute phase of AMI.[12] This is thought to be an adaptation to acute stress, and thyroid hormone is associated with cardiac contractile function, which

TABLE 2 Clinical events in patients with normal thyroid-stimulating hormone compared with elevated thyroid-stimulating hormone

	Normal TSH (n = 1846)	Elevated TSH (n = 131)	Unadjusted HR (95% CI)	*P* value
All-cause mortality	216 (11.7)	34 (26.0)	2.44 (1.70-3.50)	<0.001
Cardiac mortality	84 (4.6)	12 (9.2)	2.10 (1.15-3.85)	0.016
In-hospital mortality	44 (2.4)	8 (6.1)	2.63 (1.24-5.58)	0.012
Nonfatal stroke	38 (2.1)	5 (3.8)	1.98 (0.78-5.03)	0.151
Nonfatal myocardial infarction	35 (1.9)	1 (0.8)	0.43 (0.06-3.13)	0.404
Revascularization	259 (14.0)	15 (11.5)	0.85(0.51-1.44)	0.549

CI, confidence interval; HR , hazard ratio; TSH, thyroid-stimulating hormone.

TABLE 3 Multivariate Cox proportional hazard models of elevated thyroid-stimulating hormone for all-cause mortality

	HR (95% CI)	*P* value
Model 1: Age, gender	1.856 (1.289-2.672)	0.001
Model 2: Model 1 + AF, DM, HTN, smoking, BMI, STEMI	1.681 (1.140-2.479)	0.009
Model 3: model 2 + Hs-CRP, CK-MB	1.795 (1.172-2.748)	0.007
Model 4: model 3 + eGFR	1.560 (1.017-2.392)	0.041
Model 5: model 3 + angiographic findings[a]	1.779 (1.157-2.735)	0.009
Model 6: Model 3 + LVEF	1.358 (0.845-2.182)	0.206

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CK-MB, creatine kinase-MB fraction; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; HTN, hypertension; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; TSH, thyroid-stimulating hormone.
[a] Multivessel disease, post-PCI TIMI flow grade, and LAD culprit vessel.

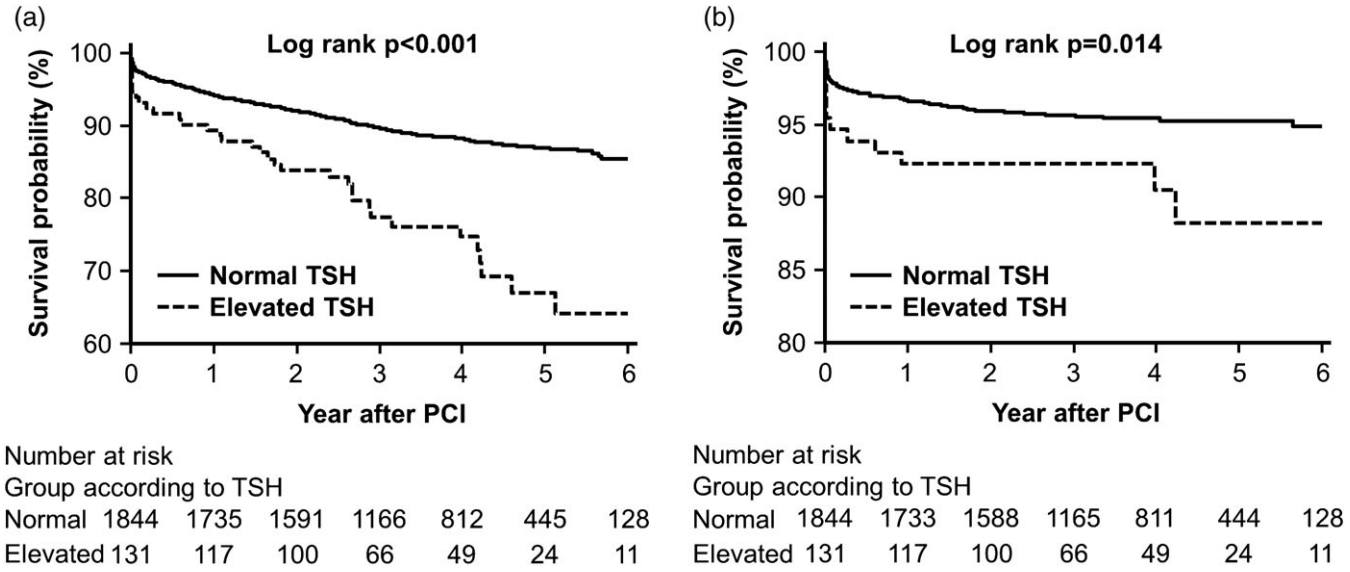

FIGURE 2 Kaplan-Meier curves. A, All-cause mortality. B, Cardiac mortality

suggests that thyroid hormone improvement may be associated with improved cardiac function. In animal models, hypothyroidism induced further increases in cardiac remodeling and replacement of thyroid hormone after AMI was associated with improved cardiac function.[16–20] The increase in carotid intima-media thickness, a surrogate cardiovascular marker, is associated with hypothyroidism, and the endothelial function assessed by brachial artery flow-mediated dilatation has improved after the improvement of thyroid hormone, accounting for the increase in cardiovascular disease due to hypothyroidism.[21,22] Changes in coagulation and fibrinolytic cascades may also be associated with stroke because of hypothyroidism.[23] Because hypothyroidism is associated with an increase in atherosclerosis, cardiovascular events are considered to be more frequent. However, in this study, elevated TSH was not related with AMI, revascularization and stoke. The cause of these results may be that many patients with SH were included in the present study. Nevertheless, elevated TSH was related with increased mortality in this study. To clarify the relationship between elevated TSH and major adverse cardiovascular and cerebral events, the bigger trial is needed.

Subclinical hypothyroidism, unlike OH, has conflicting results in the occurrence of CHD events, mortality, and HF, and there is a debate in relation to cardiovascular events.[9,24–26] In the present study, SH, like OH, had more mortality than ET. But SH has lower predictive power than OH after adjustment of other variables. However, there are limitations to this result because of the small number of SH.

Our study has some limitations. First, our findings are subject to selection bias and confounding factors because of its nonrandomized, observational design. Here is a lot of difference between the numbers of participants in both groups. However, to overcome this limitation, we performed rigorous adjustments of our data to reduce the impact of selection bias using six multivariate Cox proportion hazards regression models. Second, we measured the thyroid hormone level only once before the index PCI without tracking follow-up thyroid function test and information of treatment of impaired thyroid function, so there was no correlation between changes in thyroid function and clinical events. Detailed follow-up thyroid function may be helpful in further interpreting our findings. Third, investigation of various factors affecting thyroid function including diet and alcohol use was not sufficient. Finally, we could not identify other noncardiac causes of mortality, such as malignancy or infection which may be competing risk against cardiac mortality and should also be considered.

5 | CONCLUSIONS

Thyroid-stimulation hormone elevation was a predictor of all-cause mortality in patients with AMI. Thyroid function in patients with AMI is associated with prognosis and should be checked.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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