International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

Predictive Value of Thyroid Function and FDS Score in Subacute Combined Degeneration

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Objective: This study aimed to investigate the impact of thyroid function on the short-term prognosis of patients with SCD and to evaluate the predictive value of the Function Disability Scale (FDS) score combined with thyroid function for poor prognosis.

Methods: We conducted a retrospective analysis of clinical data from SCD patients admitted to the First Hospital of Jilin University between January 2021 and December 2022 (n=40). Neurological deficits were assessed using the FDS score at admission and the modified Rankin Scale (mRS) at 3 months post-discharge. Patients were categorized into two groups: normal thyroid function (control) and hypothyroidism (case). General characteristics, clinical features, laboratory results, Functional Disability Scale (FDS) scores, and mRS scores were compared between groups. A mRS score >2 was defined as poor prognosis. Univariate and multivariate logistic regression analyses were performed to identify risk factors for poor prognosis, and receiver operating characteristic (ROC) curve analysis was used to evaluate predictive performance.

Results: Hypothyroidism was associated with lower folic acid levels, higher mean corpuscular hemoglobin concentration (MCHC), and higher mRS scores ($P<0.05$). Poor prognosis was significantly correlated with a history of gastrointestinal disease, elevated thyroid-stimulating hormone (TSH), reduced folic acid, and higher admission FDS scores ($P<0.05$). Multivariate analysis identified elevated TSH (OR=2.152, 95% CI: 1.050~4.411, P=0.036) and high FDS scores at admission (OR=5.573, 95% CI: 1.020~30.438, $P=0.047$) as independent risk factors for poor prognosis ($P<0.05$). ROC analysis determined optimal cutoff values of 5.265 mIU/L for TSH and 7.5 for FDS score in predicting poor prognosis. The combination of FDS score and TSH levels demonstrated superior predictive accuracy (AUC=0.978, 95% CI:0.937~1.000, $P<0.001$, sensitivity=100%, specificity=91.3%).

Conclusion: Elevated TSH levels are associated with worse short-term outcomes in SCD. The combination of FDS score and TSH levels enhances prognostic prediction, potentially serving as a valuable clinical tool for risk stratification.

Limitations: This study is limited by its small sample size, single-center design, and absence of external validation.

Keywords: subacute combined degeneration of spinal cord, hypothyroidism, vitamin B12, function disability scale, short-term prognosis

Introduction

Subacute combined degeneration of the spinal cord (SCD) is a neurological disorder caused by functional vitamin B12 (VB12) deficiency (result from dysfunction in any of the key physiological processes – including dietary intake, gastrointestinal absorption, transcobalamin binding, systemic transport, or cellular metabolism of VB12), characterized by degeneration of the posterior and lateral columns of spinal cord, peripheral nerves, and occasionally cerebral white matter and optic nerve.[1] The main clinical manifestations are deep sensory impairment of both lower limbs, sensory ataxia, paresthesia at the end of the limbs and even spastic paralysis. In addition, it may cause mental and psychological status, cognitive function, and autonomic dysfunction, usually accompanied by anemia.[2] VB12 is a key nutrient that is obtained entirely through dietary intake and cannot be synthesized by the body.[3] VB12 is absorbed into the bloodstream and binds to transcobalamin (TC) in plasma; and it is transported to the liver for storage if with TCI, or to tissues throughout the body for utilization and if with TCII. Although serum VB12, methylmalonic acid (MMA), and

Received: 22 February 2025
Accepted: 26 July 2025
Published: 18 August 2025

homocysteine (Hcy) are well-established diagnostic biomarkers, their normal ranges do not necessarily reflect adequate VB12 status at the cellular level. Early diagnosis and prompt VB12 supplementation can improve quality of life by halting progression, significantly reducing disability and recurrence rates,[4] yet delayed diagnosis remains common due to nonspecific symptoms and normal biomarker levels in some cases.[5]

The thyroid gland is the main endocrine and metabolic organ of the human body, and the thyroid hormone not only participates in the maintenance of the function of the central and peripheral nervous systems, but also plays a vital role in the metabolism of substances and the promotion of growth and development.[6] Emerging evidence suggests a link between thyroid dysfunction and SCD progression. Thyroid hormones play critical roles in neuronal myelination, metabolic regulation, and VB12 metabolism. Hypothyroidism may exacerbate SCD through two mechanisms, including impaired VB12 absorption due to autoimmune gastritis or pernicious anemia, and disrupted remyelination and methylation cycles secondary to thyroid hormone deficiency. Notably, Aktaş et al reported a higher prevalence of VB12 deficiency in hypothyroid patients.[7] Hypothyroidism-related SCD has also been reported,[8] suggesting that the association between the two diseases may due to the inability of patients to effectively absorb and transport VB12 contained in food due to hypothyroidism-related pernicious anemia, which can improve the prognosis of patients by effectively promoting the further metabolism of VB12 in patients with hypothyroidism-related SCD;[9] or patients with hypothyroidism do not have sufficient thyroid hormones to fully exert their protective effect on remyelination and repair, thereby exacerbating methylation cycle dysfunction and further neurologic abnormalities (eg SCD) caused by VB12 deficiency.[10,11] With the deepening of the research on the association between thyroid disease and SCD, it is increasingly important to explore the pathogenesis between the two diseases. However, no studies have systematically evaluated whether thyroid function independently predicts short-term prognosis in SCD—particularly in relation to disability severity or therapeutic response.

This study investigates the association between thyroid function (focusing on thyroid-stimulating hormone, TSH) and short-term functional outcomes in SCD, measured by the Function Disability Scale (FDS) and modified Rankin Scale (mRS) (See Tables S1 and S2 for details). We hypothesize that elevated TSH levels correlate with poorer recovery. By analyzing a cohort of 40 SCD patients with comprehensive thyroid profiling, we aim to determine whether hypothyroidism is an independent risk factor for severe disability (mRS > 2) at 3 months, evaluate the combined predictive value of TSH and FDS scores for poor prognosis. Our findings could provide a rationale for routine thyroid screening in SCD patients, enabling earlier interventions to mitigate neurological damage.

Methods

Subjects of the Study

A total of 40 patients with SCD who were admitted to the Department of Neurology, The First Hospital of Jilin University from January 2021 to December 2022 were collected. The enrollment criteria for this study were following, (1) the first diagnosis of SCD was in the Department of Neurology, the First Hospital of Jilin University, hospitalized, and meeting the revised diagnostic criteria for SCD;[12] essential criteria: a) Clinical manifestations must include typical neurological symptoms and signs of SCD, such as impaired deep sensation (decreased vibration or proprioception), sensory ataxia (positive Romberg's sign), and pyramidal tract signs (increased muscle tone in the lower limbs, positive pathological reflexes). These may be accompanied by peripheral neuropathy (glove-and-stocking hypoesthesia) or cognitive/psychiatric symptoms (depression, memory decline); b) evidence of VB12 metabolic dysfunction must be present; supportive criteria: a) Imaging features: Spinal cord MRI may show high signal intensity in the posterior and lateral columns of the cervical or thoracic cord on T2-weighted imaging. In severe cases, brain MRI may reveal white matter demyelination; b) Etiological evidence: This includes positivity for intrinsic factor antibodies (suggesting autoimmune gastritis), gastric parietal cell antibodies, endoscopic findings of atrophic gastritis, or a history of ileal malabsorption (eg, Crohn's disease, surgical resection); c) Therapeutic response: Clinical improvement should be observed within 4 weeks of VB12 supplementation therapy;[13] (2) no other spinal cord or peripheral nerve disease; (3) no history of thyroid diseases and no history of taking relevant drugs. Exclusion Criteria: (1) no clear diagnosis of SCD; (2) coexisting with any other spinal cord or peripheral nerve disease; (3) previous thyroid diseases and family history of

thyroid diseases. According to the above criteria, 40 cases were finally enrolled. Flowchart of SCD patients enrollment and follow-up is shown in Figure 1.

Research Methods

General Clinical Data

The age, gender, previous vegetarian diet, alcohol history, previous history of anemia, previous gastrointestinal diseases, limb numbness, limb weakness, deep sensory impairment, superficial sensory impairment, pyramidal tract function changes, ataxia, and Romberg test were collected.

Laboratory Tests

In the study, thyroid function [normal range: thyroid-stimulating hormone (TSH, 0.37~4.94 mIU/L; Free Triiodothyronine, FT3, 3.10~6.80 pmol/L; FT4, 12.0~22.0pmol/L], complete blood count (Red blood cell, RBC; Hemoglobin, HB; Mean corpuscular volume, MCV; Mean corpuscular hemoglobin, MCH; Mean corpuscular hemoglobin concentration, MCHC), folic acid (normal range: 3~20ng/mL, determined by chemiluminescence immunoassay), VB12 levels (normal range: 180~914pg/mL, determined by chemiluminescence immunoassay), serum levels of Hcy, triglycerides (TG, normal range: 0.28–1.80mmol/L), total cholesterol (TC, normal range: 2.6–6.0mmol/L), serum uric acid, hypersensitivity C-reactive protein (CRP), fasting blood glucose, and HbA1c of enrolled patients are collected. All indicators were measured from fasting blood samples collected on the second morning of hospitalization, prior to the initiation of intramuscular VB12 therapy. And the results of neuroelectrophysiological examination, lumbar puncture and spinal cord MRI also were collected.

The patients with TSH > 4.94 mIU/L, or FT3 < 3.10 pmol/L, FT4 <12.0 pmol/L were defined as hypothyroidism.

SCD Patient Rating Scale

All patients were treated with systemic VB12 supplement during and after discharge. The regimen consists of an initial intramuscular VB12 dosage of 1000 μg daily for 4 weeks, followed by a maintenance phase of 1000 μg per dose administered three times weekly for 2 months. The Functional Disability Scale (FDS) was used to assess the short-term prognosis of the patients at the time of admission, and the modified Rankin scale (mRS) score was used to evaluate the short-term prognosis of the patients 3 months after discharge. The 3-month follow-up period was selected for short-term prognosis assessment based on: a) clinical evidence indicates that VB12 supplementation for at least 2 months leads to measurable improvement in signs and symptoms across all SCD patients.[14] Notably, approximately 20% of individuals with neurological manifestations due to VB12 deficiency demonstrate significant recovery by 3 months after treatment initiation,[15] and (3) the attrition rate in the study cohort became prohibitively high when the follow-up period was extended to 6 months.

FDS rating scale: including gait, sensation, cognitive function, nerve reflex and pyramidal tract function. The total score is a minimum of 0 and a maximum of 16, with higher scores indicating more severe nerve damage. It assesses the degree of neurologic deficit.[16] mRS score: to assess clinical prognosis (mRS score >2 is considered a poor prognosis)[17] (See Table S2 for details).

Statistical Processing

All data were processed using SPSS 25.0 statistical software. Continuous variables were first assessed for normality using the Shapiro–Wilk test (for sample sizes <50), with visual confirmation via Q-Q plots. For the measured data that obey the normal distribution, the mean ± standard deviation (x±s) is expressed as the independent samples *t*-test. For the non-normally distributed metrics, the median and quartiles M (Q1, Q3) were used, and the Mann–Whitney U rank-sum test was used. For counts, they are expressed as percentages (%) using a chi-square test. Statistically significant univariate was included in the multivariate logistic regression model to analyze the independent risk factors for poor prognosis. To control for potential confounding factors, we performed adjusted analyses using multiple-regression models. Key covariates including (eg, age, gender) were incorporated based on their clinical relevance and univariate associations ($P<0.05$). The ROC curve was used to obtain the TSH level, admission FDS score and the optimal cut-off

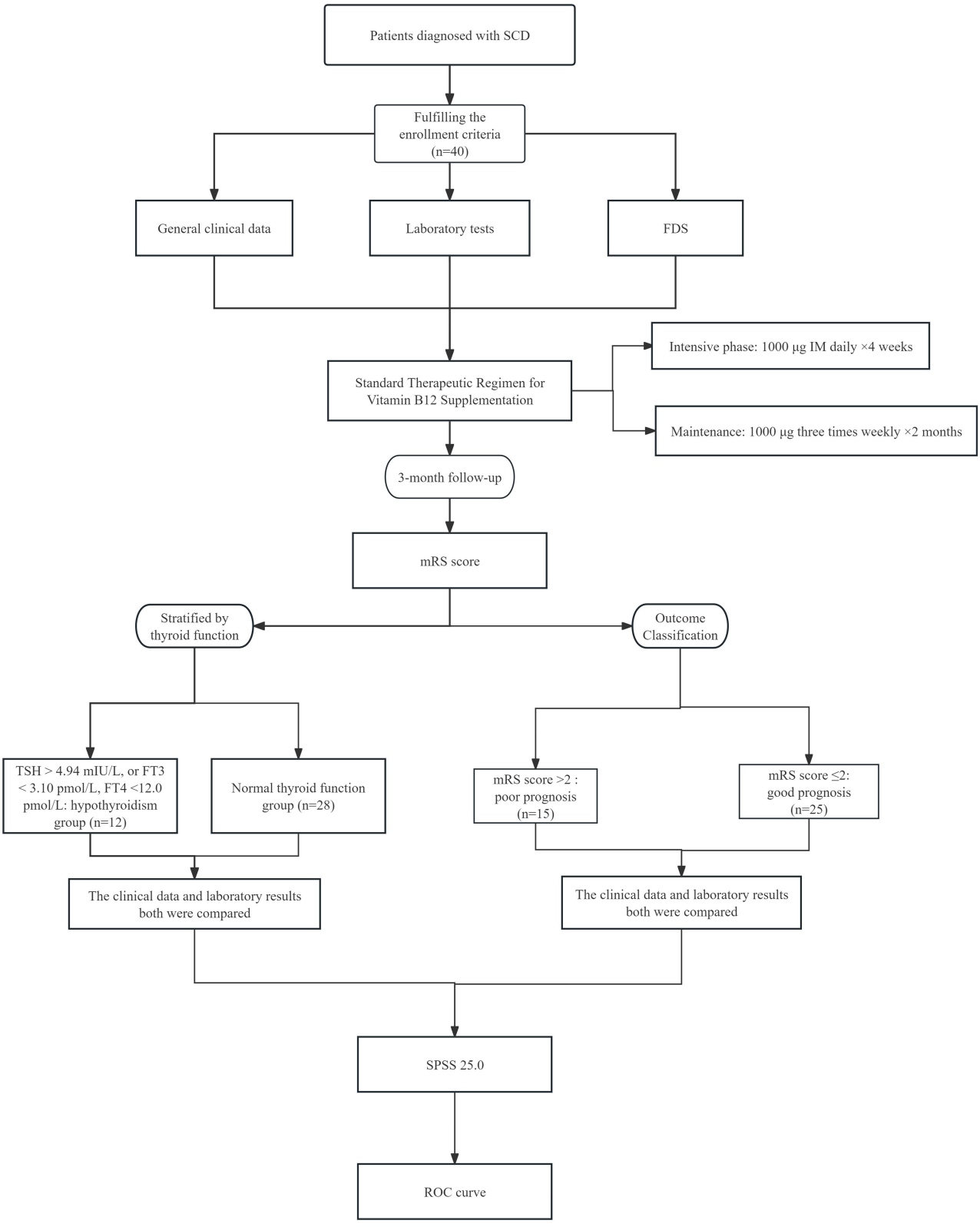

Figure 1 Flowchart of SCD patient enrollment and follow-up.
Abbreviation: SCD, subacute combined degeneration of spinal cord; TSH, thyroid-stimulating hormone; FDS, Functional Disability Scale; mRS, modified Rankin scale; ROC, receiver operating characteristic.

value of these two further to obtain and the predictive effect of TSH level, admission FDS score and the combination of these two indicators on poor prognosis. P<0.05 was considered statistically significant.

Results

General Clinical Features

A total of 40 patients with SCD were enrolled in this study, including 14 males (35.0%) and 26 females (65.0%), with an average age of 57 years. There were 15 cases with a history of anemia before the onset of the disease, accounting for a relatively high proportion (37.5%). Eight cases (20.0%) were vegetarian diets. There were 7 cases with a history of gastrointestinal diseases and 7 cases with a history of alcohol consumption, accounting for 17.5% (See Figure 2 for details).

Clinical Manifestations of Patients with SCD

Among the 40 patients, 34 cases had limb numbness, accounting for 85.0%, of which 18 cases had numbness in the limbs (52.9%), 2 cases only had numbness in the upper limbs, accounting for 5.9%, and 14 cases only had numbness in the lower limbs, accounting for 41.2%. There were 30 cases with limb muscle strength changes, accounting for 75.0%, of which 16 cases had limb muscle strength changes, accounting for 53.3%, and 14 cases only had lower limb muscle strength changes, accounting for 46.7%. Thirty-five cases had deep sensory impairment, accounting for 87.5%; 27 cases had superficial sensory impairment, accounting for 67.5%; There were 24 cases of pyramidal tract function and ataxia, accounting for 60.0%. Nineteen cases were positive for Romberg's sign, accounting for 47.5%. Among the 40 patients, 21 patients underwent nerve electrophysiological examination, and 11 cases (52.5%) had peripheral nerve injury in all four limbs, 2 cases (9.5%) had peripheral nerve injury in the upper limb, 4 cases (19.0%) had peripheral nerve injury in the lower limb, and 4 cases (19.0%) did not indicate peripheral nerve injury. Among the 40 patients, 22 patients underwent lumbar puncture, and the average cerebrospinal fluid pressure was 133.9 mmH_2O, the average protein was 0.40 g/L, the average white blood cell count was $2.0*10^6$/L, and the average immunoglobulin G (IgG) was 33.5 mg/L. In

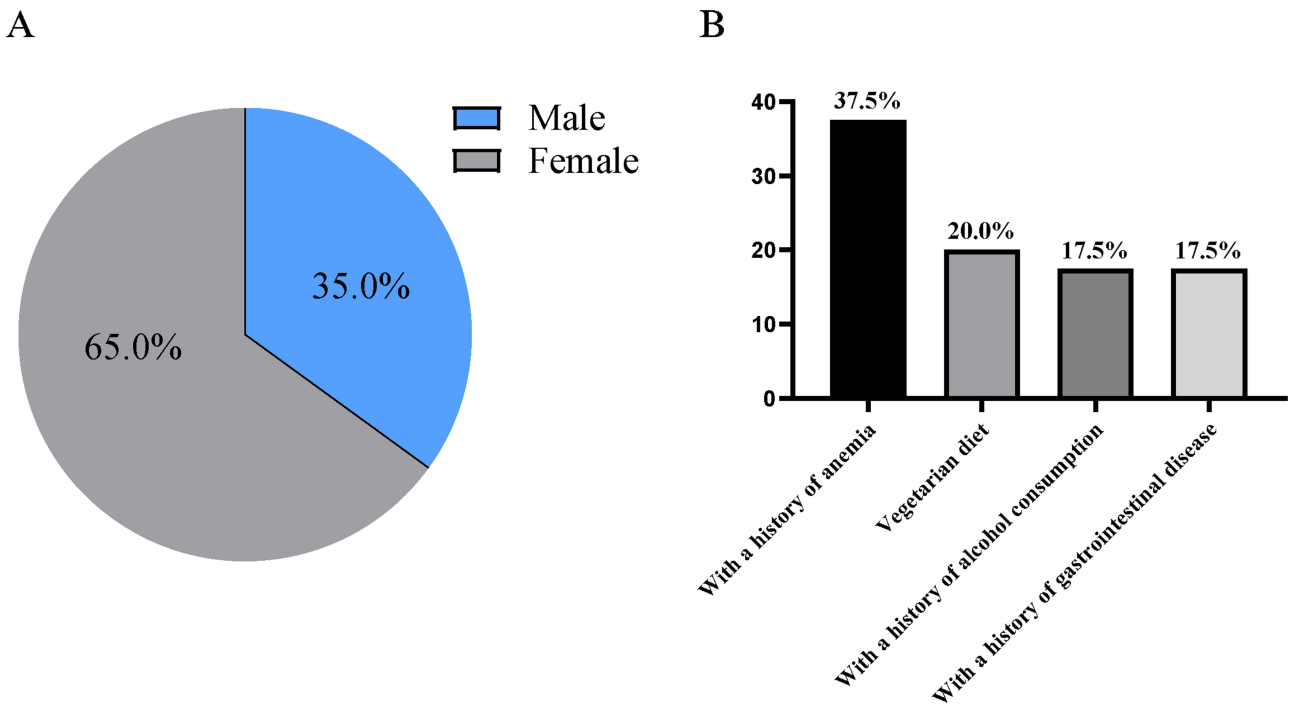

Figure 2 General clinical features of SCD patients. (**A**) Gender distribution of SCD patients. (**B**) Distribution of previous relevant medical history in patients with SCD. The enrolled 40 SCD patients included 14 males (35.0%) and 26 females (65.0%). There were 15 cases with a history of anemia before the onset of the disease, accounting for a relatively high proportion (37.5%). 8 cases (20.0%) were vegetarian diets. There were 7 cases with a history of gastrointestinal diseases and 7 cases with a history of alcohol consumption, accounting for 17.5%.
Abbreviation: SCD, subacute combined degeneration of spinal cord.

https://doi.org/10.2147/IJGM.S524393

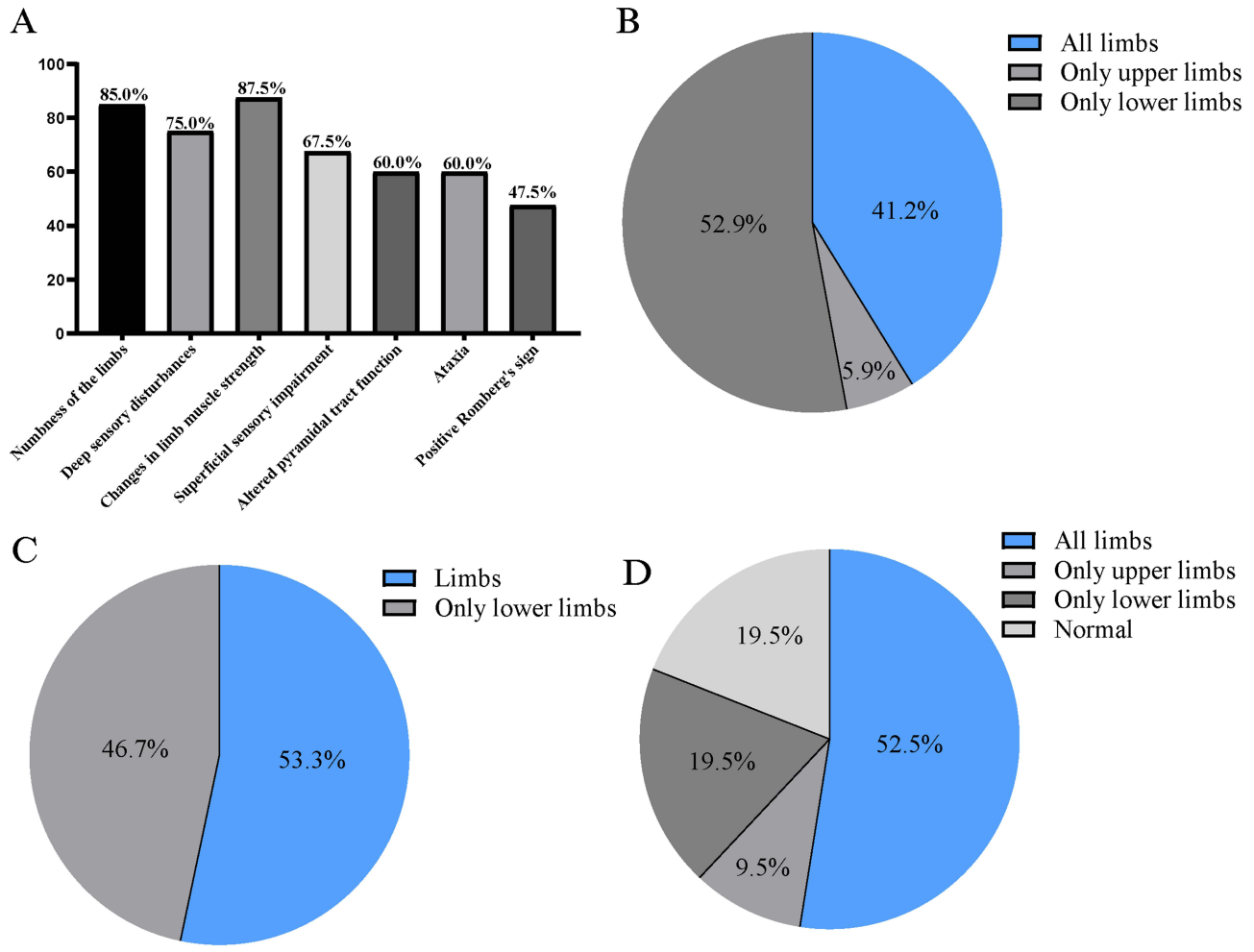

Figure 3 Clinical manifestations of SCD patients. (**A**) Distribution of clinical manifestations in patients with SCD. 35 cases had deep sensory impairment, accounting for 87.5%; 27 cases had superficial sensory impairment, accounting for 67.5%; There were 24 cases of pyramidal tract function and ataxia, accounting for 60.0%. Nineteen cases were positive for Romberg's sign, accounting for 47.5%. (**B**) Distribution of limb numbness in patients with SCD. Among the 40 patients, 34 cases had limb numbness, accounting for 85.0%, of which 18 cases had numbness in the limbs (52.9%), 2 cases only had numbness in the upper limbs, accounting for 5.9%, and 14 cases only had numbness in the lower limbs, accounting for 41.2%. (**C**) Distribution of limb weakness in patients with SCD. There were 30 cases with limb muscle strength changes, accounting for 75.0%, of which 16 cases had limb muscle strength changes, accounting for 53.3%, and 14 cases only had lower limb muscle strength changes, accounting for 46.7%. (**D**) Distribution of neuroelectrophysiological examination in patients with SCD. Among the 40 patients, 21 patients underwent nerve electrophysiological examination, and 11 cases (52.5%) had peripheral nerve injury in all four limbs, 2 cases (9.5%) had peripheral nerve injury in the upper limb, 4 cases (19.0%) had peripheral nerve injury in the lower limb, and 4 cases (19.0%) did not indicate peripheral nerve injury.
Abbreviation: SCD, subacute combined degeneration of spinal cord.

addition, 26 of the 40 patients underwent cervical spine MRI, of which 13 were abnormal, accounting for 50.0%. Thoracic spine MRI was performed in 28 cases, of which 15 cases were abnormal, accounting for 53.6%. Sixteen cases of lumbar spine MRI were performed, of which 3 cases were abnormal, accounting for 18.8% (See Figure 3 for details). Patients lacking corresponding ancillary tests were excluded from that analysis.

Comparison of Clinical Data Between the Normal Thyroid Function Group and the Hypothyroidism Group of SCD Patients

According to the normal or elevated TSH level, the 40 SCD patients in this study were divided into normal thyroid function group (control group, 28 cases) and hypothyroidism group (case group, 12 cases). There were no significant differences between the two groups in general data, related disease history, clinical symptoms, laboratory test results (excluding MCHC and folic acid), lumbar puncture results, and imaging characteristics ($P>0.05$). There were statistically significant differences in MCHC ($P=0.010$), folic acid ($P=0.013$) and mRS scores ($P=0.008$) between the two groups (See Table 1–2 for details).

Table 1 Comparison of Clinical Data Between the Normal Thyroid Function Group and the Hypothyroidism Group

	Normal Thyroid Group (n=28)	Hypothyroidism Group (n=12)	$t/x^2/z$	*P*
Gender (M/F)	10/18	4/8	−0.475	0.634
Age (Year)	52.08±3.65	63.29±1.76	−1.564	0.128
Vegetarian predominant	4/28 (14.3%)	4/12 (33.3%)	−0.791	0.429
With a history of alcohol consumption	5/28 (17.9%)	2/12 (16.7%)	−0.296	0.767
With a history of anemia	10/28 (35.7%)	5/12 (41.6%)	−0.396	0.692
With a history of gastrointestinal disease	5/28 (17.9%)	2/12 (16.7%)	−0.791	0.429
Numbness of the limbs	25/28 (89.3%)	9/12 (75.0%)	−0.995	0.320
Changes in limb muscle strength	22/28 (78.6%)	8/12 (66.7%)	−0.650	0.516
Deep sensory disturbances	24/28 (85.7%)	11/12 (91.7%)	−1.090	0.276
Superficial sensory impairment	20/28 (71.4%)	7/12 (58.3%)	−0.802	0.423
Altered cone beam function	17/28 (60.7%)	7/12 (58.3%)	−0.208	0.835
Ataxia	18/28 (64.3%)	6/12 (50.0%)	–0.401	0.688
Positive Romberg's sign	13/28 (46.4%)	6/12 (50.0%)	−0.072	0.943
FDS score on admission	6.23±1.88	7.29±2.36	−1.249	0.221
mRS score	1.88±0.99	3.14±1.22	−2.842	0.008**

Note: **, *P*<0.01.

Table 2 Comparison of Laboratory Results Between the Normal Thyroid Function Group and the Hypothyroidism Group

	Normal thyroid Group (n=28)	Hypothyroidism Group (n=12)	$t/x^2/z$	*P*
Complete blood count				
RBC ($*10^{12}$/L)	3.78±0.80	3.24±0.91	1.522	0.138
HB (g/L)	123.08±21.62	114.14±15.15	1.022	0.315
MCV (fl)	97.25±10.09	106.24±14.25	−1.916	0.065
MCH (pg)	33.10±3.95	36.60±6.25	−1.829	0.077
MCHC (g/L)	339.81±11.36	355.57±20.17	−2.738	0.010*
Folic acid (ng/mL)	10.64±6.58	18.08±7.00	−2.624	0.013*
Vitamin B12 (pg/L)	512.42±542.92	616.43±700.63	−0.423	0.675
Hcy (umol/L)	37.76 (13.55,100.90)	140.20 (6.34,170.80)	−1.013	0.311
Blood lipids				
TG (mmol/L)	1.34±0.73	1.17±0.40	0.561	0.579
TC (mmol/L)	4.21±0.72	4.28±1.22	−0.196	0.846
Uric acid (umol/L)	276.31±71.20	250.71±31.78	0.918	0.366
CRP (mg/L)	3.02 (1.69,5.01)	3.02 (1.24, 3.92)	−0.601	0.548
Glucose				
Fasting blood glucose (mmol/L)	5.15 (4.62, 5.68)	5.12 (4.43, 5.55)	−0.507	0.612
HbA1c (%)	5.22±0.75	5.25±0.34	−0.092	0.927
Electromyography				
All limbs	8/16 (50.0%)	3/5 (60.0%)	0.690	0.496
Only upper limbs	2/16 (12.5%)	0/5 (0.0%)	0.788	0.436
Only lower limbs	3/16 (18.6%)	1/5 (20.0%)	0.564	0.577
Normal	2/16 (18.6%)	2/5 (20.0%)	0.707	0.479
Lumbar puncture				
Pressure	134.23±49.15	130±0.00	0.083	0.935
Protein	0.40 (0.34, 0.45)	0.39 (0.29, 4.78)	−0.257	0.797
Number of cells	3.31±3.01	2.5±2.12	0.360	0.724
IgG	33.91±13.96	28.80±0.00	−0.124	0.901

(*Continued*)

Table 2 (Continued).

	Normal thyroid Group (n=28)	Hypothyroidism Group (n=12)	$t/x^2/z$	*P*
Spinal cord MRI				
Cervical spinal cord abnormalities	11/23 (47.8%)	2/3 (66.7%)	−1.194	0.232
Thoracic cord abnormalities	13/22 (59.1%)	2/6 (33.3%)	−1.145	0.252
Lumbar spinal cord abnormalities	3/14 (21.4%)	0/2 (0.0%)	−0.573	0.591
Normal	2/5 (40.0%)	1/2 (50.0%)	−0.556	0.578

Note: *, $P<0.05$.

Comparison and Data Analysis of Clinical Data Between the Group with Good Prognosis and the Group with Poor Prognosis

Univariate Analysis

Based on the prognosis of the mRS score obtained 3 months after discharge, 40 SCD patients were divided into two groups, including 25 cases (62.5%) in the good prognosis group and 15 cases (37.5%) in the poor prognosis group. There was no statistically significant difference in imaging results ($P>0.05$), but there were statistically significant differences in history of gastrointestinal diseases ($P=0.033$), TSH level ($P=0.002$), folic acid level ($P=0.025$) and admission FDS score ($P<0.001$) (See Table 3 for details).

From Table 3, there were statistically significant differences between the poor prognosis group and the good prognosis group in terms of history of gastrointestinal disease, TSH level, folic acid level, and admission FDS score.

Multivariate Logistic Regression Analysis

From Table 3, we found that a history of gastrointestinal disease, elevated TSH levels, decreased folate levels, and elevated FDS scores in admission were the influencing factors for the short-term poor prognosis of SCD patients, and the above influencing factors were further incorporated into the binary logistic regression model for multivariate analysis of the adverse prognosis of SCD patients. The results showed that the increased TSH level [OR=2.152, 95% confidence interval (95% CI): 1.050~4.411, $P=0.036$] and the increased FDS score on admission (OR=5.573, 95% CI: 1.020~30.438, $P=0.047$) were independent risk factors affecting the poor prognosis of SCD patients ($P<0.05$). There was no statistically significant difference between the history of gastrointestinal diseases (OR=1.802, 95% CI: 1.765~24.713, $P=0.351$),

Table 3 The Clinical Data of the Group with Good Short-Term Prognosis and the Group with Poor Short-Term Prognosis of Patients with SCD Were Compared

	The Good Short-Term Prognosis Group (n=25)	The Poor Short-Term Prognosis Group (n=15)	$t/x^2/z$	*P*
Gender (M/F)	8/17	6/9	−0.282	0.778
Age (Year)	51.35±17.42	61.60±15.16	−1.611	0.117
With a history of gastrointestinal disease	1/25 (4.0%)	6/15 (40.0%)	−2.238	0.033*
Thyroid function				
TSH (mIU/L)	2.55±1.70	6.92±5.93	−3.295	0.002**
FT3 (pmol/L)	4.18±0.74	4.16±0.68	1.188	0.244
FT4 (pmol/L)	13.72 (12.24, 16.37)	12.52 (11.62, 16.03)	−0.725	0.469
Folic acid (ng/mL)	16.43±6.39	10.39±6.94	−2.350	0.025*
Vitamin B12 (pg/L)	199.00 (61.00, 615.00)	948.50 (58.75, 1476.00)	−1.007	0.314
Hcy (umol/L)	43.47 (14.07,112.20)	16.07 (6.44,170.05)	−0.235	0.814
FDS score on admission	5.65±1.34	8.30±2.11	−4.370	<0.001

Note: *, $P<0.05$; **, $P<0.01$.

Table 4 Binary Logistic Regression Analysis

Variables	B	*P*	OR	OR 95% CI	
				Lower Limit	Upper Limit
With a history of gastrointestinal disease	2.380	0.351	1.802	1.765	24.713
TSH levels	0.766	0.036*	2.152	1.050	4.411
Folic acid levels	0.048	0.656	1.049	0.849	1.298
FDS score on admission	1.718	0.047*	5.573	1.020	30.438

Note:*, *P*<0.05.

decreased folic acid level (OR=1.049, 95% CI: 0.849~1.298, *P*=0.656) and poor short-term prognosis between SCD patients (*P*>0.05) (See Table 4 for details).

The Predictive Value of TSH Level and Admission FDS Score in Poor Short-Term Prognosis of SCD Patients

ROC curve results. The serum TSH level 5.265 mIU/L was the best cross-sectional value; the AUC was 0.739 (95% CI: 0.529~0.949, *P*<0.001), the sensitivity was 60.0%, and the specificity was 95.7%. The FDS score 7.5 was the best cross-sectional value; the AUC was 0.861 (95% CI: 0.717~1.000, *P*=0.031), the sensitivity was 70.0%, and the specificity was 95.7%. When combing FDS score and serum TSH level to predict the short-term poor prognosis of SCD patients, the AUC was 0.978 (95% CI: 0.937~1.000, *P*<0.001), the sensitivity was about 100.0%, and the specificity was 91.3% (see Figure 4 for details). These results indicated that the FDS score combined with serum TSH level was more predictive than a single index for the short-term prognosis of SCD patients.

Discussion

SCD, a neurodegenerative disease associated with VB12 deficiency, was first proposed by Russell et al more than 100 years ago and also considered a spinal cord disorder associated with pernicious anemia and named SCD. It is

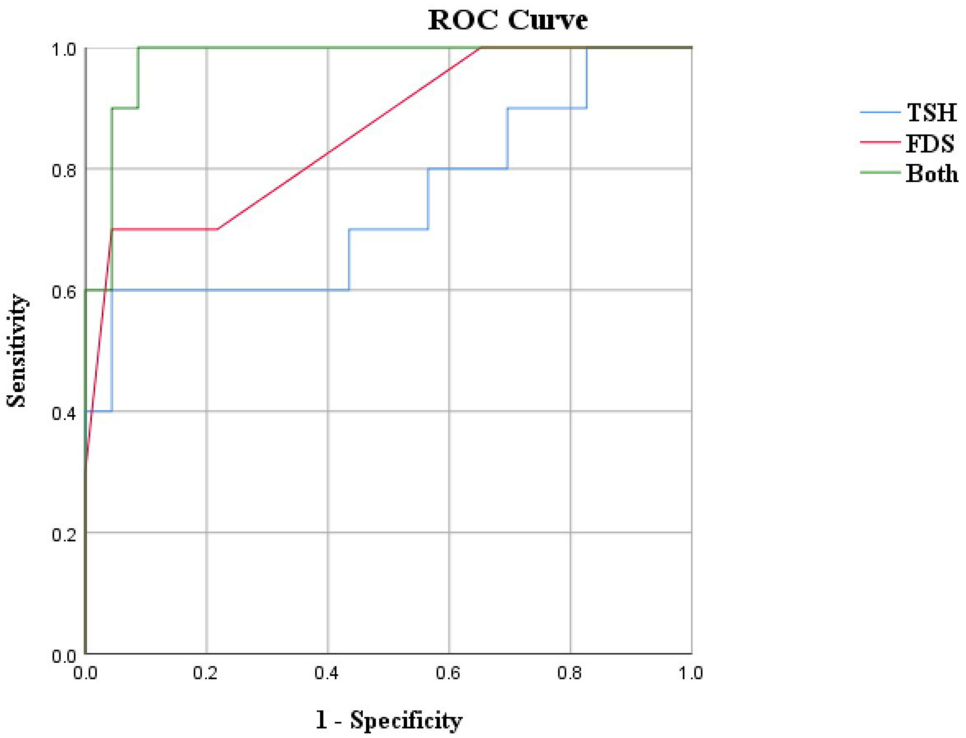

Figure 4 The predictive value of TSH level and admission FDS score on the short-term prognosis of SCD patients.
Abbreviation: SCD, subacute combined degeneration of spinal cord; TSH, thyroid-stimulating hormone; FDS, Functional Disability Scale.

https://doi.org/10.2147/IJGM.S524393

characterized by spastic paraplegia, deep sensory loss, ataxia, and peripheral nerve damage in both lower extremities, and may be accompanied by anemia such as fatigue and pale skin, cognitive impairment such as mental retardation and memory loss, or psychiatric symptoms such as depression and irritability, or autonomic nerve impairment such as orthostatic hypotension and urinary dysfunction.[2] Cerebrospinal fluid (CSF) and electromyography (EMG) do not show specific findings. The MRI findings in our study cohort revealed characteristic abnormalities consistent with subacute combined degeneration. The MRI findings demonstrated characteristic T2 hyperintensities predominantly involving the posterior and/or lateral columns of the cervical spinal cord in 50% of patients. Similar signal abnormalities were observed in 53.6% of cases on thoracic MRI, while lumbar spine involvement was less frequent, appearing in 18.8% of patients. These imaging features align with established radiological patterns of VB12 deficiency-related myelopathy (the thoracic cord is most frequently affected, followed by the cervical cord, while lumbar cord involvement is relatively uncommon), supporting both the diagnosis and severity assessment in our cohort.[18] The distribution and progression of these lesions provided important objective correlates to clinical findings and functional scores. It is usually diagnosed based on typical clinical findings, the results of lumbar puncture and electrophysiologic studies of patients. The pathogenesis of SCD is not fully understood, but it is generally thought to be associated with VB12 deficiency, which can be caused by long-term vegetarian diets,[19,20] gastrectomy,[21] presence of intrinsic factor or parietal cell antibodies,[22,23] ileal malabsorption,[24] inhaled nitrous oxide (N_2O),[25,26] copper deficiency,[27] folic acid,[28] vitamin E deficiency,[29] or mixed causative factors.[30] It is generally believed that SCD is caused by VB12 deficiency (direct or indirect), and VB12 supplementation therapy is given as soon as the disease is suspected.[31] Neurological impairment caused by SCD is reversible at an early stage, and the prognosis of patients with SCD is generally considered to be better if the course within three months, the age of onset <50 year.[32] As one of the diseases of the nervous system that can be completely cured, early diagnosis and treatment are particularly crucial. If there is no timely intervention, it will gradually worsen after 2 to 3 years and become incurable, resulting in lifelong disability.[31]

Hypothyroidism, is a systemic endocrine disorder of reduced metabolism caused by decreased synthesis and secretion of thyroid hormones or weakened tissue action. In the general population, the incidence of hypothyroidism is about 6%–18%, and the prevalence of VB12 deficiency is about 4%,[33] and abnormalities in thyroid hormones can lead to VB12 deficiency and promote the development of SCD. According to the research of Jabbar et al, the prevalence of VB12 deficiency can be as high as 40% in patients with hypothyroidism.[34] A relationship has been shown between thyroid function and homocysteine levels, with plasma Hcy being higher in patients with hypothyroidism and gradually normalizing with thyroid treatment,[35] and often lower in patients with hyperthyroidism.[36]

In this study, there was a statistically significant in mRS score between the normal thyroid group and the hypothyroidism group at 3 months after discharge (1.88±0.99 vs 3.14±1.22, P=0.008), suggesting that the degree of neurological deficit was more severe in the hypothyroidism group and indicating that there was a correlation between abnormal serum TSH level and the degree of neurological deficit in SCD patients. The association between thyroid dysfunction and slower neurological recovery in SCD may be mediated through multiple interrelated mechanisms. First, hypothyroidism directly impairs axonal regeneration and remyelination[37] by reducing the production of brain-derived neurotrophic factor (BDNF) and myelin basic protein (MBP),[38] both critical for neural repair. Second, thyroid hormone deficiency exacerbates the metabolic dysfunction caused by VB12 deficiency,[7] as both conditions disrupt mitochondrial energy production in neurons. Third, the pro-inflammatory state characteristic of hypothyroidism (elevated IL-6 and TNF-α) may potentiate neuroinflammation, creating an unfavorable microenvironment for recovery.[39] Fourth, thyroid dysfunction alters cerebral blood flow autoregulation, potentially compromising oxygen delivery to already vulnerable neural tissues.[40] These mechanisms likely operate synergistically, with thyroid hormone insufficiency amplifying the downstream effects of VB12 deficiency on methylation cycles and DNA synthesis in the nervous system. However, there were no significant differences between the two groups in terms of general clinical data, routine blood tests, neurophysiological examinations, lumbar puncture results and spinal cord MRI results. This may be related to the smaller sample size and shorter follow-up time of the study. So, not only the sample size of the included study needs to be expanded, but also the treatment and prognosis of patients need to be continued for a long time. In the diagnosis of SCD, not only folic acid, VB12 and Hcy levels should be measured, but thyroid hormone levels should also be measured as early as possible, and then periodically repeated. Most patients with SCD have

a good prognosis and a high quality of life, and those who are not treated systematically often suffer from multiple system dysfunction due to paralysis and even death. Therefore, it is important to distinguish VB12 deficiency from other causes of myelopathy, as early diagnosis of the disease and timely initiation of treatment are essential for complete clinical recovery in patients with SCD. For patients with hypothyroidism in SCD, thyroid hormone supplementation and thyroid function correction are also parts of improving patient outcomes.

In this study, we analyzed the factors affecting the prognosis of SCD patients, and found that higher FDS score and increased TSH level at admission were independent risk factors for short-term adverse prognosis in SCD patients, and the combined application of FDS score and TSH level at admission could more accurately predict the risk of short-term adverse prognosis in SCD patients. At present, thyroid dysfunction has gradually attracted the attention of clinicians, but there are still differences in the current research results, and it is necessary to conduct prospective studies with larger sample sizes and more unified standards. While the 3-month follow-up was appropriate for detecting initial treatment response – as justified by the rapid myelin repair kinetics reported in SCD[15]– longer-term follow-up would be required to evaluate sustained recovery and relapse rates. Only long-term follow-up of SCD patients to understand the treatment effect of patients can draw more convincing conclusions. Therefore, it is recommended that all patients with SCD have routine thyroid function tests, and those with hypothyroidism are treated with SCD at the same time as thyroid function improvement therapy.

At the same time, this study has the following shortcomings: For SCD patients with hypothyroidism, follow-up was only conducted 3 months after discharge, and the thyroid function of the patients in the same period could not be reviewed, so the difference in thyroid function between patients before and after treatment with VB12 system could not be compared, whether normalization of thyroid status correlates with sustained neurological improvement could not be evaluated; From January 2021 to December 2022, among the SCD patients admitted to the Department of Neurology, the First Hospital of Jilin University, there were patients with hyperthyroidism, but the hyperthyroidism group was not classified as a separate group due to the small number of cases, and further statistical analysis with the control group and the case group could not be conducted. In this study, long-term follow-up of the patients included in the study was not carried out, and whether there were differences in the prognosis of patients at different time nodes were further compared, and only the short-term prognosis of SCD patients could be analyzed; This study is a single-center study, which only includes patients from the First Hospital of Jilin University, and cannot obtain the clinical data of patients from neighboring provinces, so there are problems such as a single research population and a small sample size, and the sample size needs to be expanded in the future to verify the accuracy of the results. In our study, upon detection of thyroid dysfunction, we immediately sought expert consultation from endocrinologists and initiated appropriate management. It would be ethically impermissible to deliberately withhold treatment or randomly assign patients to a hypothyroid control group solely for comparative analysis of prognosis, as this would violate the principle of providing standard care for recognized medical conditions. The combined predictive model (FDS + TSH) demonstrated good discrimination in our cohort, but its performance may be inflated due to the limited sample size (n=40). External validation in larger, multi-center populations is needed before clinical application. According to our study, it can be found that elevated serum TSH level is an important indicator for predicting the poor short-term prognosis of SCD patients. These limitations necessitate cautious interpretation of our findings. The observed TSH-prognosis association should be considered hypothesis-generating rather than definitive, pending verification through mechanistic studies assessing thyroid-B12 interactions in myelin repair, and prospective cohorts with extended follow-up (≥12 months) and protocolized treatment monitoring.

Conclusion

(1) There is a correlation between elevated serum TSH level and poor prognosis of subacute combined degeneration of the spinal cord, and hypothyroidism may potentially contribute to for evaluating the severity of the disease and judging its clinical prognosis.

(2) Both FDS score and TSH level in admission have predictive value for the occurrence of short-term prognosis in SCD patients, and the combined application can more accurately predict the risk of short-term poor prognosis in SCD patients.

Future Research Direction

While this study identified thyroid dysfunction as a potential prognostic marker in SCD, several critical knowledge gaps require further investigation. First, prospective multicenter studies with standardized thyroid function assessment protocols are needed to validate our findings across diverse populations. Second, mechanistic research should elucidate whether thyroid hormone supplementation directly enhances neurological recovery through remyelination pathways or indirectly via improving VB12 metabolism. Third, the optimal TSH threshold for therapeutic intervention (eg, whether to treat subclinical hypothyroidism in SCD patients) warrants exploration through randomized controlled trials. Lastly, longitudinal studies with ≥12-month follow-up should evaluate whether early thyroid function normalization predicts long-term functional outcomes and prevents disease recurrence. Integrating advanced neuroimaging parameters with serial thyroid and VB12 metabolite measurements could provide novel insights into the temporal dynamics of recovery. These research priorities would substantially advance both biological understanding and clinical management of SCD.

Abbreviations

SCD, subacute combined degeneration of spinal cord; VB12, vitamin B12; TC, transcobalamin; MMA, methylmalonic acid; Hcy, homocysteine; Holo-TCII, Holo-transcobalamin II; TSH, thyroid-stimulating hormone; FT3, free Tri-iodothyronine; RBC, red blood cell; HB, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; ROC, receiver operating characteristic; TG, triglycerides; TC, total cholesterol; CRP, C-reactive protein; FDS, Functional Disability Scale; mRS, modified Rankin scale; IgG, immunoglobulin G; CSF, cerebrospinal fluid; EMG, electromyography; N_2O, nitrous oxide; BDNF, brain-derived neurotrophic factor; MBP, myelin basic protein.

Compliance with Declaration of Helsinki

This retrospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Formal ethics committee approval was not required for this secondary analysis of anonymized clinical data under institutional policies, and all patient data were de-identified prior to analysis to ensure confidentiality. The study protocol maintains compliance with all relevant components of the Declaration, including protection of patient privacy through strict data anonymization, exclusion of vulnerable populations, adherence to principles of scientific integrity and data transparency. No treatment interventions were modified for research purposes, and all clinical management decisions were made independently of this retrospective evaluation.

Written Consent for Publication

Written informed consent for publication of data was obtained from all participants included in the study. The participants grant permission for their information being used in this publication and potentially in future editions and reprints of the work.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy or ethical restrictions.

Ethics Approval

All enrolled patients provided written, informed consent to be included in the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent to Participate

Informed consent was obtained from all individual participants included in the study. We are grateful to all study participants and their family.

Acknowledgments

We are grateful to all study participants and their family.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was not supported by any funding.

Disclosure

The authors declare that they have no conflicts of interest or competing interests in this work.

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