Prognostic value of free triiodothyronine and N-terminal pro-B-type natriuretic peptide for patients with acute myocardial infarction undergoing percutaneous coronary intervention: a prospective cohort study

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Background: Altered thyroid function and increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) are prognostic factors in acute myocardial infarction (AMI). The study aims to investigate whether free triiodothyronine (fT3) and NT-proBNP are prognostic factors for long-term outcomes in patients with AMI undergoing percutaneous coronary intervention (PCI).

Methods: This was an observational, prospective, single-center study of consecutive patients enrolled at Fuwai Hospital between January, 2013 and December, 2013. The patients were divided into two groups according to fT3 levels: low fT3 (<2.5 pg/mL) and normal fT3 (2.50–4.09 pg/mL). The primary outcome of this study was the incidence of major adverse cardiovascular events (MACEs).

Results: There were 252 patients with low fT3 and 561 patients with normal fT3. After >2 years of follow-up, patients with low fT3 levels had higher rates of MACEs than those with normal fT3 (27.0% *vs.* 7.8%, P<0.001). Univariable Cox proportional hazards regression analyses showed that NT-proBNP >802.7 pg/mL [hazard ratio (HR) =5.063, 95% confidence interval (CI): 3.176–8.071, P<0.001] and fT3 <2.5 pg/mL (HR =3.867, 95% CI: 2.646–5.651, P<0.001) were the strongest predictors of MACEs. After adjustment for traditional risk predictors, fT3 <2.5 pg/mL (HR =2.570, 95% CI: 1.653–3.993, P<0.001) was one of the most important independent predictors of MACEs. Patients with NT-proBNP ≤802.7 pg/mL and fT3 ≥2.5 pg/mL had the best prognosis, while patients with NT-proBNP >802.7 pg/mL and fT3 <2.5 pg/mL had the worst outcomes (P<0.001).

Conclusions: Low fT3 is a strong predictor of poor prognosis after AMI. The fT3+NT-proBNP combination might be a valuable predictor of the long-term outcomes of PCI after AMI.

Keywords: Low T3 syndrome; N-terminal pro-B-type natriuretic peptide (NT-proBNP); acute myocardial infarction (AMI); percutaneous coronary intervention (PCI); prognosis

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Introduction

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide (1). The pathophysiology of AMI involves the rupture of an atherosclerotic plaque, coronary artery thrombosis, myocardial ischemia, hypoxia and necrosis (1-3). The outcome of AMI is highly variable, ranging from recovery to chronic heart failure (HF) or even sudden cardiac death (4-6). Many factors affect the prognosis of patients with AMI, including lesion complexity, cardiac energy metabolism, and treatment administered (1,3-6). Therefore, it is important to identify biomarkers that can accurately predict the prognosis of patients with AMI.

Thyroid hormones (THs) such as triiodothyronine (T3) play important roles in body metabolism and homeostasis, including cardiovascular homeostasis. Thyroid dysfunction is a strong predictor of mortality in patients with heart disease (7-10). TH metabolism changes after AMI, resulting in low serum T3 levels despite normal thyroid-stimulating hormone (TSH) and thyroxine (T4) levels (11). Although free T3 (fT3) level is a strong prognostic marker in patients with chronic HF (12), data are limited regarding its role as a predictor of outcomes in patients with AMI.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a well-established marker used to evaluate HF severity and progression (13). NT-proBNP is an important biomarker of myocardial cell necrosis and a strong predictor of morbidity and mortality (14). Increased NT-pro-BNP levels are associated with high cardiac-related mortality in patients with HF (15). NT-proBNP is also a good prognostic indicator in patients with AMI (16,17).

The literature suggests an inverse relationship between serum BNP and serum T3 levels in patients without hyperthyroidism (18). We hypothesized that low T3 status could serve as a prognostic indicator in AMI since there is a negative relationship between fT3 and NT-pro-BNP (18). Therefore, the aims of this study were to investigate the association between low fT3 levels and prognosis and the relationship between fT3 and NT-pro-BNP levels in patients with AMI. We present the following study in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5541).

Methods

Study design and participants

This observational, prospective, single-center study included consecutive patients with AMI who underwent percutaneous coronary intervention (PCI) at Fuwai Hospital (National Center of Cardiovascular Diseases, Beijing, China) between January 2013 and December 2013. AMI was diagnosed according to the guidelines of the ACC/AHA for the management of AMI (19), which include typical chest pain, ST-segment elevation or new left bundle branch block, and troponin I (TnI) level elevation.

All patients underwent coronary angiography to confirm the diagnosis and evaluate the severity of the coronary artery disease. Stent selection was left to the treating physician's discretion. If not already taking long-term aspirin and P2Y12 inhibitors, the patients received 300 mg of aspirin and clopidogrel (loading dose of 300 mg) or ticagrelor (loading dose of 180 mg), orally, at least 24 h before the procedure. After PCI, the patients were prescribed 100 mg of aspirin once daily indefinitely, and either 75 mg of clopidogrel once daily or 90 mg of ticagrelor twice daily for at least 1 year.

Patients without available data for thyroid function tests, with overt primary hypothyroidism [thyroid stimulating hormone (TSH) level >18 μIU/mL and free T4 (fT4) level <0.80 ng/dL], with primary hyperthyroidism (fT3 level >4.09 pg/mL or fT4 level >1.88 ng/mL, with TSH level <0.02 μIU/mL), or who had been treated before admission with drugs that might affect thyroid function (including amiodarone or thyroid medication) were excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Fuwai Hospital (approval number 2013-449). All patients provided written informed consent.

Biochemistry

Blood samples were obtained in the morning after an overnight fast during the first 24 h after admission. Blood samples were drawn into tubes containing ethylenediaminetetraacetic acid and sent to the laboratory for biochemical tests. Serum fT3, fT4, total T3 (TT3), total T4 (TT4), and TSH were measured using radioimmunoassay methods (Immulite 2000; Siemens, Germany) in the Nuclear Medicine Department of Fuwai Hospital. The reference ranges used by our laboratory were as follows: TT3, 0.65–1.91 ng/mL; TT4, 4.29–12.47 μg/mL; fT3, 1.79–4.09 pg/mL; fT4, 0.80–1.88 ng/dL;and TSH, 0.55–4.78 μIU/mL.

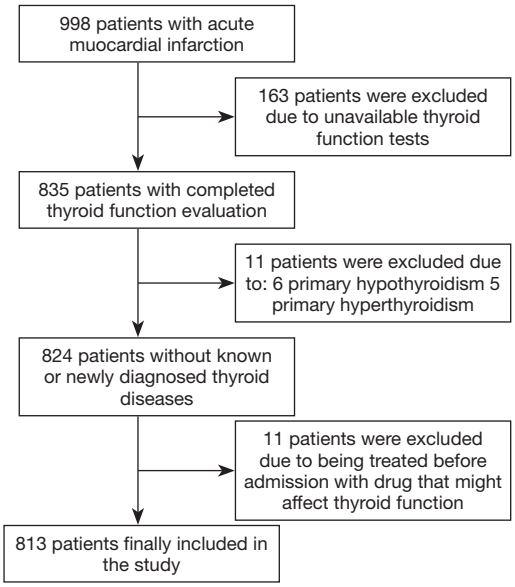

Figure 1 Flowchart of patient enrollment.

The patients were divided into a low fT3 group (fT3 <2.5 pg/mL, n=252) and a normal fT3 group (fT3 ≥2.5 pg/mL, n=561) (18). NT-proBNP levels were determined using ELISA kits (Biomedica, Austria), and the assay range was 0–6,000 pg/mL. The reference ranges used for the other biochemical factors were as follows: white blood cell count (WBC), (3.5–9.5)×10^9/L; C-reactive protein (CRP), 0–8 mg/L; creatinine, 44–133 μmol/L; total cholesterol, 3.64–5.98 mmol/L; low-density lipoprotein (LDL), <3.37 mmol/L; and TnI, 0–0.034 ng/mL.

Follow-up and outcomes

All patients were evaluated either during clinical visits or by telephone at 6 and 24 months after PCI. Patients were advised to return for coronary angiography if clinically indicated by symptoms or documentation of myocardial ischemia. Patients who reported any ischemic or bleeding events were required to submit the related source documents.

The primary outcome of this study was the incidence of major adverse cardiovascular events (MACEs) defined as: (I) the occurrence of cardiac death; (II) re-hospitalization for HF; or (III) nonfatal myocardial infarction or severe angina requiring coronary revascularization (20).

Sudden unexpected death was classified as cardiac death when it occurred outside the hospital and was not followed by autopsy. Death caused by accidents was excluded. All outcomes were adjudicated centrally by two independent cardiologists, and any disagreement was resolved by consensus.

Statistical analysis

Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Continuous variables are reported as the mean ± standard deviation (SD) and were compared between groups using Student's *t*-test. Categorical variables are presented as numbers and percentages and were compared between groups using the chi-squared test. Univariable and multivariable Cox proportional hazards analyses were used to identify variables associated with MACEs. Receiver operating characteristic (ROC) curves were generated to assess the utility of fT3 and NT-pro-BNP in the prediction of MACEs. Kaplan-Meier curves were used to evaluate the occurrence of MACEs, and MACE-free survival was compared between groups using the log-rank test. Hazard ratios (HRs) were also calculated. All tests (except the chi-squared test) were two-sided, and P values <0.05 were considered statistically significant. All analyses were performed with SPSS 18.0 (IBM Corp., Armonk, NY, USA) and Prism version 8 (GraphPad Software Inc., San Diego, CA, USA).

Results

Characteristics of the participants

Among 998 patients with AMI who underwent PCI during the study period, 179 patients were excluded because thyroid function test results were not available, 11 patients were excluded because they had overt primary hypothyroidism or hyperthyroidism, and 11 patients were excluded because they were treated before admission with drugs that might affect thyroid function. Therefore, 813 participants aged 57±11 years were included in the final analysis (*Figure 1*).

The 813 participants were divided into a low fT3 group (n=252) and a normal fT3 group (n=561). The demographic characteristics, medical history, Killip-Kimball class, laboratory parameters, medications, and admission characteristics are shown in *Table 1*. Patients in the low fT3 group had a significantly lower diastolic blood pressure (74±12 *vs.* 77±11 mmHg, P=0.006) and a significantly higher heart rate (74±14 *vs.* 71±11 beats/minute, P=0.001), rate of sustained ventricular arrhythmias (7.9% *vs.* 4.1%, P=0.028), WBC (9.8±3.6 *vs.* 7.9±2.8 ×10^9/L, P<0.001), CRP

Table 1 Clinical characteristics of the patients with acute myocardial infarction

Characteristic	Total (n=813)	Low fT3 group (n=252, 31%)	Normal fT3 group (n=561, 69%)	P
Age, years, mean ± SD	57±11	60±11	56±11	<0.001
Female, n (%)	168 (20.7)	84 (33.3)	84 (15.0)	<0.001
Body mass index, kg/m^2, mean ± SD	26.1±3.2	26.2±3.2	26.1±3.1	0.744
History of hypertension, n (%)	518 (63.7)	170 (67.5)	348 (62.0)	0.156
History of diabetes, n (%)	218 (26.8)	78 (31.0)	140 (25.0)	0.087
History of smoking, n (%)	420 (51.7)	105 (41.7)	315 (56.1)	<0.001
Vital signs at admission (mean ± SD)				
Systolic blood pressure (mmHg)	125±17	126±17	124±17	0.308
Diastolic blood pressure (mmHg)	76±12	74±12	77±11	0.006
Heart rate (beats/minute)	72±12	74±14	71±11	0.001
Killip class on admission, n (%)				<0.001
I	695 (85.5)	210 (83.3)	485 (86.5)	
II	102 (12.5)	31 (12.3)	71 (12.7)	
III	8 (1.0)	3 (1.2)	5 (0.9)	
IV	8 (1.0)	8 (3.2)	0	
Arrhythmia, n (%)				
Supraventricular tachycardia	30 (3.7)	13 (5.2)	17 (3.0)	0.159
Sustained ventricular tachycardia/fibrillation	43 (5.3)	20 (7.9)	23 (4.1)	0.028
Complete atrioventricular block	18 (2.2)	6 (2.4)	12 (2.1)	0.801
Bundle-branch block	18 (2.2)	9 (3.6)	9 (1.6)	0.118
Laboratory tests at admission				
Total triiodothyronine, ng/mL, mean ± SD	1.0±0.3	0.8±0.2	1.1±0.2	<0.001
Total thyroxine, μg/L, mean ± SD	8.5±2.1	7.5±2.2	8.9±1.9	<0.001
Free triiodothyronine, pg/mL, mean ± SD	2.8±0.4	2.3±0.2	3.0±0.3	<0.001
Free thyroxine, ng/mL, mean ± SD	1.2±0.2	1.1±0.2	1.2±0.2	<0.001
Thyroid-stimulating hormone, μIU/mL, mean ± SD	2.1±1.7	2.4±2.1	2.0±1.6	0.006
White blood cell count, 10^9/L, mean ± SD	8.5±3.2	9.8±3.6	7.9±2.8	<0.001
C-reactive protein, mg/L, mean ± SD	13.4±24.0	24.8±35.3	8.0±13.2	<0.001
Creatinine, μmol/L, mean ± SD	78.7±17.9	82.5±22.9	76.9±14.8	<0.001
Total cholesterol, mmol/L, mean ± SD	4.4±1.1	4.6±1.1	4.3±1.1	<0.001
Low-density lipoprotein, mmol/L, mean ± SD	2.7±1.0	2.8±1.0	2.6±1.0	0.007
Troponin I, ng/mL, mean ± SD	2.1±5.3	3.0±6.5	1.7±4.7	0.004
NT-proBNP, pg/mL, mean ± SD	955.1±742.3	1249.0±882.4	823.1±627.4	<0.001

Table 1 (*continued*)

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Characteristic	Total (n=813)	Low fT3 group (n=252, 31%)	Normal fT3 group (n=561, 69%)	P
Echocardiography at admission				
LVEDD, mm, mean ± SD	48.2±7.5	48.3±6.4	48.2±7.9	0.919
Left ventricular ejection fraction, %, mean ± SD	59.0±8.4	56.5±8.4	60.2±8.1	<0.001
Medications, n (%)				
Aspirin	808 (99.4)	249 (98.8)	559 (99.6)	0.176
Clopidogrel	794 (97.7)	244 (96.8)	550 (98.0)	0.318
β-blocker	717 (88.2)	215 (85.3)	502 (89.5)	0.100
ACE-I or ARB	562 (69.1)	186 (73.8)	376 (67.0)	0.059
Diuretic	163 (20.0)	61 (24.2)	102 (18.2)	0.058
Aldosterone antagonist	105 (12.9)	40 (15.9)	65 (11.6)	0.113
Calcium channel blocker	232 (28.5)	62 (24.6)	170 (30.3)	0.111
Digoxin	2 (0.2)	2 (0.8)	0	>0.999
Statin	765 (94.1)	235 (93.3)	530 (94.5)	0.518

ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker; fT3, free triiodothyronine; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(24.8±35.3 *vs.* 8.0±13.2 mg/L, P<0.001), serum creatinine (82.5±22.9 *vs.* 76.3±14.8 μmol/L, P<0.001), and low-density lipoprotein (2.8±1.0 *vs.* 2.6±1.0 mmol/L, P=0.007) than patients in the normal fT3 group. Thirty-two of the 813 patients (3.9%) were admitted to hospital for recurrence of MI, but there was no significant difference in the proportion of patients with recurrent MI between the low T3 group (9 patients, 3.6%) and normal fT3 group (23 patients, 4.1%). There were no obvious differences between the two groups in the history of hypertension or diabetes or the medical treatment received.

Serum levels of TnI and NT-ProBNP are used as indices of myocardial damage and as predictors of prognosis in patients with AMI (21). The levels of TnI and NT-ProBNP were higher in the low fT3 group than in the normal fT3 group (TnI: 3.0±6.5 *vs.* 1.7±4.7 ng/mL, P=0.004; NT-ProBNP: 1,249.0±882.4 *vs.* 823.1±627.4 pg/mL, P<0.001). Left ventricular ejection fraction (LVEF) was significantly lower in the low fT3 group than in the normal fT3 group (56.5%±8.4% *vs.* 60.2%±8.1%, P<0.001).

Severity of coronary artery disease

A single trained investigator analyzed both the baseline and follow-up coronary angiograms using quantitative coronary angiography to assess the severity of the impairment of coronary artery flow. The low fT3 group had a higher percentage of patients with three diseased vessels (53.2% *vs.* 44.7%) and a lower percentage of patients with a single diseased vessel (17.1% *vs.* 24.4%) than the normal fT3 group, but there was no significant difference in the percentage of patients with two diseased vessels between groups. The low fT3 group showed a trend toward a higher rate of left main coronary artery lesions and a trend toward a lower baseline TIMI flow grade (*Table 2*).

Correlation between fT3 and NT-proBNP levels

NT-proBNP levels were negatively correlated with fT3 levels (r=–0.311, P<0.0001, Figure S1).

ROC curve analysis of the utilities of fT3 and NT-proBNP levels in the prediction of MACEs

ROC curve analyses were used to compare the utility of fT3 level in the prediction of MACEs with that of NT-proBNP, which is an established predictor of MACEs (*Figure 2*). The sensitivity and specificity of fT3 in the

Table 2 Severity of coronary disease

Variable	Low fT3 group (n=252, 31%)	Normal fT3 group (n=561, 69%)	P
Diseased vessels, n (%)			0.031
1 vessel	43 (17.1)	137 (24.4)	
2 vessels	75 (29.8)	173 (30.8)	
≥3 vessels	134 (53.2)	251 (44.7)	
PCI lesions, n (%)			
Left main coronary artery	19 (7.5)	23 (4.1)	0.058
Left anterior descending artery	188 (74.6)	432 (77.0)	0.476
Left circumflex artery	137 (54.4)	277 (49.4)	0.198
Right coronary artery	158 (62.7)	316 (56.3)	0.091
Baseline TIMI flow, n (%)			0.032
0	173 (68.7)	326 (58.1)	
1	26 (10.3)	87 (15.5)	
2	27 (10.7)	82 (14.6)	
3	26 (10.3)	66 (11.8)	

fT3, free triiodothyronine; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

prediction of long-term MACEs in patients with AMI after PCI were 60.7% and 73.8%, respectively [area under the curve (AUC) =0.707, optimal cut-off value =2.49 pg/mL]. The sensitivity and specificity of NT-proBNP in the prediction of MACEs were 80.4% and 58.2%, respectively (AUC =0.761, optimal cut-off value =802.7 pg/mL). The sensitivity and specificity of the combination of fT3 and NT-proBNP in the prediction of MACEs were 76.8% and 63.2%, respectively (AUC =0.778).

Associations of fT3 level and NT-proBNP level with MACEs

After a mean follow-up of 2.4±0.4 years, there were 16 deaths in the low fT3 group and nine in the normal fT3 group (6.3% *vs.* 1.6%, P=0.001). During the first 6 months, 33 patients in the low fT3 group and 14 patients in the normal fT3 group experienced MACE (13.1% *vs.* 2.5%, P<0.001). During the follow-up period, 68 patients (27.0%) in the low fT3 group experienced MACEs (5 patients with cardiac death, 14 patients with myocardial infarction, 10 patients with re-hospitalization for HF, and 39 patients with coronary revascularization), and 44 patients (7.8%) in the normal fT3 group experienced MACEs (one patient with cardiac death, five patients with myocardial infarction, two patients with re-hospitalizations for HF, and 36 patients with coronary revascularization). Notably, the incidence of MACEs was significantly higher in the low fT3 group than in the normal fT3 group (27.0% *vs.* 7.8%, P<0.001; *Table 3*).

Univariable Cox regression analyses revealed that NT-proBNP >802.7 pg/mL (HR =5.063, 95% CI: 3.176–8.071, P<0.001) and fT3 <2.5 pg/mL (HR =3.867, 95% CI: 2.646–5.651, P<0.001) were the strongest predictors of MACEs followed by WBC at admission (HR =1.083, 95% CI: 1.032–1.137, P=0.001), serum creatinine (HR =1.015, 95% CI: 1.006–1.025, P=0.001), and age (HR =1.025, 95% CI: 1.009–1.042, P=0.003). In the multivariable analysis, fT3 <2.5 pg/mL (HR =2.570, 95% CI: 1.653–3.993, P<0.001) was also one of the most important independent predictors of MACEs. Therefore, low fT3 remained a strong independent predictor of MACEs in patients with AMI even after adjustment for traditional risk factors for MACEs including NT-proBNP >802.7 pg/mL, age, history of smoking, serum creatinine, and TnI (*Table 4*).

Prognostic value of fT3 and NT-pro-BNP for MACE-free survival

The long-term and 6-month Kaplan-Meier curves for MACE-free survival in patients with AMI who underwent

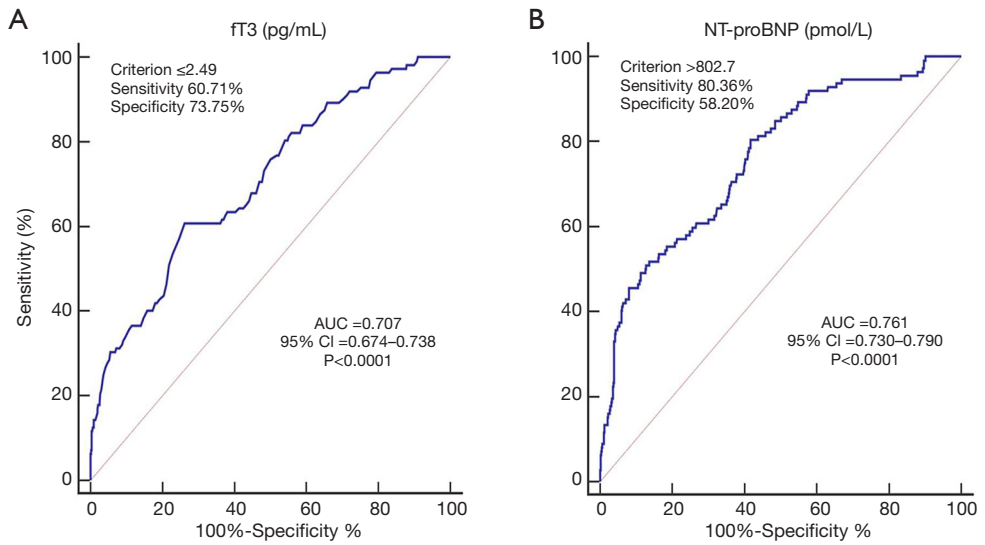

Figure 2 ROC curve analysis of the ability of fT3 (A) and NT-proBNP (B) to predict MACE in patients who have undergone PCI after AMI. The AUC, sensitivity and specificity values for fT3 were 0.707, 60.71% and 73.75%, respectively. The AUC, sensitivity and specificity values for NT-proBNP were 0.761, 80.36% and 58.20%, respectively. AMI, acute myocardial infarction; AUC, area under the curve; fT3, free triiodothyronine; MACE, major adverse cardiac event; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; ROC, receiver operating characteristic.

Table 3 Comparison of clinical outcomes between the low fT3 group and normal fT3 group

Variable	Low fT3 group (n=252, 31%)	Normal fT3 group (n=561, 69%)	P
6-month follow-up, n (%)			
Death	5 (2.0)	2 (0.4)	0.033
MACE	33 (13.1)	14 (2.5)	<0.001
Long-term follow-up, n (%)			
Death	16 (6.3)	9 (1.6)	0.001
MACE	68 (27.0)	44 (7.8)	<0.001
Cardiac death	5 (2.0)	1 (0.2)	0.009
Myocardial infarction	14 (5.6)	5 (0.9)	<0.001
Re-hospitalization for heart failure	10 (4.0)	2 (0.4)	<0.001
Revascularization with PCI	35 (13.9)	35 (6.2)	<0.001
Revascularization with CABG	4 (1.6)	1 (0.2)	0.012

CABG, coronary artery bypass grafting; fT3, free triiodothyronine; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.

PCI are shown in *Figure 3*. Differences in MACE-free survival between groups were evident during the first 6 months of follow-up: MACE-free survival rate at 6 months was lower in the low fT3 group than in the normal fT3 group (86.9% *vs.* 97.5%, log-rank P<0.001) and lower in the high NT-proBNP group than in the low NT-proBNP group (90.3% *vs.* 97.7%, log-rank P<0.001). Differences in MACE-free survival were apparent during the long-term follow-up: MACE-free survival was lower in the low fT3 group than in the normal fT3 group (73.0%

Table 4 Cox regression analysis of the factors associated with major adverse cardiac events

Variable	HR	95% CI	P
Univariable analyses			
Age, years	1.025	1.009–1.042	0.003
Female	0.790	0.513–1.219	0.287
History of smoking	0.684	0.468–0.999	0.049
Diastolic blood pressure	0.991	0.975–1.008	0.313
Heart rate	1.013	0.998–1.028	0.08
NT-proBNP >802.7 pg/mL	5.063	3.176–8.071	<0.001
Creatinine, μmol/L	1.015	1.006–1.025	0.001
Low-density lipoprotein, mmol/L	1.091	0.908–1.310	0.352
Troponin I, ng/mL	1.027	1.001–1.053	0.038
White blood cell count, 10^9/L	1.083	1.032–1.137	0.001
fT3 <2.5 pg/mL	3.867	2.646–5.651	<0.001
Free thyroxine, ng/mL	0.249	0.082–754	0.014
Thyroid-stimulating hormone, mIU/L	1.095	1.010–1.188	0.028
Multivariable analysis			
Age, years	1.015	0.996–1.034	0.115
History of smoking	0.488	0.322–0.740	0.001
White blood cell count, 10^9/L	1.025	0.970–1.083	0.375
Troponin I, ng/mL	1.009	0.980–1.038	0.555
Creatinine, μmol/L	1.004	0.994–1.015	0.383
Free thyroxine, ng/L	0.720	0.230–2.251	0.572
Thyroid-stimulating hormone, mIU/L	1.078	0.991–1.173	0.082
NT-proBNP >802.7 pg/mL	3.592	2.203–5.858	<0.001
fT3 <2.5 pg/mL	2.570	1.653–3.993	<0.001

The variables included in the multivariable Cox model were selected by a stepwise method based on factors that were significant in the univariable analyses and traditional risk predictors for prognosis reported by previous studies. CI, confidence interval; fT3, free triiodothyronine; HR, hazard ratio; NT-proBNP, N-terminal pro-B-Type natriuretic peptide.

vs. 92.2%, log-rank P<0.001) and in the high NT-proBNP group than in the low NT-proBNP group (76.5% *vs.* 94.9%, log-rank P<0.001).

Figure 4 shows MACE-free survival curves for patients who underwent PCI after AMI based on different combinations of fT3 status and NT-proBNP status. Patients with NT-proBNP ≤802.7 pg/mL and fT3 ≥2.5 pg/mL had a significantly better prognosis than patients with NT-proBNP ≤802.7 pg/mL and fT3 <2.5 pg/mL (log-rank P<0.001). Patients with NT-proBNP >802.7 pg/mL had worse outcomes than patients with NT-proBNP ≤802.7pg/mL. Patients with NT-proBNP >802.7 pg/mL and fT3 <2.5 pg/mL had the worst outcomes (log-rank P<0.001).

Conclusions

Altered thyroid function and increased NT-proBNP are prognostic factors in patients with AMI (7-10,13). The present study aimed to investigate the values of fT3 and NT-proBNP as prognostic factors for long-term outcomes in patients with AMI undergoing PCI. We found that fT3

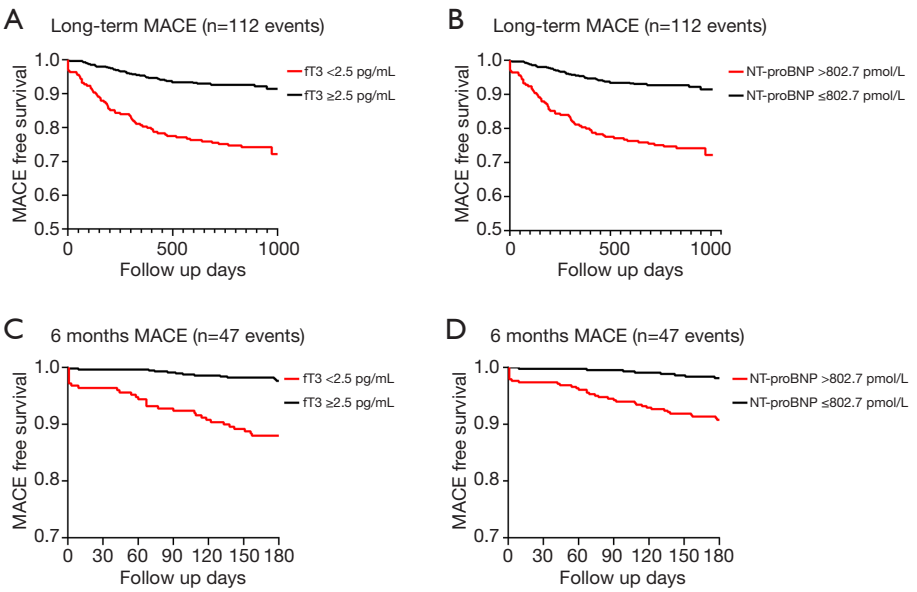

Figure 3 Long-term (A and B) and 6-month (C and D) Kaplan-Meier MACE-free survival curves for patients who underwent PCI after AMI. (A and C) fT3 group. (B and D) high NT-proBNP group. The cut-off values are labeled. AMI, acute myocardial infarctions; fT3, free triiodothyronine; MACE, major adverse cardiac event; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention.

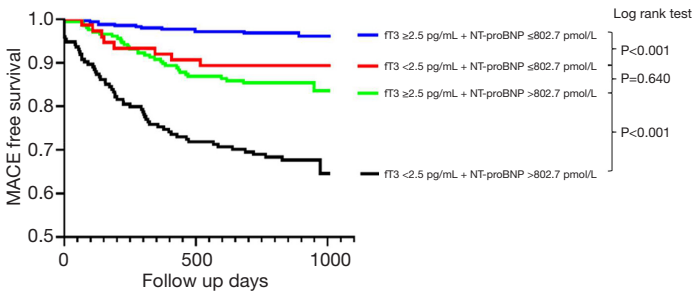

Figure 4 MACE-free survival probability curves for patients who underwent PCI after AMI stratified according to fT3 and NT-proBNP status. Patients with NT-proBNP ≤802.7 pg/mL and fT3 ≥2.5 pg/mL had a significantly better prognosis than patients with NT-proBNP ≤900 pg/mL and fT3 <2.5 pg/mL. Patients with NT-proBNP >802.7 pg/mL had worse outcomes than patients with NT-proBNP ≤802.7 pg/mL. Patients with NT-proBNP >900 pg/mL and fT3 <2.5 pg/mL had poorer outcomes than those with normal fT3 status. AMI, acute myocardial infarction; fT3, free triiodothyronine; MACE, major adverse cardiac event; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention.

and NT-proBNP were independent predictors of adverse cardiac outcomes in a cohort of patients with AMI who underwent PCI. In addition, patients with NT-proBNP ≤802.7 pg/mL and fT3 ≥2.5 pg/mL had a better prognosis than patients with NT-proBNP ≤802.7 pg/mL or fT3 ≥2.5 pg/mL, and patients with NT-proBNP >802.7 pg/mL and fT3 <2.5 pg/mL had the worst prognosis. These results suggest that the combination of fT3 and NT-pro-BNP could facilitate the identification of patients with AMI who are more likely to experience negative long-term outcomes after PCI.

In the present study, 31% of the patients who underwent PCI after AMI had a low fT3 level, which is a similar value to that reported for patients with other cardiovascular diseases (11). The low fT3 group had a higher percentage of patients with three diseased vessels and a lower percentage

of patients with a single diseased vessel. The serum levels of TnI and NT-ProBNP, which reflect the degree of cardiac injury, were higher in the low fT3 group than in the normal fT3 group. These findings indicate that serum fT3 levels are associated with the severity of AMI, but the present study was not designed to determine the causality of the association between AMI and thyroid function. Nevertheless, it is known that low fT3 levels are found in 10% of patients with early HF and 58% of patients with late HF (22). Low T3 levels are more frequently observed in patients with HF of NYHA class III–IV (23). It has also been shown that the most important decline in fT3 levels is observed between 6 h and 24–36 h after AMI (24).

NT-proBNP is used as a diagnostic, management, and prognostic tool for HF and AMI (25). Elevated NT-proBNP has a close negative relationship with thyroid dysfunction (18). A previous study reported that NT-proBNP values were several times higher in patients with AMI who had a fT3 level below the normal reference range than in patients with a fT3 level within the normal reference range (9). The present study also found that NT-proBNP levels were negatively correlated with fT3 levels (r=–0.311). These results provide some evidence that patients with an elevated NT-proBNP level and a fT3 level within the normal range may still have thyroid deficiency in their myocardial tissue. In such patients, an increased NT-proBNP level after AMI might be an indication for thyroid replacement therapy, but a well-designed clinical trial will have to be carried out to confirm this hypothesis. Nevertheless, the available evidence from a small number of studies suggests that thyroid replacement therapy might be beneficial in patients with HF (26). Pingitore *et al.* (27) reported that serum NT-proBNP level was reduced in patients with HF treated for 3 days with T3, and the protocol for a clinical trial was published in 2015 (28).

The combination of NT-proBNP level with TH level can better assess the prognosis of patients with cardiovascular disease. The significant inverse relationship between serum NT-proBNP and fT3 suggests that serum NT-proBNP is a reliable and sensitive biomarker for TH signaling in cardiac tissue. It is possible that the NT-proBNP level could be used to determine whether TH therapy is indicated in patients with HF and to assess the efficacy of TH therapy in patients with cardiac disease. Serum NT-proBNP values could be used to precisely guide low-dose T3 treatment in patients with T3 levels in the lower half of the reference range, with a reduction in serum NT-proBNP confirming the restoration of cardiac TH signaling. In the present study, patients with low NT-proBNP and high fT3 levels had the best prognosis, while those with high NT-proBNP and low fT3 levels had the worst prognosis. She *et al.* (9) concluded that fT3 level had no impact on the prognosis of AMI, but they did not examine the combination of fT3 and NT-proBNP. Brozaitiene *et al.* (29) showed that high NT-proBNP level and low fT3 level was each independently associated with the prognosis of AMI, as observed in the present multivariable analysis. Furthermore, they observed that patients with a low NT-proBNP level and a high fT3/fT4 ratio had the best prognosis and that those with a high NT-proBNP level and a low fT3/fT4 ratio had the worst prognosis, supporting the present study. Similar results were reported by Passino *et al.* (30). Hence, the combination of fT3 and NT-proBNP levels should be evaluated in large cohorts of patients to establish whether this marker combination could be used in the clinic.

There were several limitations to the present study. First, the patients included in this study were from a single center, which resulted in a small sample size and might limit the generalizability of the results. This is particularly true when considering the homogeneity of the population with regard to ethnicity (Chinese Han). Second, this study did not investigate the mechanism by which fT3 may lead to the downregulation of NT-proBNP. Potential mechanisms by which fT3 negatively regulates gene expression are poorly understood. Third, this was a retrospective study. In addition, this study could not assess the fT3 levels during follow-up because they were not measured, hence we do not know whether and how the fT3 and NT-proBNP levels changed after AMI. Therefore, the present results should be viewed as preliminary, and a prospective, multicenter study of a larger number of patients is needed. Nevertheless, the strengths of our study include the completeness of the thyroid function data, the long-term follow-up for MACEs, and the exclusion of patients using drugs that might affect thyroid status.

This study identified a low fT3 level as a significant independent predictor of poor prognosis for patients with AMI who underwent PCI. Serum fT3 level combined with NT-proBNP level might be a valuable predictor of the long-term outcomes of patients with AMI who undergo PCI.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-5541

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-5541

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5541). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Fuwai Hospital (2013-449). All patients provided written informed consent.

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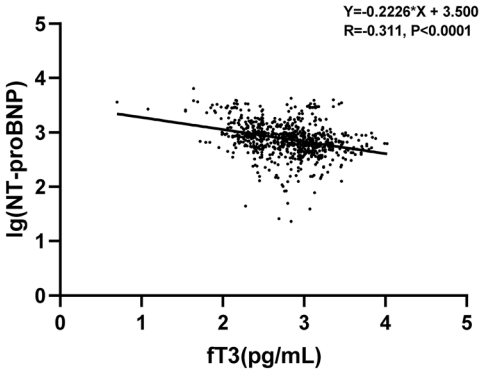

Figure S1 Linear correlation between fT3 level and lg(NT-ProBNP). A linear regression analysis was performed to evaluate the relationship between fT3 level and NT-ProBNP level in the entire population. An inverse correlation was found between fT3 level and the logarithm of NT-ProBNP. fT3, free triiodothyronine; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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