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ORIGINAL ARTICLE

Admission thyroid function in relation to 90-day outcome of acute ischemic stroke

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Abstract

OBJECTIVE: Thyroid function may be useful prognostic predictor of acute ischemic stroke. However, the relationship between thyroid function and stroke prognosis remains controversial. We aimed to explore the correlation between thyroid function at admission and 90-day functional outcome in patients with acute ischemic stroke.

METHODS: Our data were collected from patients with AIS (acute ischemic stroke) registered in the Stroke Center of Jiangsu Provincial Hospital of Chinese Medicine from January 2021 to July 2021.The outcome was divided into good outcome as mRS (Modified Rankin Scale) score <3, poor outcome as mRS≥3 (including hemorrhage, recurrence, and death within 90 days after stroke).Univariate, multivariate logistic regression analysis, tertile analysis and subgroup analysis were used to evaluate the relationship between TSH (Thyroid-stimulating hormone), FT3 (Free Triiodothyronine), FT4 (Free thyroxine) and 90-day outcome.

RESULTS: 699 patients with AIS were included in this study. In univariate analysis, FT3 was negatively correlated with poor outcome of AIS patients at 90-day, TSH was not statistically correlated with 90-day outcome. Multivariate analysis showed that FT3 was negatively correlated poor outcome of AIS patients at 90-day. After adjusting for potential confounders, TSH was negatively correlated with poor outcome. Participants were categorized based on the tertile cut-off points of FT3 and TSH. With the increase of TSH value, the incidence of poor outcomes in Q3 was 0.57 times higher than that of Q1. Similarly, with the increase of FT3 value, the incidence of poor outcomes in Q3 is 0.3 times than that of Q1.

CONCLUSIONS: FT3 and TSH were negatively correlated with poor 90-day outcome in patients with AIS. Measurement of thyroid function on admission may provide independent prognostic information for 90-day outcome of AIS.

INTRODUCTION

Ischemic stroke is one of the leading causes of death and disability in the world (Saini *et al.* 2021). Previous studies have shown that dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis is a risk factor and affects the outcome of acute ischemic stroke (Talhada *et al.* 2019; Zhang *et al.* 2019; Wang *et al.* 2017b; Alevizaki *et al.* 2006). Hypothyroidism can lead to hypertension, hypercholesterolemia, cardiac dysfunction, and hypercoagulability, which are risk factors for acute ischemic stroke. Hyperthyroidism is also associated with atrial fibrillation (Zubair Khan *et al.* 2021; Ellervik *et al.* 2019; Selmer *et al.* 2012; Auer *et al.* 2001), a common cause of cardiogenic stroke (Suzuki *et al.* 2021; Singer *et al.* 2021; Schattner 2019; Jaakkola *et al.* 2016). There is a complex relationship between thyroid hormone and function outcome of acute ischemic stroke. Current data suggest that low FT3 level is associated with more severe stroke, higher mortality, and worse functional outcomes (Zhang *et al.* 2019; Lamba *et al.* 2018; Wang *et al.* 2017b). However, these studies reported conflicting results on the association between TSH level and functional outcomes of acute ischemic stroke (Suda *et al.* 2016; Leonards *et al.* 2014). The relationship between TSH level and stroke prognosis is unclear, and few studies focus on the combined value of TSH, FT3 and FT4 in predicting the outcome of ischemic stroke. Therefore, this study investigated the relationship between thyroid hormone levels (FT3, FT4, and TSH) on admission and 90-day outcomes in China patients with acute ischemic stroke.

MATERIAL AND METHODS

Date Collection

Our data were from the Stroke Center Registry database of Jiangsu Provincial Hospital of Chinese Medicine between January 2021 and July 2021, approved by the Institutional Research Review Board of the Affiliated Hospital of Nanjing University of Chinese Medicine in following the Declaration of Helsinki.

Patients

The database included 564 patients with AIS in this retrospective study from January 2021 to July 2021. All patients visited to the hospital within 24 hours of the onset of symptoms. All of them met the diagnostic criteria of "Guidelines for diagnosis and treatment of acute ischemic stroke in China 2018" and were confirmed by magnetic resonance imaging (MRI). Exclusion criteria were as follows: (1) diagnosed as hemorrhagic cerebral infarction; (2) pre-existing thyroid glands diseases, anti-thyroid medications, or diseases that might affect thyroid function; (3) pregnant women, or had a history of malignant tumors; (4) could not complete the thyroid function test within 24 hours of admission; (5) aged < 18 years; (6) were lost to follow-up within 90 days. (Fig1)

Clinical assessment

Baseline admission information of patients was collected as follows: age, sex, medical history (hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary heart disease, stroke or transient ischemic attack, tumour, renal insufficiency, smoking, drinking), National Institutes of Health Stroke Scale (NIHSS) score, Modified Ranking Scale (mRS), thrombolysis or thrombectomy, and treatment during hospitalization and after discharge(antiplatelet, anticoagulation, lipid-lowering, hypoglycemic and antihypertension).Venous blood samples were collected from all participants within 24 hours after admission. Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) levels were determined for each patient by electrochemiluminescence immunoassay. Reference ranges for FT4 were 0.59-1.25ng/dl , for FT3 were 2.5-3.9pg/ml, and for TSH were 0.56-5.91uIU/ml.

Follow-up and outcomes

The patients' follow-up information was obtained through a semiquantitative phone interview 90 days after onset of AIS . The phone interviews were conducted by two postgraduates who trained and certified for data collection. Guardians were contacted if patients died or could not cooperate with the inquiry. Functional outcomes of patients were evaluated and divided into good outcome and poor outcome according to the mRS scale. Good outcome was defined as mRS<3, and poor outcome was defined as mRS≥3 (including hemorrhage, recurrence, and death within 90 days after stroke).

Statistical analysis

Participants were dichotomized based on mRS scores. Continuous variables are expressed as median (interquartile range). Differences in continuous variables between groups were compared by Student's t-test or Mann-Whitney U test. Categorical variables were expressed as proportions and analyzed using the χ test or Fisher's exact test. The association between thyroid hormones and clinical outcomes was tested by univariate logistic analysis. The clinically important factors were input into multivariate logistic analysis. We selected covariates a priori based on clinical signs and studies from other literature suggesting that they may confound the association between thyroid function profile and AIS prognosis. In addition, we performed a logistic subgroup analysis. All statistical analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.4.

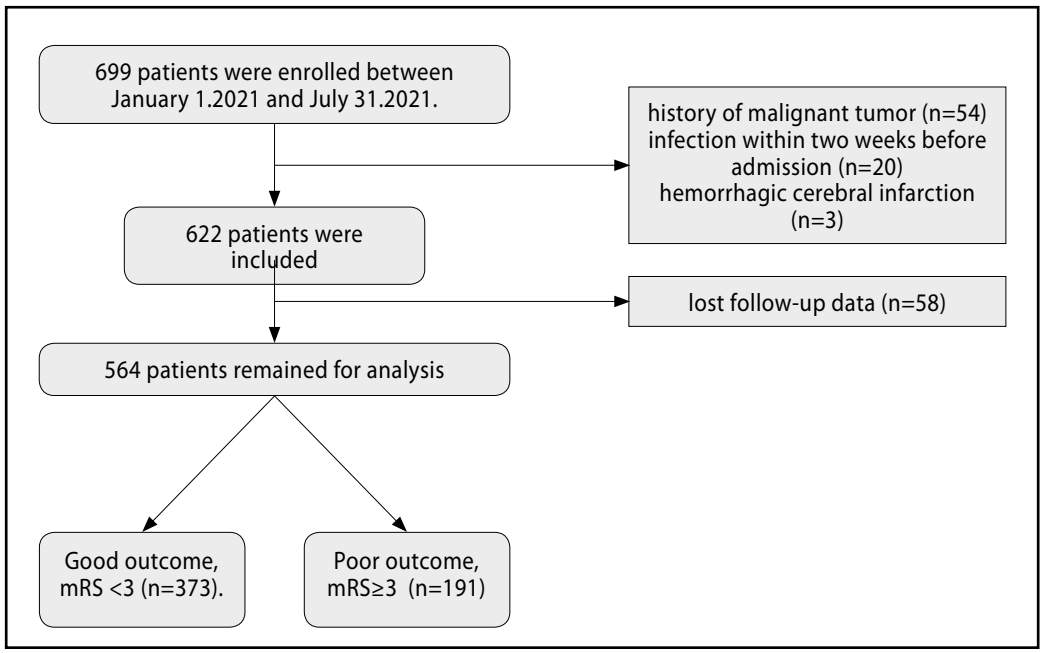

Fig. 1. Flow chart. A flowchart of patients enrollment

RESULTS

Patient Characteristics

699 patients were admitted to the stroke centre of Jiangsu Provincial Hospital of Chinese Medicine, and 135 patients were excluded because of history of malignant tumor (n=54), infection within two weeks before admission (n=20), hemorrhagic cerebral infarction (n=3), or without follow-up data (n=58). Finally, 564 patients remained for analysis. A flowchart of patients' enrollment is shown in Figure 1.

Baseline demographic, clinical and laboratory characteristics of the study population were listed in Table 1. The average age of the patients was 69.0 (60.0, 77.0) years old, and 64.7% of them were male. On admission, the median baseline NIHSS score was 2 points (IQR 1-4). Good outcome was observed in 373 patients (66.13%), and poor outcome was observed in 191 patients (33.87%). Significant differences between the patients with good outcome and poor outcome are described as follows: age (p<0.01), gender (p<0.01), AF (Atrial Fibrillation) (p<0.01), smoking history (p<0.01), NIHSS (p<0.01), Hypoglycemics (p<0.01), FT3 (p<0.01), FT4 (p<0.01), and TSH (p<0.05). Compared to the patients with favorable outcome, the patients with unfavorable outcome possessed lower levels of TSH and FT3. TSH median 1.7 (1.1-2.7), FT3 median 2.8 (2.5-3.1), FT4 median 1.0 (0.8-1.1).

Relationship Between thyroid function and 90-day outcome in AIS Patients

As shown in Table 2, by univariate logistic regression analysis, we found that FT3 was negatively correlated with the poor outcome in AIS patients (OR=0.28, 95%CI: 0.15-0.52, p<0.001), and FT4 was positively correlated with poor outcome in AIS patients (OR=4.46, 95CI: 1.52-13.08, p<0.01). TSH was not found to be significantly associated with poor outcome in AIS patients (OR=0.85, 95%CI:0.7- 1.02, p>0.05). Then, multivariate logistic regression analysis was performed after adjusting potential confounders (including age, sex, coronary heart disease, hypertension, DM, history of alcohol use, history of smoking). It was found that FT3 showed more significant negatively correlation with poor outcome (OR=0.46, 95%CI: 0.23-0.9, p<0.05). TSH also showed significant negative correlation with poor outcome in AIS patients (OR=0.81, 95%CI: 0.67-0.97, p<0.05).

Tertile analysis

We divided TSH and FT3 values into three groups using a triquantile analysis. As shown in Table 3, TSH values in Q1/Q2/Q3 were ranked from low to high, Q1group was the lowest and Q3 group was the highest. The OR values of Q1 and Q3 groups were 1 and 0.57 respectively, and Q3 group is 0.57 times than that of Q1.With the increase of TSH value, the incidence of poor outcomes in Q1 group was 0.57 times than that of Q3 group. The value of FT3 in Q3 group was 0.3 times than that of Q1 group. With the increase of FT3 value, the incidence of poor outcomes in Q3 group was 0.3 times than that of Q1 group (Table 4).

Subgroup analysis

Subgroup analysis showed that TSH level was significantly different between male and female patients, and patients with hyperlipidemia (Table 5). FT3 level was significantly different in male and female patients, and patients with hypertension, diabetes, elderly, hyperlipidemia, without thrombolysis, coronary heart disease

Tab. 1. Characteristics of patients

Variables	Total (n = 564)	0 (n = 494)	1 (n = 70)	*p*
Age, Median (IQR)	69.0(60.0,77.0)	67.5(59.0,76.0)	78.5(70.0,85.0)	<0.001
Gender				0.004
Men	365 (64.7)	331 (67)	34 (48.6)	
Women	199 (35.3)	163 (33)	36 (51.4)	
TSH, Median (IQR)	1.7 (1.1, 2.7)	1.8 (1.2, 2.8)	1.5 (0.8, 2.5)	0.024
FT3, Median (IQR)	2.8 (2.5, 3.1)	2.8 (2.6, 3.1)	2.6 (2.3, 2.9)	< 0.001
FT4, Median (IQR)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	1.0 (0.9, 1.1)	< 0.001
Coronary Heart disease,n%				0.845
YES	104 (18.4)	90 (18.2)	14 (20)	
NO	460 (81.6)	404 (81.8)	56 (80)	
Hypertension, n (%)				0.741
YES	422 (74.8)	368 (74.5)	54 (77.1)	
NO	142 (25.2)	126 (25.5)	16 (22.9)	
Diabetes mellitus,n(%)				0.112
YES	221 (39.2)	187 (37.9)	34 (48.6)	
NO	343 (60.8)	307 (62.1)	36 (51.4)	
Atrial Fibrillation,n%				<0.001
YES	60 (10.6)	44 (8.9)	16 (22.9)	
NO	504 (89.4)	450 (91.1)	54 (77.1)	
Hyperlipidemia, n (%)				1
YES	534 (94.7)	467 (94.5)	67 (95.7)	
NO	30 (5.3)	27 (5.5)	3 (4.3)	
History of tumour, n (%)				0.4
YES	53 (9.4)	44 (8.9)	9 (12.9)	
NO	511 (90.6)	450 (91.1)	61 (87.1)	
Renal insufficiency, n (%)				0.423
YES	35 (6.2)	29 (5.9)	6 (8.6)	
NO	529 (93.8)	465 (94.1)	64 (91.4)	
History of drinking, n (%)				0.038
YES	103 (18.3)	97 (19.6)	6 (8.6)	
NO	461 (81.7)	397 (80.4)	64 (91.4)	
History of Smoking, n (%)				0.001
YES	161 (28.5)	153 (31)	8 (11.4)	
NO	403 (71.5)	341 (69)	62 (88.6)	
History of thyroid disease				0.21
YES	40(7.1)	38(7.7)	2(2.9)	
NO	524(92.9)	456(92.3)	68(97.1)	
NIHSS, Median (IQR)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	9.0 (5.0, 12.0)	< 0.001
mRS, n (%)				< 0.001
0	16 (2.9)	16 (3.3)	0 (0)	
1	264 (47.6)	259 (53)	5 (7.6)	
2	93 (16.8)	90 (18.4)	3 (4.5)	
3	64 (11.5)	57 (11.7)	7 (10.6)	
4	91 (16.4)	58 (11.9)	33 (50)	
5	22 (4.0)	8 (1.6)	14 (21.2)	
6	5 (0.9)	1 (0.2)	4 (6.1)	

A good outcome is denoted by 0; A poor outcome is denoted by 1; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale;TSH, Thyroid-stimulating hormone; FT3, Free Triiodothyronine; FT4, Free thyroxine.

Tab. 2. Univariate and multivariate analysis of thyroid function and 90-day outcome in patients with AIS

Variable	n.total	n.event_%	OR	95CI	*p*	adj.OR	adj.95CI	adj.P
TSH	564.0	70 (12.4)	0.85	0.7~1.02	0.073	0.81	0.67~0.97	0.025
FT3	564.0	70 (12.4)	0.28	0.15~0.52	<0.001	0.46	0.23~0.9	0.024
FT4	564.0	70 (12.4)	4.46	1.52~13.08	0.006	2.53	0.82~7.78	0.107

Adjusted variables: age,sex,coronary heart disease, hypertension, diabetes mellitus, history of alcohol use, history of smoking;
TSH, Thyroid-stimulating hormone; FT3, Free Triiodothyronine; FT4, Free thyroxine.

Tab. 3. Tertile analysis of the association between serum TSH levels on admission and 90-day outcome in AIS patients

Variable	n.total	n.event_%	OR	95CI	*p*	adj.OR	adj.95CI	adj.P
Q1	188	34(18.1)	1(Ref)	1(Ref)				
Q2	187	15(8)	0.4	0.21-0,75	0.005	0.43	0.22-0.86	0.017
Q3	189	21(11.1)	0.57	0.32-1.02	0.057	0.52	0.28-0.98	0.045
Trend.test	564	70(12.4)	0.72	0.53-0.99	0.042	0.71	0.51-0.98	0.037

Adjusted variables:age,sex,coronary heart disease,hypertension,diabetes mellitus, history of alcohol use, history of smoking.

Tab. 4. Tertile analysis of the association between serum FT3 levels on admission and 90-day outcome in AIS patients

Variable	n.total	n.event_%	OR	95CI	*p*	adj.OR	adj.95CI	adj.P
Q1	146	29(19.9)	1(Ref)	1(Ref)				
Q2	200	26(13)	0.6	0.34-1.08	0.087	0.92	0.49-1.71	0.786
Q3	218	15(6.9)	0.3	0.15-0.58	< 0.001	0.57	0.28-1.19	0.133
Trend.test	564	70(12.4)	0.55	0.4-0.76	< 0.001	0.77	0.54-1.09	0.143

Adjusted variables: age, sex, coronary heart disease, hypertension, diabetes mellitus , history of alcohol use, history of smoking.

and atrial fibrillation. The interaction effect of the Gender subgroup was more obvious in TSH ($P1$<0.05), and the interaction effect of the hypertension subgroup was more significant in FT3 ($P1$<0.05) (Table 6).

DISCUSSION

Ischemic stroke is one of the leading causes of death and disability in the world. Patients with ischemic stroke often experience varying degrees of dysfunction or disability, causing great distress in their lives. Therefore, it is of great significance to study the prognosis of ischemic stroke for guiding rehabilitation treatment and improving the quality of life of stroke survivors. Several factors, including stroke severity, age, sex, vascular risk factors, and comorbidities, have been found to be associated with ischemic stroke outcome. However, recent prognostic studies of other factors, such as thyroid function, have not shown consistent results.

In the process of human aging, the disorder of the circadian rhythm results in the decrease of thyroid-stimulating hormone (TSH) secretion, and thyroid hormone levels in peripheral blood (Bensenor *et al.* 2012; Chakraborti *et al.* 1999). At this time, FT3 level decreases most obviously. Hypothyroidism and reduced thyroid hormone utilization in the brain have been recognized as critical risk factors for ischemic stroke. Epidemiological studies have shown that low levels of FT3 are associated with poor functional outcomes after acute ischemic stroke (Zhang *et al.* 2019; Lamba *et al.* 2018). A prospective cohort study showed that thyroid dysfunction (lower TSH levels) was associated with worse clinical outcomes in ischemic stroke patients (Chaker *et al.* 2016).One possible mechanism is the dysfunction of the neuroendocrine hypothalamic-pituitary-thyroid axis. Disturbance of the hypothalamic-pituitary-thyroid (HPT) axis affects the outcome of stroke. Hypothyroidism can lead to hypertension, hypercholesterolemia, cardiac insufficiency, hypocoagulable and hypercoagulable states, all of which are risk factors of stroke (Iwen *et al.* 2013; Gao *et al.* 2013). Hyperthyroidism is also associated with atrial fibrillation (Zubair Khan *et al.* 2021; Marouli *et al.* 2020; Ellervik *et al.* 2019; Selmer *et al.* 2012; Auer *et al.* 2001), a common cause of cardioembolic stroke (Suzuki *et al.* 2021; Singer *et al.* 2021; Schattner 2019; Jaakkola *et al.* 2016). The relationship between thyroid functioning and AIS is complex, and current results suggest that lower FT3 levels in patients with AIS are associated with higher stroke severity and mortality (Wang *et al.* 2017b; Lamba *et al.* 2018; Zhang *et al.* 2019), as well as poorer functional outcomes (Suda *et al.* 2016). In some cell and MOCA animal studies (Mdzinarishvili *et al.* 2013; Genovese *et al.* 2013; Hiroi *et al.* 2006), T3

Tab. 5. TSH subgroup analysis

Subgroup	n.total	n.event_%	crude.OR	crude.95CI	*p*	adj.OR	adj.95CI	adj.P	P.for. interaction
Gender									0.029
Male	365.0	34 (9.3)	0.62	0.42~0.92	0.017	0.61	0.42~0.9	0.012	
Female	199.0	36 (18.1)	0.92	0.76~1.11	0.368	0.93	0.76~1.13	0.444	
Age									0.066
≤65	203.0	11 (5.4)	0.86	0.72~1.03	0.096	0.34	0.13~0.88	0.027	
⊠65	361.0	59 (16.3)	0.64	0.32~1.28	0.207	0.84	0.7~1.01	0.065	
TICI									0.218
YES	57.0	14 (24.6)	0.64	0.32~1.28	0.207	0.6	0.27~1.35	0.22	
NO	507.0	56 (11)	0.89	0.75~1.06	0.201	0.84	0.7~1.01	0.065	
CHD									0.448
YES	104.0	14 (13.5)	0.92	0.75~1.13	0.443	0.9	0.69~1.18	0.445	
NO	460.0	56 (12.2)	0.77	0.6~0.99	0.039	0.77	0.6~0.98	0.031	
HTN									0.049
YES	422.0	54 (12.8)	0.9	0.75~1.08	0.248	0.87	0.73~1.05	0.161	
NO	142.0	16 (11.3)	0.53	0.27~1.01	0.052	0.4	0.18~0.85	0.018	
HL									0.329
YES	534.0	67 (12.5)	1.41	0.69~2.89	0.048	0.8	0.66~0.97	0.022	
NO	30.0	3 (10)	0.91	0.74~1.12	0.35	0.86	0.26~2.81	0.805	
DM									0.268
YES	221.0	34 (15.4)	0.91	0.74~1.12	0.364	0.89	0.71~1.12	0.328	
NO	343.0	36 (10.5)	0.74	0.55~1.01	0.062	0.73	0.54~0.98	0.037	
AF									0.544
YES	60.0	16(26.7)	0.95	0.69~1.31	0.772	0.96	0.64~1.44	0.85	
NO	504.0	54(10.7)	0.8	0.64~1.01	0.057	0.77	0.62~0.97	0.023	

Abbreviations 1: TSH, Thyroid-stimulating hormone; FT3, Free Triiodothyronine; FT4, Free thyroxine;AF, Atrial Fibrillation; CHD, coronary heart disease;DM, diabetes mellitus;HTN, hypertension;NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; HL,hy perlipidemia;TICI,Thrombolysis in Cerebral Infarction.
Adjusted variables: age, sex, coronary heart disease, hypertension, diabetes mellitus , history of alcohol use, history of smoking.

has been shown to increase eNOS (endothelial nitric oxide synthase) activity through rapid activation of the PI3-kinase /Akt pathway, resulting in a series of acute neurovascular protective effects such as lower mean blood pressure, enhanced CBF, and reduced cerebral infarction size. This ability to induce neuroprotective effects is weaker in patients with low T3 than in patients with normal thyroid function, and normal function of the hypothalamic-pituitary-thyroid axis (HPT) is affected by critical conditions such as acute ischemic stroke (Lamba *et al.* 2018). Hypothalamic thyrotropin releasing hormone and pituitary thyrotropin production are reduced and the ability of extrathyroid T4 to convert to T3 is impaired. Under such a series of influences, the neurovascular protective effect caused by thyroid hormone is more significantly weakened in patients with low T3 after acute ischemic stroke, thus making the prognosis of patients with low T3 worse after acute ischemic stroke. However, the association between TSH levels and functional outcomes after stroke is conflicting.

In a study of German scholars (Leonards *et al.* 2014), they concluded that there was no significant correlation between TSH and one-year outcome in patients with AIS. In another study (Imaizumi *et al.* 2004), someone investigated possible associations between subclinical hypothyroidism and the mortality of atherosclerotic diseases (ischemic heart disease and cerebrovascular disease). They concluded that there was no association between subclinical hypothyroidism and cerebrovascular disease. Although some investigators have suggested that subclinical hypothyroidism was associated with a lower risk of poor outcomes of stroke, but they failed to confirm their conjecture (Wollenweber *et al.* 2013). In contrast to these studies, some researchers concluded that hypothyroidism plays a protective role

Tab. 6. FT3 subgroup analysis

Subgroup	n.total	n.event_%	crude.OR	crude.95CI	*p*	adj.OR	adj.95CI	adj.P	P.for. interaction
Gender									0.424
Male	365.0	34 (9.3)	0.22	0.09~0.55	0.001	0.31	0.11~0.88	0.027	
Female	199.0	36 (18.1)	0.42	0.18~0.97	0.043	0.65	0.25~1.71	0.387	
Age									0.588
≤65	203.0	11(5.4)	0.3	0.08~1.05	0.059	0.22	0.05~1.02	0.054	
>65	361.0	59 (16.3)	0.34	0.17~0.71	0.004	0.54	0.25~1.15	0.111	
TICI									0.849
YES	57.0	14 (24.6)	0.29	0.05~1.67	0.166	0.48	0.05~4.37	0.517	
NO	507.0	56 (11)	0.3	0.15~0.59	0.001	0.5	0.24~1.05	0.066	
CHD									0.883
YES	104.0	14 (13.5)	0.35	0.08~1.64	0.184	0.62	0.1~4.06	0.622	
NO	460.0	56 (12.2)	0.26	0.13~0.53	<0.001	0.45	0.21~0.94	0.033	
HTN									0.019
YES	422.0	54 (12.8)	0.41	0.2~0.82	0.012	0.72	0.33~1.57	0.413	
NO	142.0	16 (11.3)	0.07	0.02~0.33	0.001	0.13	0.02~0.72	0.019	
HL									0.152
YES	534.0	67 (12.5)	0.3	0.16~0.56	<0.001	0.5	0.25~0.98	0.045	
NO	30.0	3 (10)	0.02	0~2.23	0.104	0.14	0~124.44	0.57	
DM									0.617
YES	221.0	34 (15.4)	0.32	0.12~0.84	0.020	0.55	0.2~1.52	0.247	
NO	343.0	36 (10.5)	0.25	0.11~0.56	0.001	0.38	0.15~0.94	0.035	
AF									0.532
YES	60.0	16 (26.7)	0.16	0.02~1.09	0.061	0.39	0.04~4.05	0.434	
NO	504.0	54 (10.7)	0.35	0.18~0.68	0.002	0.55	0.26~1.15	0.11	

Abbreviations 2: TSH, Thyroid-stimulating hormone; FT3, Free Triiodothyronine; FT4, Free thyroxine;AF, Atrial Fibrillation; CHD, coronary heart disease;DM, diabetes mellitus;HTN, hypertension;NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; HL,hy perlipidemia;TICI,Thrombolysis in Cerebral Infarction.
Adjusted variables: age, sex, coronary heart disease, hypertension, diabetes mellitus , history of alcohol use, history of smoking.

in patients with acute stroke (Alevizaki *et al.* 2006). Subclinical hypothyroidism was associated with a good outcome in patients with acute stroke. Many previous studies have shown that FT3 was associated with the outcome of patients with AIS (Taroza *et al.* 2020; Jiang *et al.* 2017). The focus of debate is mainly on whether TSH was associated with the outcome of acute ischemic stroke. In our study, both univariate and multivariate analyses indicated that FT3 was closely associated with 90-day outcome in patients with AIS. TSH was negatively associated with 90-day poor outcomes after adjusting for potential confounders (including age, sex, coronary heart disease, hypertension, diabetes mellitus, history of alcohol use, history of smoking). With the decrease of serum TSH level, the probability of poor outcomes increased gradually. The novelty of our study is that we focused on the combined value of TSH, FT3 and FT4 in predicting the outcome of ischemic stroke and found that both FT3 and TSH were associated with 90-day outcomes of AIS.

In our subgroup analysis, the levels of FT3 and TSH were significantly different between male and female patients, and patients with hyperlipidemia. The interaction between male subgroups in TSH was more significant ($P1<0.05$). Previous studies showed that gender may be related to ischemic stroke and was one of the risk factors of the disease (Arauz *et al.* 2020), but the mechanism is not clear. The possible reason is that there are more bad living habits in male, such as smoking and drinking, among which increase the risk of poor outcomes. Hyperlipidemia is a common risk factor for stroke, which can damage the vascular endothelium and lead to atherosclerosis. Thyroid dysfunction in humans can lead to inappropriate autoimmune response. This immune response causes related vascular damage. The vascular injury leads to endothelial dysfunction and

atherosclerosis, which aggravate the severity of stroke and the probability of poor prognosis (Tatar *et al.* 2011; Imaizumi *et al.* 2004; Cappola & Ladenson 2003).

Some researchers have shown that male (Arauz *et al.* 2020), diabetes mellitus, dyslipidemia, and hypertension were key risk factors for intracranial stenosis and injury in patients with AIS (Wang *et al.* 2017a). In our subgroup analysis, FT3 was statistically significant in the patients without hypertension, coronary heart disease, diabetes mellitus, and atrial fibrillation. After adjusting for potential confounders, TSH was statistically significant in the patients without hypertension, coronary heart disease, diabetes mellitus, and atrial fibrillation. This indicates that FT3 and TSH may be independent risk factors for aggravating the severity of stroke and poor prognosis. In stroke patients with poor outcomes, FT3 level was generally low, and low FT3 syndrome is an early warning factor for cardiovascular and cerebrovascular diseases. Current data suggest that low FT3 levels immediately after acute ischemic stroke (AIS) are associated with more severe stroke , higher mortality and poorer functional outcomes.

In summary, our study found that FT3 and TSH were associated with 90-day poor outcomes in patients with AIS, and patients with low FT3 or TSH may have a worse outcome than other patients. These clinical indicators can help clinicians identify poor prognosis early and implement appropriate interventions. The limitation of this study is that a single-centre retrospective study with small sample may lead to bias. In addition, we measured thyroid hormone levels only once, rather than dynamic changed with time. Therefore, our results are preliminary conclusions and need to be replicated in more larger patient samples.

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AUTHORS' CONTRIBUTIONS

MWu and WlLi designed the research study. QHF performed the research. YZL provided help and advice. QHF, YJYX, TRZ and MYH were in charge of follow-up of patients and collected data. YZ analyzed the data. QHF wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Jiangsu Province Hospital of Chinese Medicine. The ethical statement No. is 2017NL-012-01. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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REFERENCES

1 Alevizaki M, Synetou M, Xynos K, Alevizaki CC,Vemmos KN (2006). Hypothyroidism as a protective factor in acute stroke patients. Clin Endocrinol (Oxf). **65**: 369–372.
2 Arauz A, Serrano F, Ameriso SF, Pujol-Lereis V, Flores A, Bayona H, et al. (2020). Sex Differences Among Participants in the Latin American Stroke Registry. J Am Heart Assoc. **9**: e013903.
3 Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B (2001). Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J. **142**: 838–842.
4 Bensenor IM, Olmos RD,Lotufo PA (2012). Hypothyroidism in the elderly: diagnosis and management. Clin Interv Aging. **7**: 97–111.
5 Cappola AR, Ladenson PW (2003). Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab. **88**: 2438–2444.
6 Chaker L, Baumgartner C, Den Elzen WP, Collet TH, Ikram MA, Blum MR, et al. (2016). Thyroid Function Within the Reference Range and the Risk of Stroke: An Individual Participant Data Analysis. J Clin Endocrinol Metab. **101**: 4270–4282.
7 Chakraborti S, Chakraborti T, Mandal M, Das S, Batabyal SK (1999). Hypothalamic–pituitary–thyroid axis status of humans during development of ageing process. Clinica Chimica Acta. **288**: 137–145.
8 Ellervik C, Roselli C, Christophersen IE, Alonso A, Pietzner M, Sitlani CM, et al. (2019). Assessment of the Relationship Between Genetic Determinants of Thyroid Function and Atrial Fibrillation: A Mendelian Randomization Study. JAMA Cardiol. **4**: 144–152.
9 Gao N, Zhang W, Zhang YZ, Yang Q,Chen SH (2013). Carotid intima-media thickness in patients with subclinical hypothyroidism: a meta-analysis. Atherosclerosis. **227**: 18–25.
10 Genovese T, Impellizzeri D, Ahmad A, Cornelius C, Campolo M, Cuzzocrea S,Esposito E (2013). Post-ischaemic thyroid hormone treatment in a rat model of acute stroke. Brain Res. **1513**: 92–102.
11 Hiroi Y, Kim H, Ying H, Furuya F, Huang Z, Simoncini T, et al. (2006). Rapid nongenomic actions of thyroid hormone. Proceedings of the National Academy of Sciences of the United States of America. **103**: 14104–14109.
12 Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, et al. (2004). Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab. **89**: 3365–3370.
13 Iwen KA, Schroder E,Brabant G (2013). Thyroid hormones and the metabolic syndrome. Eur Thyroid J. **2**: 83–92.
14 Jaakkola J, Mustonen P, Kiviniemi T, Hartikainen JE, Palomaki A, Hartikainen P, et al. (2016). Stroke as the First Manifestation of Atrial Fibrillation. PLoS One. **11**: e0168010.
15 Jiang X, Xing H, Wu J, Du R, Liu H, Chen J, et al. (2017). Prognostic value of thyroid hormones in acute ischemic stroke - a meta analysis. Sci Rep. **7**: 16256.

16 Lamba N, Liu C, Zaidi H, Broekman MLD, Simjian T, Shi C, et al. (2018). A prognostic role for Low tri-iodothyronine syndrome in acute stroke patients: A systematic review and meta-analysis. Clin Neurol Neurosurg. **169**: 55–63.
17 Leonards CO, Schneider HJ, Liman TG, Fiebach JB, Endres M,Ebinger M (2014). Thyroid-stimulating hormone, white matter hyperintensities, and functional outcome in acute ischemic stroke patients. Cerebrovasc Dis Extra. **4**: 61–68.
18 Marouli E, Kus A, Del Greco MF, Chaker L, Peeters R, Teumer A, et al. (2020). Thyroid Function Affects the Risk of Stroke via Atrial Fibrillation: A Mendelian Randomization Study. J Clin Endocrinol Metab. **105**.
19 Mdzinarishvili A, Sutariya V, Talasila PK, Geldenhuys WJ,Sadana P (2013). Engineering triiodothyronine (T3) nanoparticle for use in ischemic brain stroke. Drug Deliv Transl Res. **3**: 309–317.
20 Saini V, Guada L, Yavagal DR (2021). Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. Neurology. **97**: S6–S16.
21 Schattner A (2019). Primary stroke prevention: a paradigm shift focusing on silent paroxysmal atrial fibrillation. QJM. **112**: 247–249.
22 Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. (2012). The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. **345**: e7895.
23 Singer DE, Ziegler PD, Koehler JL, Sarkar S, Passman RS (2021). Temporal Association Between Episodes of Atrial Fibrillation and Risk of Ischemic Stroke. JAMA Cardiol. **6**: 1364–1369.
24 Suda S, Muraga K, Kanamaru T, Okubo S, Abe A, Aoki J, et al. (2016). Low free triiodothyronine predicts poor functional outcome after acute ischemic stroke. J Neurol Sci. **368**: 89–93.
25 Suzuki M, Furuya K, Ozawa M, Miura K, Ozawa T, Matsuzono K, et al. (2021). Complex Aortic Arch Atherosclerosis in Acute Ischemic Stroke Patients with Non-Valvular Atrial Fibrillation. J Atheroscler Thromb. **28**: 776–785.
26 Talhada D, Santos CRA, Goncalves I, Ruscher K (2019). Thyroid Hormones in the Brain and Their Impact in Recovery Mechanisms After Stroke. Front Neurol. **10**: 1103.
27 Taroza S, Rastenyte D, Podlipskyte A, Kazlauskas H,Mickuviene N (2020). Nonthyroidal Illness Syndrome in Ischaemic Stroke Patients is Associated with Increased Mortality. Exp Clin Endocrinol Diabetes. **128**: 811–818.
28 Tatar E, Kircelli F, Asci G, Carrero JJ, Gungor O, Demirci MS, et al. (2011). Associations of triiodothyronine levels with carotid atherosclerosis and arterial stiffness in hemodialysis patients. Clin J Am Soc Nephrol. **6**: 2240–2246.
29 Wang J, Wen X, Li W, Li X, Wang Y,Lu W (2017a). Risk Factors for Stroke in the Chinese Population: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis. **26**: 509–517.
30 Wang Y, Zhou S, Bao J, Pan S, Zhang X (2017b). Low T3 levels as a predictor marker predict the prognosis of patients with acute ischemic stroke. Int J Neurosci. **127**: 559–566.
31 Wollenweber FA, Zietemann V, Gschwendtner A, Opherk C,Dichgans M (2013). Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke. Stroke. **44**: 1446–1448.
32 Zhang S, Zhao X, Xu S, Yuan J, Si Z, Yang Y, et al. (2019). Low free triiodothyronineis predicts worsen neurological outcome of patients with acute ischemic stroke: a retrospective study with bioinformatics analysis. BMC Neurol. **19**: 272.
33 Zubair Khan M, Gupta A, Hodge J, Patel K, Patel K, Zarak MS, et al. (2021). Clinical outcomes of atrial fibrillation with hyperthyroidism. J Arrhythm. **37**: 942–948.