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Correlation between serum free triiodothyronine levels and risk stratification in Chinese patients with acute coronary syndrome receiving percutaneous coronary intervention

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Abstract

Objective: Low serum free triiodothyronine (FT3) levels are associated with the occurrence of coronary heart disease and with the prognosis of cardiovascular diseases. This study aimed to investigate the relationship between FT3 levels and risk stratification in Chinese Han patients with acute coronary syndrome (ACS) receiving percutaneous coronary intervention (PCI) treatment.
Methods: Plasma FT3 levels and other parameters were measured in 191 patients with ACS who received PCI. The risk of adverse cardiovascular events was assessed using the Age, Creatinine, and Ejection Fraction (ACEF) score.
Results: FT3 levels were significantly lower in the high-risk group than in the medium- and low-risk groups. Serum FT3 levels were negatively linearly correlated with the ACEF score ($r = -0.590$). Stepwise regression analysis showed a negative correlation between FT3 levels and the risk of adverse cardiovascular events as measured by the ACEF score (standardized $\beta = -0.261$).

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Conclusion: Serum FT3 levels are negatively related to risk stratification in patients with ACS. Serum FT3 levels may be used as a potential predictor for adverse outcomes of patients with ACS undergoing PCI.

Keywords
Free triiodothyronine, acute coronary syndrome, percutaneous coronary intervention, Age, Creatinine, and Ejection fraction score, thyroid hormone, risk stratification

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Introduction

Acute coronary syndrome (ACS) is a main cause of death of patients with cardiovascular disease. The proportion of patients with ACS receiving percutaneous coronary intervention (PCI) treatment is increasing, but the occurrence of adverse cardiovascular events is inevitable. A randomized, controlled trial showed that the incidence of major adverse cardiovascular events (MACE) within 1 year in patients with ACS who received the most appropriate treatment was approximately 10%.[1] This rate is nearly twice as high as that in a real-world population. Additionally, a previous study showed that the rate of MACE was approximately 20% in the following 3 years for patients who did not experience a cardiovascular event within 1 year after PCI.[2] Identifying risk factors for a poor prognosis of patients with ACS after PCI is of great clinical significance to strengthen risk assessment and stratification and to decrease the incidence of adverse cardiovascular events after PCI.

Thyroid hormones play a major regulatory role in the internal environment. Low serum triiodothyronine (T3) levels can predict the short-term and long-term prognosis of patients with coronary heart disease and heart failure, directly indicating a poor prognosis of heart disease.[3,4] Free triiodothyronine (FT3), which can penetrate tissue cells through cell membranes, is the active form of T3 and is a major physiological component of thyroid hormones. Low FT3 levels are associated with the occurrence of coronary heart disease and with the prognosis of cardiovascular diseases, such as acute myocardial infarction.[5–7] This finding may be because low FT3 and T3 levels are correlated with risk factors of adverse cardiovascular events, such as abnormal lipid metabolism, dysfunction of vascular endothelial cells, hyperglycemia, and a decreased left ventricular ejection fraction. However, few reports have investigated the relationship between FT3 levels and the prognosis of patients with ACS after receiving PCI treatment in the Chinese Han population.

This study aimed to examine the correlation between FT3 levels and risk stratification of Chinese Han patients with ACS who receive PCI. Risk was assessed by the Age, Creatinine, and Ejection Fraction (ACEF) score, which is a risk stratification tool for percutaneous myocardial revascularization.

Material and methods

Subjects

Chinese patients with ACS who received PCI and were hospitalized in the

Cardiovascular Internal Medicine Department of PLA General Hospital were enrolled between November 2018 and June 2019. Patients with cachexia, severe systemic diseases of the liver and kidney, cardiomyopathy, unstable hemodynamics, infectious or systemic inflammatory diseases, immune system diseases, or those who were reluctant to join the study were excluded. Detailed records of the participants included the following data: (1) age, sex, height, weight, and other general characteristics; and (2) smoking, hypertension, diabetes, hyperlipidemia and other medical histories.

Written informed consent was obtained from all participants. The study protocol was approved by the institutional review board of the Chinese PLA General Hospital (IRB number: S2019-260-01).

Plasma collection and measurement of biochemical indicators

A total of 156 consecutive patients with ACS (81.7%) who were ready for selective coronary intervention fasted for longer than 8 hours, and then a venous blood sample was drawn the next morning to detect thyroid function and other indices. Blood samples of the remaining 35 patients with ACS (18.3%) who were going to receive emergency PCI were also obtained before the intervention procedure. T3, FT3, thyroxine, free thyroxine, and thyroid-stimulating hormone levels were detected by an automatic electrochemical luminescence immunoassay system (Cobas e 601; Roche, Basle, Switzerland). Parameters of blood routine experiments were determined by an automatic hematology analyzer (XN-3000; Sysmex Corporation, Kobe, Japan). Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL), triglycerides, uric acid, urea, lactate dehydrogenase (LDH), hemoglobin A1c, creatinine, and other biochemical indicators were detected by an automatic biochemical analyzer (Cobas c 501; Roche). Brain natriuretic peptide (BNP) levels were detected by an automatic biochemical analyzer (Dimension EXL with LM system; Siemens, Munich, Germany). The left ventricular ejection fraction was measured by PILIPS IE33 color Doppler echocardiography with the S5-1 probe.

ACEF score

The ACEF score was calculated as follows: ACEF score = age (years)/left ventricular ejection fraction (%)+1 (if creatinine levels are >200 μmol/L). The ACEF score was developed and validated by Ranucci et al.[8] in 2009 and was initially used for patients undergoing coronary artery bypass grafting. The prognostic value of the ACEF score was then strongly confirmed in patients receiving PCI.[9–12] For patients with ACS, the ACEF score is no less effective than the Global Registry for Acute Coronary Events score and other risk models.[13] Currently, the ACEF score is incorporated into the guidelines of the European Heart Association and the Association of Cardiothoracic Surgery for cardiac revascularization as a risk stratification tool for surgical and percutaneous myocardial revascularization.[14]

Risk grouping of patients with ACS

On the basis of the patients' ACEF scores, they were divided into the low-risk group (ACEF score $\leq$0.96, n = 63), medium-risk group (ACEF score >0.96 and $\leq$1.19, n = 63), and high-risk group (ACEF score >1.19, n = 62). FT3 and other indicator levels were compared among the three risk groups.

Statistical analyses

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data are expressed as the mean ± standard deviation or median and interquartile range. One-way ANOVA or the Kruskal–Wallis H test was used for comparisons between multiple groups. Count data are expressed by the rate, and comparison of rates between two or multiple groups was carried out by the chi-square test. Pearson correlation analysis or point-biserial correlation analysis was used to analyze the correlation between two variables. Stepwise multiple linear regression was used to determine the risk factors of MACE as measured by the ACEF score. A P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 191 patients enrolled, 152 (79.6%) had unstable angina and 39 (20.4%) had acute myocardial infarction (20 with ST-elevation myocardial infarction and 19 with non-ST-elevation myocardial infarction). Because only 3 of the 191 patients had creatinine levels >200 μmol/L and the ACEF values of these 3 patients would have affected the distribution of the ACEF scores, they were excluded from the study. Finally, 188 subjects were included in this study. Baseline characteristics of the patients are shown in Table 1.

Comparison of FT3 levels and other indicators among the ACS-PCI risk stratification groups

Levels of FT3, T3, hemoglobin (Hb), hematocrit (HCT), urea, BNP, and LDH, and the Gensini score and body mass index (BMI) showed a gradient trend with an increase in risk stratification in patients with ACS who had PCI (all $P < 0.05$). FT3 levels were significantly lower in the high-risk group than in the low-risk and medium-risk groups (both $P < 0.05$, Table 1).

Correlation analysis between biochemical parameters and the ACEF score

Pearson correlation analysis was performed between all indicators and the ACEF score in patients with ACS. FT3 levels, T3 levels, BMI, Hb levels, and HCT were negatively correlated with the ACEF score, while diabetes, levels of creatinine, UA, urea, BNP, and LDH, and the Gensini score were positively correlated with the ACEF score (all $P < 0.05$, Table 2). Pearson correlation analysis and a scatter plot showed that there was a significant negative linear correlation between FT3 levels and the ACEF score ($r = -0.590$, $P < 0.001$, Figure 1).

Stepwise multiple linear regression analysis of clinical variables and the ACEF score

The stepwise method provided by multivariate linear regression in SPSS software was used to identify the risk factors associated with the ACEF score. In the regression model, T3 and HCT, which are collinear with FT3 and Hb, respectively, were removed in advance. Finally, the regression model, which included BNP, age, creatinine, FT3, and Hb, was significant ($F = 91.896$, $P < 0.001$). A total of 80.1% of the dependent variable ACEF could be explained by the included independent variables (determination coefficient $r = 0.899$, $r^2 = 0.808$, adjusted $r^2 = 0.801$, Table 3).

Discussion

FT3 and T3 are important functional hormones of the endocrine system and they

Table 1. Clinical features and biochemical parameters in risk stratification subgroups.

	Low-risk group, ACEF score $\leq$0.96 (n = 63)	Medium-risk group, ACEF score >0.96 and $\leq$1.19 (n = 63)	High-risk group, ACEF score >1.19 (n = 62)	F/χ^2/H	P
Baseline clinical features					
Age, years	52.21 ± 6.88	64.54 ± 6.31	70.89 ± 10.63	85.011	<0.001
Male sex, n (%)	51 (81.0)	36 (57.1)	43 (69.4)	8.372	0.015
BMI, kg/m^2	26.65 ± 3.55	25.79 ± 2.84	24.40 ± 3.63* **	7.025	0.001
Smoking history, n (%)	25 (39.6)	20 (31.7)	20 (32.3)	1.097	0.578
Diabetes, n (%)	16 (25.4)	20 (31.7)	27 (43.5)	4.753	0.093
Hyperlipidemia, n (%)	19 (30.2)	22 (34.9)	16 (25.8)	1.23	0.540
Hypertension, n (%)	40 (63.5)	49 (77.8)	46 (74.2)	3.436	0.179
Biochemical parameters (mean ± standard deviation)					
T3, nmol/L	1.68 ± 0.31	1.59 ± 0.28	1.34 ± 0.32* **	20.52	<0.001
FT3, pmol/L	4.68 ± 0.74	4.28 ± 0.62*	3.74 ± 0.73* **	28.89	<0.001
FT4, pmol/L	14.77 ± 3.01	14.30 ± 2.05	14.67 ± 2.66	0.571	0.566
T4, nmol/L	101.04 ± 23.71	98.91 ± 19.86	95.60 ± 18.01	1.096	0.336
TSH, μIU/mL	2.42 ± 2.87	2.53 ± 3.41	2.33 ± 2.93	0.064	0.938
TC, mmol/L	3.60 ± 1.11	3.81 ± 1.10	3.87 ± 1.26	0.892	0.412
TG, mmol/L	1.89 ± 1.47	1.44 ± 0.76	1.48 ± 0.70	3.686	0.027
LDL, mmol/L	2.16 ± 0.86	2.27 ± 0.78	2.37 ± 1.01	0.882	0.416
HDL, mmol/L	1.02 ± 0.32	1.07 ± 0.29	1.06 ± 0.33	0.53	0.590
Hemoglobin, g/L	141.57 ± 13.71	135.76 ± 16.37	124.71 ± 22.84* **	14.1	<0.001
Hematocrit, %	0.416 ± 0.041	0.404 ± 0.046	0.372 ± 0.065* **	12.167	<0.001
Uric acid, μmol/L	326.94 ± 83.39	305.41 ± 77.84	354.41 ± 116.28	4.271	0.015
Urea, mol/L	5.62 ± 2.59	5.85 ± 2.25	7.23 ± 4.33* **	4.668	0.011
Creatinine, μmol/L	80.44 ± 47.15	77.67 ± 21.28	116.54 ± 129.93	4.537	0.012
BNP, pg/mL	202.93 ± 496.60	215.61 ± 340.04	2442.02 ± 3159.62	16.14	<0.001
LDH, U/L	151.01 ± 48.33	170.42 ± 54.64	233.54 ± 210.96	5.13	0.007
HbA1c, %	6.23 ± 1.26	6.40 ± 1.05	6.55 ± 1.80	0.776	0.462
Gensini score	35.08 ± 21.10	36.35 ± 21.95	47.02 ± 30.53	4.338	0.014
	32 (20, 48)	34 (20, 46)	38 (26, 62)	5.193	0.075

ACEF, Age, Creatinine, and Ejection fraction; BMI, body mass index; T3, triiodothyronine; FT3, free triiodothyronine; FT4, free thyroxine; T4, thyroxine; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; LDH, lactate dehydrogenase; HbA1c, hemoglobin A1c.

Data are shown as n (%), mean ± standard deviation, or median (interquartile range). One-way ANOVA was used for comparisons between three or more groups. Comparison of rates between two or multiple groups was carried out by the chi-square test. *P<0.05 compared with the low-risk group; **P<0.05 compared with the medium-risk group.

affect lipid metabolism. FT3 is positively correlated with the activity of 7α-hydroxylase, which is involved in the first step of cholesterol degradation.[15] Additionally, 7α-hydroxylase binds to thyroid receptor binding elements in the promoter region of the liver LDL receptor gene, upregulating its expression, and thus increasing cholesterol clearance.[16] Therefore, plasma LDL levels and other cholesterol levels are increased in patients with a low FT3 level. Furthermore, low thyroid hormone levels are associated with elevated oxidative levels of LDL, which promote formation of atherosclerosis.[17] Thyroid hormone deficiency can increase circulating triglyceride

Table 2. Correlations between the ACEF score and clinical variables.

	ACEF score	
Clinical variables	r	P
Age, years	0.564	<0.001
Male sex, n (%)	−0.054	0.464
BMI, kg/m^2	−0.305	<0.001
Smoking history, n (%)	0.113	0.122
Diabetes, n (%)	0.205	0.005
Hyperlipidemia, n (%)	0.089	0.227
Hypertension, n (%)	0.023	0.756
Hemoglobin (g/L)	−0.371	<0.001
Hematocrit (%)	−0.347	<0.001
Creatinine (μmol/L)	0.317	<0.001
TC (mmol/L)	0.015	0.838
LDL (mmol/L)	0.011	0.883
HDL (mmol/L)	−0.070	0.339
TG (mmol/L)	-0.038	0.608
Uric acid (μmol/L)	0.239	0.001
Urea (mol/L)	0.361	<0.001
T4 (nmol/L)	−0.072	0.324
T3 (nmol/L)	−0.449	<0.001
FT3 (pmol/L)	−0.590	<0.001
FT4 (pmol/L)	0.065	0.376
TSH (μIU/mL)	−0.040	0.589
HbA1c (%)	0.034	0.657
BNP (pg/mL)	0.647	<0.001
LDH (U/L)	0.381	<0.001
Gensini score	0.175	0.017

ACEF, Age, Creatinine, and Ejection fraction; BMI, body mass index; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; T4, thyroxine; T3, triiodothyronine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; HbA1c, hemoglobin A1c; BNP, brain natriuretic peptide; LDH, lactate dehydrogenase.
All numerical variables in the analysis were treated as continuous variables, while sex, smoking, and disease history were considered as dichotomous variables. Their relationships with the ACEF score were analyzed using Pearson analysis or point-biserial correlation analysis.

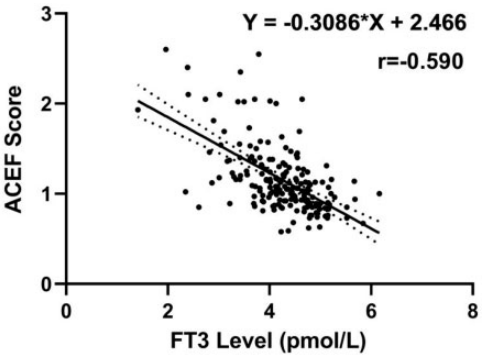

Figure 1. Linear correlation of FT3 levels with the ACEF score.
ACEF, Age, Creatinine, and Ejection Fraction; FT3, free triiodothyronine. The scatter plot shows a significant linear correlation between FT3 levels and the ACEF score (P<0.001).

concentrations by decreasing the activity of lipoprotein lipase, sterol regulatory factor binding protein-2, and apolipoprotein A1.[18] In mice, thyroid hormones affect the reverse transport of cholesterol by increasing high-density lipoprotein receptor levels in the liver.[19] Angelin et al.[20] showed that, after 12 weeks of administration of iroterol (liver-specific thyroid hormone receptor agonist), plasma LDL levels declined by 20% to 30%, while other cholesterol levels and apolipoprotein B levels similarly declined. Sjouke et al.[21] also found that combined iroterol and statin therapy reduced the LDL level of familial hypercholesterolemia, which indirectly confirmed the atherogenic effect of low thyroid hormone levels. In our study, LDL and total cholesterol levels were not significantly different among the three risk groups. However, triglyceride levels were lower in the high-risk group than in the low-risk group. This finding may be due to the popularized application of statins and other lipid-regulating drugs and recommendations of a reasonable diet for patients with more severe ACS.

In addition to disordered lipid metabolism, endothelial dysfunction and many other risk factors link a low TF3/T3 state with adverse cardiovascular events. Thyroid hormones regulate production of endothelial nitric oxide and vascular tension.

Table 3. Stepwise multiple linear regression analysis of clinical variables and the ACEF score in patients with acute coronary syndrome.

	β	Standardized β	t	VIF	P
Constant	0.524		2.683		0.009
BNP (pg/mL)	0.000	0.505	10.323	1.106	<0.001
Age (years)	0.012	0.424	8.171	1.243	<0.001
Creatinine (μmol/L)	0.001	0.314	6.163	1.202	<0.001
FT3 (pmol/L)	−0.002	−0.261	−4.801	1.059	<0.001
Hemoglobin (g/L)	−0.002	−0.140	−2.583	1.347	0.014

ACEF, Age, Creatinine, and Ejection fraction; VIF, variance inflation factor; BNP, brain natriuretic peptide; FT3, free triiodothyronine. Independent predictors of adverse cardiovascular events as evaluated by the ACEF score were determined by multivariate linear regression. In this model, common confounding factors (age, sex), traditional risk factors that are related to the prognosis of patients with acute coronary syndrome who received percutaneous intervention (smoking history, diabetes history, hypertension history, uric acid, BNP), and the variables significantly correlated with the ACEF score in Pearson single factor analysis (hemoglobin, creatinine, urea, FT3, lactate dehydrogenase, Gensini score) were considered. Hematocrit and triiodothyronine were not included in this model because of their significant collinearity with hemoglobin and FT3, respectively.

Endothelial cell function of patients with hypothyroidism, whether clinical or subclinical, is weakened. Studies have shown that after hormone replacement therapy, endothelial cell function is significantly improved.[22–24] Tests have confirmed that T3 leads to blood vessel relaxation within hours after its injection in patients undergoing coronary artery bypass grafting.[25] The disturbed balance between vasoactive substances in a low T3 state results in abnormal contraction, tension of the coronary artery, and occurrence of coronary ischemic adverse events. There also been many studies on the relationship between FT3 and other risk factors as follows. Studies have shown that FT3 levels affect the left ventricular ejection fraction in patients with acute myocardial infarction,[26] and subclinical hypothyroidism is associated with more severe complications of type 2 diabetes.[27] Risk factors, such as increased carotid intima thickness, a hypercoagulation state, and higher levels of uric acid phosphate and C-reactive protein, are also related to a low thyroid hormone state.[28]

In our study, BMI, HCT, the Gensini score, and levels of Hb, urea, BNP, and LDH showed significant gradient changes with an increase in risk stratification. The mean BMI of all of the three groups of patients with ACS was above the normal range, indicating that patients with obesity are more likely to develop coronary heart disease. Hb and HCT, which are important indicators in the hematological system, decreased with an increased risk stratification in patients with ACS, and both showed linear correlations with the ACEF score (Table 2). In fact, Hb and HCT are included into the ACEF II score, which is an upgraded version of the ACEF score. We found that urea levels were linearly correlated with the ACEF score (Table 2). This finding is consistent with previous studies that high urea nitrogen levels may be one cause of cardiac dysfunction in patients with coronary heart disease, and are also one of the main risk factors of prognosis in patients with decompensated heart failure.[29,30]

Coceani et al.[4] showed that FT3 levels were inversely correlated with the presence of coronary artery disease and low T3 syndrome conferred an adverse prognosis. In the NHANES population of 7116 people,

researchers found that a low FT3 level that was still within the normal range was significantly correlated with a higher risk of cardiovascular mortality.[5] In our study, a similar correlation between FT3 levels and the risk stratification of patients with ACS who received PCI was observed. FT3 levels were significantly lower in the high-risk group than in the low-risk and medium-risk groups. A scatter plot and Pearson correlation analysis showed a significant linear correlation between FT3 levels and the ACEF score. FT3 levels, together with BNP levels, age, creatinine levels, and Hb levels, were finally included in a multiple stepwise linear regression model for the risk of adverse cardiovascular events. BNP is an index of cardiac function in circulatory system, age is an indicator of population characteristics, creatinine is an important index of the urinary system, FT3 is an important hormone of endocrine system, and Hb is a key index of the hematological system. Therefore, the joint effect of including BNP, age, creatinine, FT3, and Hb in a regression model enables better risk stratification of patients with ACS who receive PCI. As a risk stratification tool for percutaneous myocardial revascularization, our results strongly suggest that FT3 has prognostic value in Chinese Han patients with ACS who receive PCI.

There are certain limitations in our study. First, this was a single-center study with a small sample size, and no follow-up analysis was performed. Second, we only took one blood sample for testing serum thyroid hormone levels, which may have led to bias of the results. Third, we found that thyroid hormone had a great influence on lipid metabolism. However, because of the popularity of secondary prevention of coronary heart disease, we did not find a relationship between FT3 levels and blood lipid indices. Moreover, we were not able to obtain B-mode ultrasound or computed tomographic images of arterial plaques in patients with different thyroid hormone levels. Future studies with a larger sample size and examination of the relationship between FT3 levels and arterial plaques in patients are required.

Conclusion

Serum FT3 levels are negatively related to risk stratification in patents with ACS who receive PCI. Low FT3 levels have prognostic value in these patients. We consider that incorporating FT3, which is an important hormone of the endocrine system, into a concise and efficient risk prediction model would be reasonable.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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