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ORIGINAL RESEARCH ARTICLE

Sex differences in thyroid hormone and ferritin levels and short-term functional outcomes in acute ischemic stroke

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Abstract

Introduction: Acute ischemic stroke (AIS) is a major cause of death and disability worldwide. Thyroid hormones and ferritin are involved in neuronal recovery and iron metabolism after cerebral ischemia. However, their association with short-term functional outcomes in AIS, particularly potential sex-specific differences, remains unclear. This study investigated the relationship between thyroid hormone and ferritin levels and short-term functional prognosis in AIS patients.

Objective: This study aims to investigate the relationship between thyroid hormones and ferritin and the prognosis of patients with AIS, and to evaluate whether there is a sex-specific difference, which could provide a reference for predicting the short-term functional outcome of patients with AIS.

Methods: A total of 961 patients with AIS were recruited from January 2019 to December 2021. Patient demographic and clinical data were collected, and thyroid hormones (free triiodothyronine [FT3], free thyroxine, total triiodothyronine [TT3], and total thyroxine) and ferritin levels were measured on admission. Statistical methods, including t-test, chi-square test, logistic regression analysis, and correlation analysis, were used to analyze the predictive value of thyroid hormone and ferritin levels regarding short-term functional outcome in AIS patients stratified by sex.

Results: Lower FT3 and TT3 levels and higher ferritin levels were observed in patients with poor outcomes ($p < 0.05$). After adjustment for confounders, the findings revealed that TT3 was independently associated with poor short-term functional outcome (odds ratio = 0.405, 95% confidence interval: 0.203–0.807, $p = 0.010$). In sex-stratified analyses, TT3 levels were statistically correlated with poor outcomes among male patients, whereas free thyroxine, TT3, and ferritin were associated with poor outcomes in female patients. FT3 and TT3 were negatively correlated with modified Rankin Scale scores in both sexes, while ferritin showed a positive correlation with poor outcome only in female patients.

Conclusion: Thyroid hormone and ferritin levels can serve as potential predictors of

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short-term functional outcome in patients with AIS, and sex-specific differences exist in their effects.

Keywords: Acute ischemic stroke; Short-term functional outcome; Thyroid hormones; Iron metabolism; Ferritin

1. Introduction

Stroke represents one of the most prevalent and fatal diseases in adults, characterized by sudden onset and rapid progression, resulting in localized or diffuse cerebral impairment.[1-3] Owing to these clinical features, stroke often leads to rapid neurological deterioration and severe functional deficits, posing a major challenge to both acute management and long-term rehabilitation.

In recent years, stroke has risen markedly in China's ranking of causes of death, becoming the leading contributor to mortality nationwide, while its overall prevalence continues to increase annually.[4] This epidemiological trend reflects not only population aging but also changes in lifestyle and an increasing burden of vascular risk factors. Large-scale survey data indicate that the annual incidence of stroke in China is 246.8 cases per 100,000 persons, with a corresponding annual mortality of 114.8 deaths per 100,000 persons.[5]

Despite advances in acute treatment strategies, a substantial proportion of stroke survivors experience persistent neurological impairment. More than 50% of patients develop varying degrees of post-stroke sequelae, among which limb motor dysfunction remains the most common and disabling complication. These long-term functional limitations frequently require prolonged medical care and rehabilitation support, resulting in increased healthcare expenditures and nursing demands, thus imposing a considerable socioeconomic burden on both families and the healthcare system.[5] Therefore, the identification of reliable early prognostic indicators is of critical importance for optimizing clinical decision-making, improving rehabilitation planning, and promoting functional recovery in patients with stroke.

Thyroid hormones are of great importance in the development of the human brain.[6] From the early stages of embryonic development, thyroid hormones participate in multiple critical neurodevelopmental processes, including neuronal proliferation, migration, and differentiation, as well as synaptogenesis, synaptic plasticity, and myelin formation, all of which are essential for the establishment of normal neural networks and cognitive function.[7] Adequate thyroid hormone availability during these periods is therefore indispensable for maintaining the structural and functional integrity of the central nervous system. Clinical evidence has demonstrated that stroke can induce alterations in thyroid function even in patients without pre-existing thyroid disease. It has been reported that approximately 17.8% of stroke patients experience changes in thyroid hormone profiles, reflecting a stress-related endocrine response following cerebral ischemic injury.[8] After acute ischemic stroke (AIS), circulating thyroid hormone levels, particularly free triiodothyronine (FT3), show a rapid decline during the acute phase, reaching a nadir shortly after stroke onset, followed by a gradual recovery during the chronic stage of disease progression.[8] This dynamic fluctuation suggests that thyroid hormone metabolism is closely linked to the pathophysiological response to ischemic brain injury.

In addition, elevated thyroid-stimulating hormone and FT3 levels have been reported to be associated with stroke incidence and appear to accumulate progressively over time, indicating a potential long-term interaction between thyroid function and cerebrovascular risk.[9] Together, these observations highlight the complex bidirectional relationship between thyroid hormone regulation and stroke pathology and provide a biological basis for exploring the prognostic value of thyroid hormone alterations in patients with AIS.

Ferritin levels are associated with an increased risk of stroke.[10] Increasing evidence suggests that iron ion-mediated oxidative stress plays a critical role in the pathogenesis of acute stroke.[11] Following stroke onset, excessive oxidative stress leads to the release of iron from ferritin, thereby increasing the pool of labile iron within the cytosol and exacerbating intracellular iron overload.[11] This accumulation of free iron further amplifies oxidative damage by promoting the generation of reactive oxygen species, creating a vicious cycle of oxidative injury within ischemic brain tissue. Iron can be released from ferritin either directly or indirectly through lipid peroxidation processes. These pathological changes disrupt cell membrane integrity by altering membrane fluidity and impairing membrane-bound enzyme complexes, ultimately resulting in cellular edema, membrane rupture, and even irreversible cell death.[11] Such structural and

biochemical damage contributes to neuronal vulnerability and accelerates ischemia-induced tissue injury.

Ferritin is an intracellular protein complex responsible for binding and storing free iron in a non-toxic form, thereby maintaining iron homeostasis under physiological conditions. Clinically, ferritin serves as an important biomarker reflecting systemic iron reserves. Elevated circulating ferritin levels have been consistently linked to an increased risk of stroke, indicating that excessive iron storage may predispose individuals to cerebrovascular events and worsen ischemic susceptibility.[12]

Previous studies have shown a strong correlation between thyroid hormones and ferritin with the functional outcomes of stroke patients.[13] However, substantial heterogeneity exists regarding study design, endpoints, and clinical applicability (Table A1). There is a lack of research focusing on the connection between these hormone and protein levels and the short-term prognosis in AIS patients, especially when considering gender as a stratification factor. Therefore, the present study aimed to explore the sex-specific differences in thyroid hormone and ferritin levels on the short-term functional prognosis of acute stroke, with the aim of providing a reference for early predictors of prognosis in cerebrovascular disease.

2. Methodology

2.1. Study population

This study was designed as a retrospective observational analysis. Consecutive patients diagnosed with AIS and admitted to the hospital during the study period were screened for eligibility. AIS was confirmed by computed tomography or magnetic resonance imaging. Eligible patients were enrolled according to predefined inclusion and exclusion criteria to ensure data completeness and diagnostic accuracy. Ultimately, a total of 961 patients with AIS were included in accordance with the established criteria.

Inclusion criteria were as follows:

(i) Patients with AIS of vascular etiology.
(ii) Aged 18 years and above.
(iii) Hospitalized within seven days of stroke onset.
(iv) AIS diagnosed based on computed tomography and/or magnetic resonance imaging.

Exclusion criteria were as follows:

(i) Patients with severe comorbidities, including cardiac, pulmonary, hepatic, and renal insufficiency.
(ii) Patients with insufficient laboratory data or missing information on their modified Rankin Scale (mRS) score at discharge.

The study received approval from the Ethics Committee of the First Hospital of Hebei Medical University (approval number: 20220642). All participants provided written informed consent prior to participation in the study.

2.2. Data collection

We extracted demographic and clinical information for all enrolled patients, encompassing various aspects such as age, gender, height, weight, body mass index, blood pressure, length of hospital stay, and details regarding their lifestyle habits, including smoking and alcohol consumption. Additionally, we documented their medical history, which included previous diagnoses of hypertension, diabetes, stroke, atrial fibrillation, and coronary heart disease. We also reviewed their medication history, focusing on the use of lipid-lowering, hypoglycemic, antihypertensive, and antiplatelet medications.[14]

2.3. National Institutes of Health Stroke Scale

The National Institutes of Health Stroke Scale (NIHSS) comprises 15 items that evaluate a broad range of neurological domains, including level of consciousness, ocular movements, visual field function, facial motor performance, muscle strength of the upper and lower limbs, sensory function, coordination, speech, language, and neglect. The total score ranges from 0 to 42, with higher values reflecting greater neurological impairment and more severe deficits across the assessed functional domains.

2.4. Modified Rankin Scale

In this study, the short-term functional outcomes of patients were evaluated using the mRS score at the time of hospital discharge. The mRS scores ranged from 0 to 6. Higher scores indicate poorer functional status. Patients were grouped into two categories: a group with a good prognosis (mRS: 0–2) and a group with a poor prognosis (mRS: 3–6) on the basis of their mRS scores at discharge.

2.5. Laboratory examination

Venous blood samples were collected from all participants within 24 hours after hospital admission. Serum levels of FT3, free thyroxine (FT4), total triiodothyronine (TT3), thyroid-stimulating hormone, and ferritin were measured using standardized automated immunoassay techniques in the hospital central laboratory. All laboratory procedures were performed according to the manufacturer's instructions and institutional quality control protocols. Internal quality control samples were routinely used to

ensure measurement reliability and reproducibility.

2.6. Statistical analysis

All statistical analyses were performed using SPSS software (version 27.0, IBM Corp., USA). Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed variables were presented as mean ± standard deviation and compared using the independent samples *t*-test, whereas non-normally distributed variables were expressed as the median with interquartile range and compared using the Mann–Whitney *U* test. Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

Univariate logistic regression analysis was initially performed to identify potential predictors associated with poor short-term functional outcomes. Variables with statistical significance ($p < 0.05$) in the univariate analysis were subsequently entered into a multivariate logistic regression model to determine independent prognostic factors while adjusting for potential confounders. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to quantify the strength of the associations. Spearman's correlation analysis was conducted to evaluate the relationships between thyroid hormone levels, ferritin concentrations, and short-term functional outcomes. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Receiver operating characteristic curve analysis demonstrated that the multivariable logistic regression model achieved an area under the curve of 0.837, indicating good discriminative performance in predicting poor short-term functional outcomes (Figure 1).

As shown in Table A2, based on clinical relevance and prior literature, the prognostic prediction models incorporated demographic, clinical, and biomarker parameters. Demographic variables included age and sex. Clinical variables included admission NIHSS score, length of hospital stay, and history of previous stroke. Thyroid hormone biomarkers included FT3, FT4, TT3, and TT4. Ferritin was included as an indicator of iron metabolism status. Univariate logistic regression was initially conducted to screen for potential predictors of poor short-term functional outcomes. Variables showing statistical significance ($p < 0.05$) in the univariate analysis were subsequently included in the multivariate logistic regression model.

3. Results

3.1. Baseline characteristics

In this study, a total of 961 patients with AIS were enrolled, with an average age of 63.34 ± 12.38 years. Among them, 606 were men and 355 were women. Patients were stratified

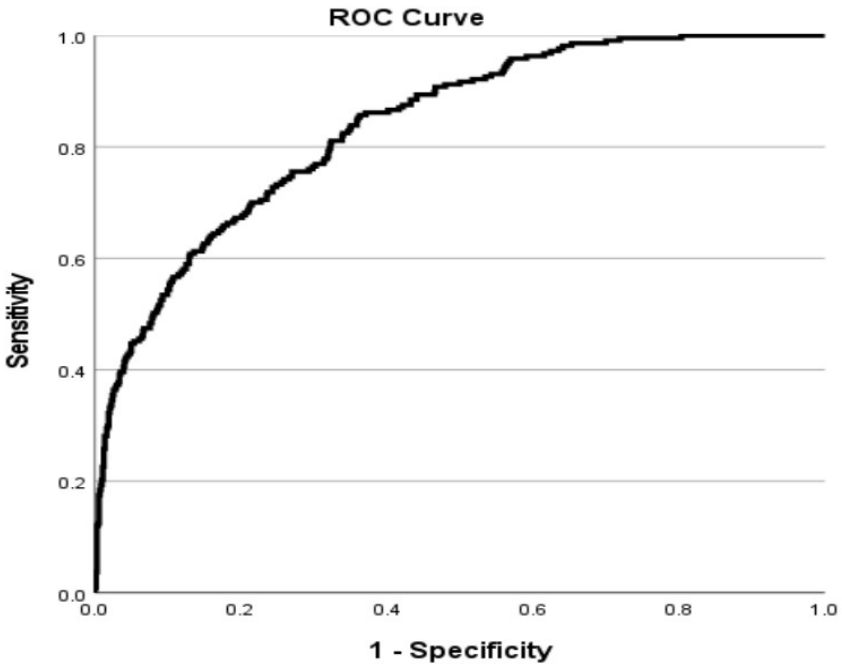

Figure 1. Receiver operating characteristic curve of the logistic model

into two groups according to their discharge mRS scores: those with a good short-term functional outcome (mRS: 0–2; $n = 744$) and those with a poor short-term functional outcome (mRS: 3–6; $n = 217$).

Table 1 summarizes the baseline characteristics of the participants. Several significant differences were observed between the two groups. Specifically, patients with poor short-term functional outcomes were significantly older (67 vs. 63.5 years; $p < 0.001$), had a higher proportion of men (56.2% vs. 65.1%; $p = 0.018$), higher admission NIHSS score (6 vs. 2; $p < 0.001$), longer hospital stays (12 vs. 11; $p < 0.001$), and a higher prevalence of a history of stroke (33.2% vs. 26.3%; $p = 0.048$). Furthermore, these patients also exhibited lower levels of FT3 (4.54 mmol/L vs. 4.77 mmol/L; $p < 0.001$) and TT3 (1.21 mmol/L vs. 1.31 mmol/L; $p < 0.001$) compared to those with good short-term functional outcomes.

3.2. Comparison of clinical characteristics between male and female patients

When analyzing sex-specific differences, the findings revealed that among male patients, those with poor short-term functional outcomes had lower levels of FT3 (4.60 mmol/L vs. 4.83 mmol/L; $p = 0.003$) and TT3 (1.23 mmol/L vs. 1.34 mmol/L; $p = 0.001$) (Table 2), whereas among female patients, participants with poor short-term functional outcomes not only had lower levels of FT3 and TT3, but also higher levels of ferritin (84.55 mmol/L vs. 65.10 mmol/L; $p = 0.017$) (Table 3).

3.3. Single-variable logistic regression analysis of short-term functional outcomes in acute ischemic stroke patients

Based on Table 4, factors such as age, sex, admission NIHSS score, length of hospital stay, history of stroke, as well as FT4, TT3, and ferritin levels were significantly associated with poor short-term functional outcomes in patients with AIS ($p < 0.05$). For male patients, age, NIHSS score on admission, length of hospitalization, high-density lipoprotein, and TT3 were significantly associated with poor short-term functional outcomes ($p < 0.05$). For female patients, age, NIHSS score on admission, FT4, TT3, and ferritin were significantly associated with poor short-term functional outcomes ($p < 0.05$). These findings indicate that reduced thyroid hormone levels and elevated ferritin concentrations may be associated with poorer short-term neurological recovery after AIS. Lower FT3 and TT3 levels may reflect impaired neuroendocrine regulation or metabolic stress following ischemic injury, whereas increased ferritin levels may reflect a heightened inflammatory response.

3.4. Multivariate logistic regression analysis of short-term functional outcomes in acute ischemic stroke patients

Based on Table 5, after controlling for factors such as age, sex, admission NIHSS score, length of hospital stay, and history of stroke, TT3 (OR = 0.405, 95% CI = 0.203–0.807) was identified as an independent predictor of poor short-term functional outcomes in AIS patients. In the subgroup of male patients, TT3 (OR = 0.420, 95% CI = 0.176–1.005) was identified as an independent predictor for poor short-term functional outcomes. However, in the subgroup of female patients, neither thyroid hormone levels nor ferritin levels independently predicted poor short-term functional outcomes.

3.5. Correlation analysis of thyroid hormone and ferritin levels with short-term functional outcomes in acute ischemic stroke patients

As presented in Table 6, the levels of FT3 and TT3 exhibited a negative correlation with short-term functional outcomes in patients with AIS ($p < 0.001$). Specifically, in male patients, both FT3 ($p = 0.003$) and TT3 ($p = 0.001$) were negatively associated with short-term functional outcomes. This finding suggests that lower levels of FT3 and TT3 are associated with poorer short-term functional outcomes in male patients.

Similarly, in female patients, FT3 ($p = 0.042$) and TT3 ($p = 0.002$) were also negatively associated with short-term functional outcomes. Furthermore, in female patients, ferritin levels were positively correlated with short-term functional outcomes ($p = 0.017$). This finding suggests that lower levels of FT3 and TT3, coupled with higher ferritin levels, are associated with poorer short-term functional outcomes in female patients.

4. Discussion

This study examined the correlation between thyroid hormone levels—specifically FT4, TT3, and ferritin levels—and early functional outcomes after acute stroke, and highlighted the significance of sex-specific differences in these correlations. The findings indicate that in AIS patients, FT4, TT3, and ferritin levels are associated with poor short-term functional outcomes. Notably, in male patients, TT3 was associated with poor short-term functional outcomes, while in female patients, both FT4 and TT3, along with ferritin levels, were associated with poor short-term functional outcomes. After adjusting for various potential confounding factors such as age, sex, admission NIHSS score, length of hospital stay, and history of stroke, TT3 was identified as an independent predictor

Table 1. Patient characteristics by short-term functional outcome at discharge

Characteristics	Good functional outcome (*n* = 744)	Poor functional outcome (*n* = 217)	*p*-value
Demographic			
Age (years; median [IQR])	63.5 [54, 71.5]	67 [59, 75]	<0.001
Age of female participants (years; median [IQR])	68 [59, 74]	71 [63, 77]	0.010
Male (*n* [%])	484 (65.1%)	122 (56.2%)	0.018
Smoker (*n* [%])	267 (35.9%)	63 (29.0%)	0.061
Alcohol consumption (*n* [%])	239 (32.1%)	56 (25.8%)	0.076
Clinical features (median [IQR])			
Length of hospital stay (days)	11 [9, 13]	12 [10, 15]	<0.001
SBP (mmHg)	151 [138, 166]	153 [140, 165]	0.412
DBP (mmHg)	90 [82, 100.5]	89 [81, 101]	0.422
Admission NIHSS score	2 [1, 4]	6 [4, 10]	<0.001
Laboratory data (median [IQR])			
TC (mmol/L)	4.63 [3.94, 5.33]	4.68 [3.96, 5.43]	0.463
TG (mmol/L)	1.26 [0.93, 1.79]	1.26 [0.92, 1.69]	0.489
HDL-C (mmol/L)	1.00 [0.84, 1.16]	1.03 [0.85, 1.18]	0.168
LDL-C (mmol/L)	2.94 [2.39, 3.45]	3.02 [2.37, 3.67]	0.170
GLU (mmol/L)	5.49 [4.86, 6.73]	5.49 [4.86, 7.28]	0.524
FT3 (mmol/L)	4.77 [4.33, 5.23]	4.54 [4.05, 5.07]	<0.001
FT4 (mmol/L)	11.55 [10.35, 12.91]	11.88 [10.52, 13.20]	0.055
TT3 (mmol/L)	1.31 [1.12, 1.51]	1.21 [1.03, 1.44]	<0.001
TT4 (mmol/L)	115.73 [101.07, 129.78]	115.80 [101.57, 132.51]	0.442
Ferritin (mmol/L)	94.90 [55.15, 147.90]	105.05 [61.10, 168.80]	0.076
Folate (mmol/L)	6.60 [4.80, 9.00]	6.30 [4.60, 9.80]	0.750
Vitamin B12 (mmol/L)	226.00 [162.25, 346.40]	219.50 [152.50, 367.00]	0.562
Medical history (*n* [%])			
Hypertension	492 (66.1%)	150 (69.1%)	0.410
Diabetes	195 (26.2%)	69 (31.8%)	0.105
Stroke	196 (26.3%)	72 (33.2%)	0.048
Atrial fibrillation	30 (4.0%)	13 (6.0%)	0.219
Coronary heart disease	80 (10.8%)	19 (8.8%)	0.395
Medication use history (n [%])			
Lipid-lowering drugs	80 (10.8%)	20 (9.2%)	0.514
Hypoglycemic drugs	151 (20.3%)	44 (20.3%)	0.995
Antihypertensive drugs	323 (43.4%)	84 (38.7%)	0.217
Antiplatelet drugs	125 (16.8%)	30 (13.8%)	0.294
Thrombolysis	31 (4.2%)	12 (5.5%)	0.393

Abbreviations: DBP: Diastolic blood pressure; FT3: Free triiodothyronine; FT4: Free thyroxine; GLU: Plasma glucose; HDL-C: High-density lipoprotein cholesterol; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TT3: Total triiodothyronine; TT4: Total thyroxine.

Table 2. Male patient characteristics by short-term functional outcome at discharge

Characteristics	Good functional outcome (*n* = 484)	Poor functional outcome (*n* = 122)	*p*-value
Demographic			
Age (years; median [IQR])	61 [52, 70]	63 [55, 72]	0.029
Smoker (*n* [%])	265 (54.8%)	61 (50.0%)	0.347
Alcohol consumption (*n* [%])	237 (49.0%)	55 (45.1%)	0.443
Clinical features (median [IQR])			
Length of hospital stay (days)	11 [9, 13]	12 [10, 15]	< 0.001
SBP (mmHg)	150 [138, 165]	151 [139, 163]	0.958
DBP (mmHg)	92 [83, 102]	92.5 [83, 102]	0.836
Admission NIHSS score	2 [1, 4]	6 [3, 11]	< 0.001
Laboratory data (median [IQR])			
TC (mmol/L)	4.47 [3.83, 5.26]	4.59 [3.80, 5.38]	0.587
TG (mmol/L)	1.29 [0.95, 1.88]	1.26 [0.91, 1.67]	0.276
HDL-C (mmol/L)	0.96 [0.81, 1.11]	0.98 [0.84, 1.14]	0.104
LDL-C (mmol/L)	2.85 [2.34, 3.39]	2.95 [2.29, 3.70]	0.340
GLU (mmol/L)	5.47 [4.87, 6.59]	5.29 [4.82, 6.96]	0.622
FT3 (mmol/L)	4.83 [4.38, 5.35]	4.60 [4.15, 5.15]	0.003
FT4 (mmol/L)	11.64 [10.45, 12.98]	11.96 [10.58, 13.48]	0.206
TT3 (mmol/L)	1.34 [1.14, 1.52]	1.23 [1.05, 1.45]	0.001
TT4 (mmol/L)	113.48 [99.81, 127.52]	112.91 [100.60, 130.08]	0.730
Ferritin (mmol/L)	105.30 [71.15, 175.05]	130.40 [69.20, 200.60]	0.160
Folate (mmol/L)	5.90 [4.40, 7.95]	5.70 [4.20, 8.30]	0.952
Vitamin B12 (mmol/L)	222.00 [153.95, 319.50]	210.00 [137.00, 340.00]	0.469
Medical history (*n* [%])			
Hypertension	321 (66.3%)	81 (66.4%)	0.988
Diabetes	120 (24.8%)	34 (27.9%)	0.486
Stroke	136 (28.1%)	45 (36.9%)	0.058
Atrial fibrillation	21 (4.3%)	5 (4.1%)	0.907
Coronary heart disease	44 (9.1%)	11 (9.0%)	0.980
Medication use history (*n* [%])			
Lipid-lowering drugs	52 (10.7%)	11 (9.0%)	0.576
Hypoglycemic drugs	106 (21.9%)	23 (18.9%)	0.462
Antihypertensive drugs	203 (41.9%)	42 (34.4%)	0.131
Antiplatelet drugs	75 (15.5%)	18 (14.8%)	0.839
Thrombolysis	21 (4.3%)	9 (7.4%)	0.167

Abbreviations: DBP: Diastolic blood pressure; FT3: Free triiodothyronine; FT4: Free thyroxine; GLU: Plasma glucose; HDL-C: High-density lipoprotein cholesterol; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TT3: Total triiodothyronine; TT4: Total thyroxine.

Table 3. Female patient characteristics by short-term functional outcome at discharge

Characteristics	Good functional outcome (*n* = 260)	Poor functional outcome (*n* = 95)	*p*-value
Demographic			
Age (years; median [IQR])	68 [59, 74]	71 [63, 77]	0.010
Smoker (*n* [%])	2 (0.8%)	2 (2.1%)	0.626
Alcohol consumption (*n* [%])	2 (0.8%)	1 (1.1%)	1.000
Clinical features (median [IQR])			
Length of hospital stay (days)	11 [9, 13]	12 [10, 15]	0.047
SBP (mmHg)	153 [139, 168]	157 [143, 167]	0.253
DBP (mmHg)	88 [79, 98]	87 [79, 98]	0.584
Admission NIHSS score	2 [1, 4]	6 [4, 10]	< 0.001
Laboratory data (median [IQR])			
TC (mmol/L)	4.79 [4.17, 5.46]	4.91 [4.08, 5.52]	0.888
TG (mmol/L)	1.19 [0.93, 1.64]	1.27 [0.94, 1.76]	0.639
HDL-C (mmol/L)	1.06 [0.92, 1.24]	1.06 [0.88, 1.24]	0.727
LDL-C (mmol/L)	3.09 [2.53, 3.53]	3.14 [2.53, 3.65]	0.604
GLU (mmol/L)	5.57 [4.81, 6.98]	5.84 [4.88, 7.85]	0.209
FT3 (mmol/L)	4.65 [4.25, 5.03]	4.48 [4.00, 5.00]	0.042
FT4 (mmol/L)	11.38 [10.11, 12.66]	11.71 [10.43, 13.19]	0.080
TT3 (mmol/L)	1.29 [1.11, 1.48]	1.17 [1.02, 1.42]	0.002
TT4 (mmol/L)	118.67 [105.40, 132.79]	119.31 [103.65, 136.60]	0.734
Ferritin (mmol/L)	65.10 [41.45, 108.15]	84.55 [54.60, 131.90]	0.017
Folate (mmol/L)	7.90 [6.00, 10.75]	6.75 [5.00, 10.90]	0.144
Vitamin B12 (mmol/L)	229.95 [174.95, 398.50]	232.20 [165.30, 423.70]	0.724
Medical history (*n* [%])			
Hypertension	171 (65.8%)	69 (72.6%)	0.273
Diabetes	75 (28.8%)	35 (36.8%)	0.189
Stroke	60 (23.1%)	27 (28.4%)	0.370
Atrial fibrillation	9 (3.5%)	8 (8.4%)	0.098
Coronary heart disease	36 (13.8%)	8 (8.4%)	0.234
Medication use history (*n* [%])			
Lipid-lowering drugs	28 (10.8%)	9 (9.5%)	0.875
Hypoglycemic drugs	45 (17.3%)	21 (22.1%)	0.382
Antihypertensive drugs	120 (46.2%)	42 (44.2%)	0.837
Antiplatelet drugs	50 (19.2%)	12 (12.6%)	0.196
Thrombolysis	10 (3.8%)	3 (3.2%)	1.000

Abbreviations: DBP: Diastolic blood pressure; FT3: Free triiodothyronine; FT4: Free thyroxine; GLU: Plasma glucose; HDL-C: High-density lipoprotein cholesterol; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TT3: Total triiodothyronine; TT4: Total thyroxine.

Table 4. Univariate logistic regression of factors associated with poor short-term functional outcome

Variable	Poor short-term functional outcome (mRS = 3–6)					
	All patients (*n* = 961)		Male patients (*n* = 606)		Female patients (*n* = 355)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographic						
Age (years)	1.025 [1.012–1.038]	<0.001	1.018 [1.002–1.035]	0.027	1.031 [1.008–1.055]	0.009
Male	0.690 [0.507–0.938]	0.018	-	-	-	-
Smoker	0.731 [0.526–1.016]	0.062	0.826 [0.555–1.230]	0.347	2.774 [0.385–19.978]	0.311
Alcohol consumption	0.735 [0.523–1.033]	0.077	0.856 [0.574–1.275]	0.443	1.372 [0.123–15.311]	0.797
Clinical features						
Length of hospital stay	1.071 [1.033–1.109]	<0.001	1.079 [1.030–1.131]	0.001	1.056 [0.999–1.115]	0.053
SBP	1.004 [0.997–1.011]	0.284	1.000 [0.991–1.009]	1.000	1.007 [0.997–1.018]	0.179
DBP	0.995 [0.984–1.005]	0.322	0.999 [0.986–1.013]	0.902	0.992 [0.975–1.009]	0.356
Admission NIHSS score	1.418 [1.340–1.500]	<0.001	1.366 [1.277–1.461]	<0.001	1.535 [1.381–1.707]	<0.001
Laboratory data						
TC	1.057 [0.927–1.205]	0.407	1.021 [0.861–1.212]	0.810	1.072 [0.868–1.324]	0.520
TG	1.005 [0.880–1.147]	0.944	0.964 [0.805–1.154]	0.689	1.117 [0.888–1.406]	0.343
HDL	1.622 [0.917–2.870]	0.096	2.130 [1.025–4.427]	0.043	0.781 [0.300–2.031]	0.612
LDL	1.123 [0.936–1.346]	0.213	1.085 [0.858–1.374]	0.495	1.127 [0.840–1.512]	0.426
GLU	1.027 [0.972–1.084]	0.346	1.026 [0.947–1.112]	0.529	1.018 [0.944–1.098]	0.638
FT3	1.002 [0.996–1.008]	0.451	1.009 [0.991–1.028]	0.332	0.705 [0.497–1.001]	0.051
FT4	1.111 [1.031–1.196]	0.006	1.089 [0.983–1.208]	0.104	1.140 [1.024–1.269]	0.017
TT3	0.248 [0.140–0.437]	<0.001	0.293 [0.142–0.602]	0.001	0.209 [0.082–0.528]	0.001
TT4	1.004 [0.997–1.010]	0.272	1.002 [0.993–1.011]	0.710	1.003 [0.994–1.013]	0.463
Ferritin	1.002 [1.000–1.003]	0.021	1.001 [1.000–1.003]	0.079	1.003 [1.000–1.005]	0.020
Folate	1.007 [0.995–1.019]	0.258	1.008 [0.963–1.055]	0.726	1.005 [0.993–1.017]	0.445
Vitamin B12	1.000 [1.000–1.001]	0.481	1.000 [0.999–1.001]	0.897	1.000 [1.000–1.001]	0.426

(*cont'd...*)

Table 4. (*Continued*)

Variable	Poor short-term functional outcome (mRS = 3–6)					
	All patients (*n* = 961)		Male patients (*n* = 606)		Female patients (*n* = 355)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Medical history						
Hypertension	1.147 [0.828–1.588]	0.410	1.003 [0.659–1.527]	0.988	1.381 [0.822–2.320]	0.222
Diabetes	1.313 [0.944–1.824]	0.105	1.172 [0.750–1.831]	0.486	1.439 [0.876–2.362]	0.150
Stroke	1.388 [1.002–1.924]	0.049	1.495 [0.985–2.271]	0.059	1.324 [0.778–2.251]	0.301
Atrial fibrillation	1.517 [0.777–2.961]	0.222	0.942 [0.348–2.551]	0.907	2.564 [0.960–6.854]	0.060
Coronary heart disease	0.796 [0.471–1.346]	0.395	0.991 [0.496–1.981]	0.980	0.572 [0.256–1.280]	0.174
Medication use history						
Lipid-lowering drugs	0.843 [0.503–1.410]	0.515	0.823 [0.416–1.630]	0.577	0.867 [0.393–1.912]	0.724
Hypoglycemic drugs	0.999 [0.686–1.455]	0.995	0.828 [0.501–1.369]	0.463	1.356 [0.758–2.425]	0.305
Antihypertensive drugs	0.823 [0.604–1.122]	0.218	0.727 [0.480–1.100]	0.132	0.925 [0.576–1.483]	0.745
Antiplatelet drugs	0.794 [0.516–1.222]	0.295	0.944 [0.540–1.648]	0.839	0.607 [0.308–1.198]	0.150
Thrombolysis	1.346 [0.679–2.669]	0.394	1.756 [0.783–3.937]	0.172	0.815 [0.219–3.028]	0.760

Abbreviations: CI: Confidence interval; DBP: Diastolic blood pressure; FT3: Free triiodothyronine; FT4: Free thyroxine; GLU: Plasma glucose; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TT3: Total triiodothyronine; TT4: Total thyroxine.

Table 5. Multivariate logistic regression analysis of risk factors for poor short-term functional outcome

Risk factor	All patients (*n* = 961)		Male patients (*n* = 606)		Female patients (*n* = 355)	
	p-value	OR (95% CI)	*p*-value	*p*-value	OR (95% CI)	*p*-value
FT4	1.051 [0.962–1.149]	0.269	1.064 [0.945–1.198]	0.304	1.023 [0.887–1.180]	0.754
TT3	0.405 [0.203–0.807]	0.010	0.420 [0.176–1.005]	0.051	0.379 [0.118–1.211]	0.102
TT4	0.998 [0.991–1.006]	0.687	1.002 [0.991–1.012]	0.759	0.994 [0.980–1.007]	0.369
Ferritin	1.002 [1.000–1.003]	0.057	1.002 [0.999–1.004]	0.141	1.003 [1.000–1.006]	0.086
Folate	1.006 [0.992–1.019]	0.403	1.002 [0.951–1.056]	0.935	1.005 [0.991–1.020]	0.466
Vitamin B12	1.000 [0.999–1.001]	0.944	1.000 [0.999–1.001]	0.967	1.000 [0.999–1.001]	0.925

Abbreviations: CI: Confidence interval; FT4: Free thyroxine; OR: Odds ratio; TT3: Total triiodothyronine; TT4: Total thyroxine.

Table 6. Correlation of thyroid hormones and ferritin with poor short-term functional outcome

Biomarker	All patients (n = 961)		Male patients (n = 606)		Female patients (n = 355)	
	r	p	r	p	r	p
FT3	−0.124	< 0.001	−0.121	0.003	−0.108	0.042
FT4	0.062	0.055	0.051	0.207	0.093	0.08
TT3	−0.148	< 0.001	−0.13	0.001	−0.166	0.002
TT4	0.025	0.442	0.014	0.73	0.018	0.735
Ferritin	0.057	0.076	0.057	0.16	0.126	0.017
Folate	−0.01	0.75	0.002	0.952	−0.078	0.144
Vitamin B12	−0.019	0.562	−0.029	0.47	−0.019	0.724

Abbreviations: FT3: Free triiodothyronine; FT4: Free thyroxine; TT3: Total triiodothyronine; TT4: Total thyroxine.

of poor short-term functional outcomes in AIS patients.

Neuroplasticity following ischemic stroke is intricately linked to thyroid hormone levels, as shown in previous studies.[15] Thyroid hormone triiodothyronine (T3) significantly influences astrocytes, whose response to T3 is correlated with their maturity.[15,16] T3-mediated transcriptional regulation controls a number of genes, thereby affecting astrocyte function. Astrocytes are pivotal in the deiodination of thyroid hormones, a process that is compromised by ischemic stroke.[17] This disruption in deiodination can have profound effects on the recovery and plasticity of the brain post-stroke. Sex-specific differences significantly impact astrocyte maturation and differentiation. Male astrocytes mature more rapidly than their female counterparts, exhibit higher levels of glial fibrillary acidic protein, and possess a greater capacity for differentiation.[18]

Estrogen is a key factor in these sex differences, as it modulates gene expression in astrocytes. Women, who have higher estrogen levels, may experience different astrocyte activities compared to men.[19] In the context of ischemic injury, these biological differences may lead to distinct cellular responses to thyroid hormone signaling between males and females. Alterations in astrocyte activity can influence synaptic remodeling, neuroinflammatory regulation, and metabolic support for neurons, all of which are critical processes involved in post-stroke recovery. Consequently, variations in thyroid hormone availability and astrocyte responsiveness may contribute to heterogeneous patterns of neurological repair and functional restoration across sexes. Furthermore, sex-dependent differences in hormone–glial interactions may partly explain the observed divergence in the prognostic value of thyroid hormones between male and female patients. Taken together, these findings suggest that the interaction between thyroid hormone signaling, astrocyte biology, and sex-specific endocrine regulation represents an important mechanistic pathway underlying post-stroke neuroplasticity and recovery.

In addition, the findings demonstrate the relevance of sex-specific differences in the prognostic implications of thyroid hormone alterations and further support the association between thyroid hormone levels and functional outcomes in patients with stroke. These results suggest that the impact of endocrine biomarkers on post-stroke recovery varies by biological sex. In male patients, TT3 was identified as an independent predictor of unfavorable functional outcomes, indicating that TT3 may serve as a clinically relevant marker of early functional impairment in this population. This finding underscores the potential importance of incorporating TT3 into prognostic assessment models for male patients with AIS.

In contrast, among female patients, neither thyroid hormone parameters nor ferritin concentrations showed independent predictive value for short-term functional prognosis, suggesting that these biomarkers alone may not adequately capture prognostic information in this subgroup. This discrepancy emphasizes the presence of sex-related heterogeneity in biomarker performance and highlights the need for sex-specific considerations when interpreting endocrine and metabolic indicators in stroke populations.

Furthermore, Spearman's correlation analysis revealed that both FT3 and TT3 levels were inversely correlated with short-term functional outcomes in both male and female

cohorts. This indicates that lower circulating concentrations of these thyroid hormones are associated with poorer short-term neurological recovery, reinforcing the potential role of thyroid hormone dysregulation in influencing early post-stroke functional status. The consistency of this correlation across sexes suggests that thyroid hormone levels may reflect common pathophysiological mechanisms involved in AIS and recovery.

Additionally, in female patients, ferritin levels showed a positive correlation with short-term functional outcomes, suggesting that increased ferritin concentrations may be linked to poor functional outcomes in women with AIS. This finding indicates that iron metabolism and inflammatory burden may contribute to functional deterioration in female patients and may represent important biological factors influencing early recovery trajectories.

Ferritin levels are markedly elevated in the hippocampus following ischemic stroke and are closely associated with enhanced iron oxidation processes.[20] This abnormal accumulation of ferritin reflects a disturbance in iron homeostasis within ischemic brain tissue and may contribute to secondary neuronal injury. Increasing evidence indicates that ferritin autophagy, also known as ferritinophagy, promotes the release of labile iron, leading to intracellular iron overload and triggering ferroptosis, a regulated form of iron-dependent cell death.[21,22] Moreover, ferritin autophagy has been identified as an important pathogenic mechanism involved in ischemia/reperfusion-induced brain injury, further aggravating oxidative stress and lipid peroxidation in vulnerable neural cells.[23]

Under physiological conditions, cells tightly regulate intracellular iron concentrations through iron autophagy pathways to maintain iron balance and prevent iron-mediated toxicity. When iron deficiency occurs, cells activate adaptive regulatory mechanisms to increase intracellular iron availability. Specifically, the interaction between divalent metal transporter 1 and transferrin facilitates iron uptake through the endosomal pathway, while binding of ferritin to nuclear receptor coactivator 4 mediates ferritin autophagy, promoting intracellular iron mobilization. Conversely, under conditions of sufficient iron supply, cellular iron export and redistribution are primarily controlled through the ferroportin–iron transporter protein regulatory axis, which limits excessive iron accumulation and maintains systemic iron homeostasis.[24] Together, these regulatory pathways highlight the dynamic balance of iron metabolism following ischemic injury and provide mechanistic insight into how dysregulated ferritin turnover and iron handling may contribute to oxidative damage and adverse neurological outcomes after stroke.

The findings reveal that ferritin levels are associated with poor short-term functional outcomes among female patients but are not an independent predictor of poor short-term functional outcome in all patients, indicating that ferritin levels do not independently predict functional prognosis, which partially contrasts with previous studies.[13] Elevated ferritin levels have been linked to the development of depression after stroke,[25] suggesting that ferritin may indirectly affect recovery by influencing patients' mental health. Furthermore, serum ferritin levels are an important predictor of hemorrhagic transformation in AIS.[26]

From a clinical perspective, these findings have important implications for early prognostic evaluation and individualized management of patients with AIS. Thyroid hormone and ferritin measurements are routinely available in clinical laboratories, cost-effective, and can be rapidly obtained upon hospital admission, making them feasible biomarkers for early risk assessment. The identification of TT3 as an independent prognostic indicator in male patients suggests that incorporating TT3 into early evaluation models may help clinicians identify individuals at higher risk of unfavorable functional recovery and guide closer monitoring, rehabilitation planning, and follow-up strategies.

Moreover, the observed sex-specific differences emphasize the importance of a personalized approach when interpreting endocrine and metabolic biomarkers in stroke management. The differential prognostic value of TT3 in male patients and ferritin in female patients indicates that sex may modify biomarker performance and should be considered when establishing prognostic assessment strategies. Integrating thyroid hormone and ferritin parameters with conventional neurological severity scales and functional outcome measures may further improve prognostic accuracy and support more targeted intervention strategies. Collectively, these findings suggest that thyroid hormone and ferritin assessment may serve as useful adjunctive tools in clinical decision-making and contribute to the development of individualized, sex-specific management pathways for patients with AIS.

5. Conclusion

In summary, thyroid hormone and ferritin levels were significantly associated with short-term functional outcomes in AIS patients, with evident sex-specific differences. TT3 was identified as an independent predictor of poor short-term functional outcomes, with its predictive value more prominent in male patients. In female patients, neither thyroid hormone levels nor ferritin levels exhibited independent predictive value for short-term functional prognosis. These findings suggest that incorporating biomarker assessment may improve early risk stratification

and highlight the importance of sex-specific evaluation in AIS.

Several limitations of this study warrant consideration. First, the exclusion of patients lacking thyroid hormone and ferritin data may affect the generalizability of the findings. Second, we focused solely on the impact of these levels within 24 hours of admission, without accounting for potential changes during hospitalization. Third, short-term functional outcomes were assessed by multiple neurologists, which may introduce variability in mRS evaluations. Finally, as all participants were Chinese, further validation of the relationships between thyroid hormone, ferritin levels, and short-term functional outcomes is required in diverse populations from other countries.

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Conflict of interest

The authors declare they have no conflict of interest.

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Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the First Hospital of Hebei Medical University (No. 20220642). All participants provided written informed consent prior to participation in the study. All research studies on humans (individuals, samples, or data) were conducted in accordance with the principles stated in the Declaration of Helsinki.

Consent for publication

The authors have obtained the patients' written consent to publish this data

Availability of data

The underlying raw data that support the conclusions drawn in this article can be accessed by contacting the corresponding author with a reasonable request.

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Appendix

Table A1. Previous studies on thyroid hormones, ferritin, and stroke outcomes

Study	Data used	Models used	Main findings	Limitations
Talhada *et al.*[7]	Experimental and clinical review data	Mechanistic analysis	Thyroid hormones regulate neuroplasticity and astrocyte-mediated recovery after ischemic stroke	Mainly mechanistic evidence; lack of large-scale clinical outcome validation
Fu *et al.*[8]	Meta-analysis of acute stroke patients	Meta-regression analysis	Lower FT3 levels in acute stage were associated with increased risk of post-stroke depression and poor neurological recovery	Heterogeneity across included studies; limited sex-stratified analysis
Papaleontiou *et al.*[9]	Large cohort database	Cox proportional hazard model	Thyroid hormone therapy and abnormal hormone levels were associated with increased stroke incidence	Did not evaluate functional prognosis after stroke
Zheng *et al.*[10]	Meta-analysis of observational studies	Pooled effect size analysis	Elevated ferritin levels were associated with increased stroke risk	Focused on stroke incidence rather than short-term functional outcome
Sakib et a l.[11]	Clinical cohort	Logistic regression	High serum ferritin levels were associated with early poor prognosis in stroke patients	Small sample size; lack of confounder adjustment
Xia *et al.*[12]	Multicenter observational dataset	Multivariate regression	Higher ferritin levels were associated with increased all-cause mortality after stroke	Mortality endpoint only; functional outcome not evaluated
Shafia *et al.*[13]	Review of experimental and clinical studies	Narrative synthesis	Thyroid hormones potentially influence stroke recovery, but clinical evidence remains inconsistent	Lack of unified outcome indicators and sex-based analysis
Taroza *et al.*[25]	Prospective clinical cohort	Correlation analysis	Lower FT3 levels were associated with post-stroke depression symptoms	Mental outcome only; no functional disability evaluation
He *et al.*[26]	AIS cohort	Logistic regression	Elevated ferritin predicted hemorrhagic transformation after AIS	Did not analyze neurological functional prognosis

Abbreviations: AIS: Acute ischemic stroke; FT3: Free triiodothyronine.

Table A2. Variables used for constructing and evaluating the prognostic model

Category	Parameters
Demographic variables	Age and sex
Clinical variables	Admission NIHSS score, length of hospital stay, and history of stroke
Thyroid hormone biomarkers	FT3, FT4, TT3, and TT4
Iron metabolism biomarkers	Ferritin
Outcome variable	Modified Rankin Scale at discharge
Evaluation metrics	Odds ratio, 95% confidence interval, *p*-value, and Spearman's correlation coefficient (ρ)

Abbreviations: FT3: Free triiodothyronine; FT4: Free thyroxine; NIHSS: National Institutes of Health Stroke Scale; TT3: Total triiodothyronine; TT4: Total thyroxine.