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ORIGINAL RESEARCH

The Impact of Non-Thyroidal Illness Syndromes on The Prognosis and Immune Profile in Severe Fever with Thrombocytopenia Syndrome Patients

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Background: Non-thyroidal illness syndrome (NTIS) is the most common endocrine dysfunction in critically ill patients and is often associated with poor prognosis. Thyroid dysfunction and immune cell disturbances are frequently observed in patients with severe fever with thrombocytopenia syndrome (SFTS). This study aims to evaluate the impact of NTIS on the prognosis of SFTS patients and to explore the relationship between thyroid hormones (THs) and immune cell profiles.

Methods: Adult patients admitted to Yantai Qishan Hospital for SFTS from January 2023 to December 2023 with no prior history of thyroid disease were retrospectively recruited. Multivariable regressions were used to assess the associations between NTIS and clinical outcomes. Spearman correlation analysis was conducted to evaluate the relationships between immune cells and THs. SFTS patients with NTIS were categorized into four subtypes based on different levels of FT4 and TSH, and the association between NTIS subtypes and mortality was further analyzed.

Results: Of the 84 SFTS patients included in the study, 62 (73.8%) were diagnosed with NTIS. Independent risk predictors which may affect prognosis of SFTS patients include NTIS subtype (P =0.002), viral load (P = 0.029), FT3 (P = 0.032), and FT4 (P = 0.041). SFTS patients with NTIS exhibited a higher mortality rate compared to euthyroid patients (P = 0.033). Spearman correlation analysis revealed that LYM, LYM%, MONO, MONO%, BAS, CD3+T, CD3+T%, Th, and Th% were positively correlated with FT3, FT4, or TSH levels. NTIS patients were more likely to present with coagulation abnormalities (APTT, P = 0.005; D-Dimer, P < 0.001), liver enzyme abnormalities (AST, P = 0.001), electrolyte imbalances (Sodium, P = 0.003), elevated LDH (P = 0.001), and increased α-HBDH (P = 0.003).

Conclusion: NTIS is common in SFTS patients, and SFTS patients with NTIS have a lower survival rate compared to euthyroid patients. The mortality risk in NTIS type 3 patients is higher than in those with NTIS type 1.

Keywords: SFTS, non-thyroidal illness syndrome, thyroid dysfunction, immune cells

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease that poses a significant public health threat, particularly in East Asia, including China, Japan, and South Korea, the disease was first identified in China in 2009 and has since been reported in other regions, with increasing case numbers and geographic expansion.[1,2] The causative agent of SFTS is Dabie bandavirus (DBV), a member of the order Banyavirales, family Phenuiviridae, and genus Bandavirus.[3] Common clinical manifestations include high-grade fever, thrombocytopenia, leukocytopenia, muscle and joint pain, and gastrointestinal symptom, one of the most important manifestations is multi-organ function damage. There is

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currently no effective specific treatment,[4] and the disease can rapidly progress to a critical state, with a high fatality rate ranging from 12 to 30%.[5] Non-thyroidal illness syndrome (NTIS), one of the most common but underrecognized complications in critically ill patients, including those with severe SFTS, also known as "low T3 syndrome", "the sick euthyroid syndrome (SES)", or "the euthyroid sick syndrome (ESS)", is a systemic endocrine disorder that occurs in response to severe illness, trauma, or metabolic stress.[6,7] The primary laboratory finding in NTIS is a reduced serum free triiodothyronine (FT3) level, along with low or normal levels of free thyroxine (FT4) and thyroid-stimulating hormone (TSH).[6] However, mounting evidence suggests that persistent or severe NTIS is associated with worse clinical outcomes, including higher mortality rates in sepsis and other severe infections.[8–10]

The mechanism of NTIS in viral infectious diseases remains poorly understood. One plausible explanation is that inflammatory cytokine disrupt the hypothalamic-pituitary-thyroid (HPT) axis, a theory supported by evidence showing decreased TSH levels in some critically ill patients.[6,11] There is a bi-directional interaction among the immune and endocrine system; severe infections or autoimmune conditions can disrupt thyroid hormones (THs), while THs also influence immune function by regulating both innate and adaptive immune cells.[12] Additionally, circulating TH levels are positively associated with immune responsiveness in healthy individuals.[13] Under pathophysiological conditions, this interaction is evident: thyroid-stimulating hormone (TSH) and free triiodothyronine (FT3) levels have shown positive correlations with lymphocyte counts (LYM) among COVID-19 patients,[14] while low levels of FT3, free thyroxine (FT4), and TSH concentrations have been linked to higher rates of critical illness and mortality.[15,16]

In Intensive Care UNTIS (ICUs), NTIS frequently arises as a complication of critical illness, impacting nearly all organs and systems. It is observed in up to 70% of critically ill patients across age groups, and is associated with an increased risk of morbidity and mortality.[17] Research has shown that low serum FT3 levels correlate with poorer outcome in SFTS patients.[15] However, little is known about the specific prognostic impact of NTIS in SFTS patients. Therefore, this study aims to assess the impact of NTIS on the prognosis of SFTS patients and explore the relationship between THs and immune cells profiles, potentially providing deeper insights into the management and outcomes of SFTS patients comorbid NTIS.

Methods

Participants and Data Collection

Adult patients diagnosed with SFTS and hospitalized at Qishan Hospital in Yantai, Shandong Province, China, from January 2023 to December 2023 were recruited. The diagnostic criteria included one of the following: (1) positive DBV nucleic acid test in patient samples; (2) seroconversion of DBV-specific IgG antibody or a fourfold increase in antibody level during the convalescent phase compared to the acute phase in patient samples; (3) isolation of DBV from patient samples. Exclusion criteria were: (1) lack of thyroid hormones testing within 48 hours of admission; (2) a history of thyroid or pituitary disease; (3) use of medications that may interfere with the test results, including but not limited to thyroxine and thyroid suppressants, prior to thyroid function testing; (4) a history of malignant tumors or autoimmune diseases; (5) incomplete case data. Basic patient information, including age, gender, blood pressure, and temperature, was collected, along with laboratory test indicators such as blood count, liver and kidney function, coagulation profile, and thyroid function. The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Ditan Hospital (NO.DTEC-KY2022-022-02), affiliated with Capital Medical University, with informed consent from all participants.

Definition

In our research, NTIS is defined as serum FT3 levels below the lower limit of normal (<2.76 pmol/L) without an elevated TSH level (>5.1 IU/mL). The normal reference ranges of serum thyroid hormones are as follows: FT3, 2.76–6.45 pmol/L; FT4, 11.20–23.81 pmol/L; and TSH, 0.35–5.1 μIU/mL. As previously described in the literature, NTIS can be categorized into four subtypes: type 1, low FT3, normal range of FT4 and TSH; type 2, low FT3 and low TSH, normal range of FT4; type 3, low FT3 and FT4, normal range of TSH; type 4, low FT3, low FT4, and low TSH.[6] The diagnosis of SFTS with central nervous system complications includes altered consciousness and neurologic signs. Changes in

consciousness are mainly manifested as apathy, dysphoria, delirium, drowsiness, lethargy, confusion, and coma. Neurological signs are characterized by paroxysmal involuntary muscle tremors and limb tremors.

Outcome Measures

The primary outcome of this study was the mortality rate among patients with different thyroid function types, particularly comparing NTIS patients with those having normal thyroid function. Secondary outcomes included the lymphocyte count and immune cell subsets (such as CD3+ T cells, NK cells, etc) in NTIS patients, as well as changes in FT3, FT4, and TSH levels and their correlation with other clinical outcomes.

Statistical Approach

Continuous data were presented as median ± interquartile range (IQR) and/or mean ± standard deviation (SD), and were compared using the *t*-test for normally distributed data or the Wilcoxon rank sum test (Mann–Whitney *U*-test) for non-normally distributed data. Categorical variables were described by frequency or proportion and were compared using chi-square tests (x^2 test) or Fisher's exact test. Spearman correlation analysis was used to assess univariate correlations among various immune cells and FT3, FT4, and TSH levels. Multivariate stepwise linear regression analysis was conducted to identify independent variables associated with immune cell counts. Univariate and multivariate cox regression analyses were performed to determine independent risk factors associated with SFTS severity. Variables with a *P* value less than 0.1 in the univariate cox regression were included in the multivariate cox regression. Kaplan-Meier and Log rank tests were employed to estimate survival curves and corresponding *P* values. All statistical analyses were performed using SPSS v26.0 (IBM, Inc., New York), with a two-sided significance level < 0.05 considered statistically significant.

Results

From January 2023 to December 2023, 170 SFTS patients were confirmed at Qishan Hospital. According to the exclusion criteria, 3 patients were excluded due to a history of previous thyroid disease (1 thyroid cancer, 2 with a history of hyperthyroidism), 4 patients due to a history of other tumors, and 1 patients due to a prior autoimmune disease. Additionally, patients who did not complete TH testing within 48 hours of admission were excluded. The left 84 patients with completed thyroid function tests included in the study (Figure 1). Among these patients, 16 (19.0%) patients had normal thyroidism; 62 (73.8%) were diagnosed with NTIS; and 6 (7.1%) exhibited other thyroid hormone abnormalities. The NTIS group was further divided into four subtypes based on FT4 and TSH levels: 22 patients with type 1, 4 with type 2, 35 with type 3, and 1 with type 4.

Patients' Characteristics

The median age of enrolled patients was 65.50 years (IQR: 58.75–72.25), with 34 (43.6%) being male. Baseline characteristics were summarized in Table 1. As expected, NTIS was related to the severity of the disease. Patients with NTIS had significantly higher baseline viral loads (3.77 log10 copies/UL vs 1.57 log10 copies/mL, $P < 0.001$), were more likely to be admitted to the ICU (35.5% vs 6.3%, $P = 0.002$), and showed a higher incidence of consciousness changes (35.5% vs 12.5%, $P = 0.036$), and ecchymosis (21.0% vs 0%, $P<0.001$). Among SFTS patients admitted to the ICU (29.5%, 23/78), the majority had thyroid dysfunction (95.7%, 22/23, $P = 0.002$). Compared to patients with normal thyroid function, those with NTIS were more likely to experience coagulation abnormalities (APTT, 52s vs 38s, $P = 0.005$; D-Dimer, 2.68 ug/mL vs 1.10 ug/mL, $P < 0.001$), liver enzyme abnormalities (AST, 161.65 U/L vs 85.60 U/L, $P = 0.001$), electrolyte disorders (Sodium, 133.40 mmol/L vs 136.65 mmol/L, $P = 0.003$), LDH (603.00 U/L vs 407.00 U/L, $P = 0.001$), and α-HBDH (437.76 U/L vs 292.86 U/L, $P = 0.003$).

Independent Risk Factors for SFTS Patients

Independent risk predictors affecting the prognosis of SFTS patients were investigated. Significant factors ($P < 0.1$) identified in univariate cox regression analysis (Supplement Table 1) were selected, and adjustments were made to the variables included in the multivariate cox regression analysis to address multicollinearity and potential overfitting. The final results are as follows: NTIS type (hazard ratio (HR), 0.002; 95% confidence interval (CI): 0.000–0.635; $P = 0.002$),

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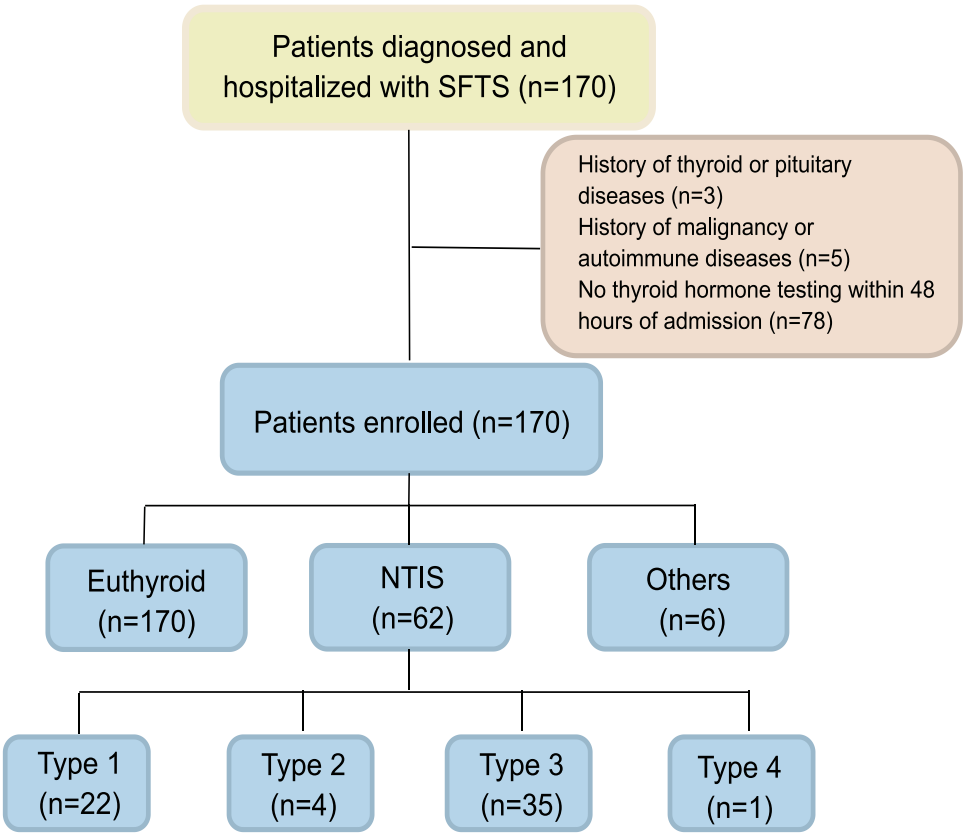

Figure 1 Screening flow chart for patients with SFTS combined with NTIS.

viral load (HR, 12.288; 95% CI: 1.284–117.597; $P = 0.029$), FT3 (HR, 0.004; 95% CI: 0.000–0.627; $P = 0.032$), FT4 (HR, 0.063; 95% CI: 0.004–0.897; $P = 0.041$).

Characteristics and Outcomes of SFTS Patients with Different NTIS Types

The 62 patients with NTIS were categorized into four subtypes based on TSH and FT4 levels: 22 (35.5%) patients were classified as type 1; 4 patients (6.5%) as type 2; 35 patients (56.5%) as type 3, and 1 patient (1.6%) as type 4. The thyroid hormones characteristics of each NTIS type are detailed in Table 2. Figure 2 displays survival proportions among euthyroid patients and those with different types of thyroid dysfunction. Due to the low proportions of NTIS type 2 and type 4, survival analysis focused on euthyroid patients and those with NTIS type 1 and 3. As shown in Figure 2, SFTS patients with

Table 1 Baseline Characteristics Among Patients

Characteristics	Total	Euthyroid	NTIS	*P* value	Others	*P* value
Number	84	16	62	–	6	–
Age, years	65.50(58.75–72.25)	71.50(57.50–74.00)	64.00(58.75–71.00)	0.109	67.50(52.25–83.00)	0.876
Sex (Male%)	38(45.2%)	8(50.0%)	26(41.9%)	0.081	4(66.7%)	0.508
SP (mmHg)	111.00(98.00–123.75)	118.50(105.25–126.00)	111.50(98.00–124.25)	0.426	93.50(80.25–108.75)	0.011*
DP (mmHg)	71.50(63.25–76.00)	71.00(64.25–75.75)	71.00(62.75–77.00)	0.482	63.00(56.25–70.50)	0.086
Comorbidities						
Hypertension	20(23.8%)	3(18.8%)	16(25.8%)	0.564	1(16.7%)	0.915
Diabetes	10(11.9%)	1(6.3%)	9(14.5%)	0.384	0(0%)	0.553

(*Continued*)

Table 1 (Continued).

Characteristics	Total	Euthyroid	NTIS	*P* value	Others	*P* value
TFTs						
FT3 (pmol/L)	2.14(1.79–2.92)	3.57(3.06–4.19)	1.94(1.71–2.26)	<0.001*	3.16(3.05–3.77)	0.274
FT4 (pmol/L)	11.44(9.83–13.27)	14.23(13.11–16.04)	10.80(9.36–12.07)	<0.001*	12.23(10.14–13.42)	0.007*
TSH (mIU/L)	1.35(0.72–2.33)	2.07(1.41–3.79)	1.02(0.61–1.77)	0.015*	6.50(6.14–8.82)	<0.001*
Manifestations						
Fever	82(97.6%)	14(77.5%)	62(100%)	0.164	6(100%)	0.388
Maximum temperature	38.70(38.20–39.00)	38.50(38.00–39.00)	38.80(38.20–39.13)	0.310	39.00(37.9–39.13)	0.582
Chills/Shiver	40(47.6%)	8(50.0%)	27(43.5%)	0.649	5(83.3%)	0.141
Myalgias	41(48.8%)	10(62.5%)	27(43.5%)	0.180	4(66.7%)	0.865
Fatigue	84(100%)	16(100%)	62(100%)	–	6(100%)	–
Headache	7(8.3%)	0(0%)	6(9.7%)	0.013*	1(16.7%)	0.363
Dizziness	11(13.1%)	2(12.5%)	8(12.9%)	0.905	1(16.7%)	0.811
Nausea/Vomit	40(47.6%)	8(50.0%)	28(45.2%)	0.733	4(66.7%)	0.508
Abdominal	10(11.9%)	1(6.3%)	7(11.3%)	0.560	2(33.3%)	0.265
Diarrhea	31(36.9%)	5(31.1%)	23(37.1%)	0.669	3(50.0%)	0.440
Bleeding/ Ecchymosis	13(15.5%)	0(0%)	13(21.0%)	<0.001*	0(0%)	–
Combined with infection	52(61.9%)	9(56.3%)	41(66.1%)	0.469	2(33.3%)	0.362
Consciousness changes	25(29.8%)	2(12.5%)	22(35.5%)	0.036*	1(16.7%)	0.811
Neurological signs	20(23.8%)	2(12.5%)	17(27.4%)	0.157	1(16.7%)	0.811
Viral load						
Ct value at baseline	24.96(21.82–27.96)	30.36(26.24–32.37)	23.49(20.61–26.59)	<0.001*	28.73(23.26–31.20)	0.276
RNA (log10) at baseline, copies/mL	3.70(2.67–4.56)	1.57(1.03–3.04)	3.77(2.99–4.44)	<0.001*	2.58(1.64–4.03)	0.256
Admitted to ICU	23(27.4%)	1(6.3%)	22(35.5%)	0.002*	0(0%)	0.553
Laboratory indicators						
WBC (3.5–9.5×10^9/L)	2.48(1.48–3.68)	2.75(2.17–4.69)	1.89(1.37–3.41)	0.160	2.80(2.38–4.84)	0.615
NEUT (1.8–6.3×10^9/L)	1.27(0.79–2.30)	1.40(0.76–2.42)	1.18(0.81–2.40)	0.489	1.06(0.79–1.85)	0.413
NEUT% (40–75%)	68.95(50.20–80.68)	48.10(34.23–78.28)	74.15(62.25–81.98)	0.010*	35.15(30.85–46.60)	0.032*
LYM (1.1–3.2×10^9/L)	0.60(0.30–0.98)	1.00(0.77–1.50)	0.39(0.26–0.76)	0.004*	1.33(0.95–2.38)	0.094
LYM% (20–50%)	21.65(13.50–35.80)	34.25(15.70–48.23)	19.5(12.18–28.55)	0.003*	43.70(36.35–58.30)	0.112
MONO (0.1–0.6×10^9/L)	0.17(0.08–0.32)	0.34(0.20–0.65)	0.10(0.08–0.24)	0.755	0.37(0.23–0.62)	0.946
MONO% (3–10%)	6.60(4.13–12.83)	11.30(5.30–16.63)	5.70(3.90–8.98)	0.009*	12.10(7.23–22.58)	0.437
EOS (0.02–0.5×10^9/L)	0(0–0.01)	0.01(0–0.02)	0(0–0.01)	0.118	0.01(0–0.01)	0.572
EOS% (0.4–8%)	0.20(0–0.40)	0.20(0–0.58)	0.20(0–0.40)	0.981	0.30(0–0.43)	0.644
BAS (0–0.06×10^9/L)	0.01(0–0.01)	0.01(0–0.02)	0(0–0.01)	0.615	0.01(0.01–0.04)	0.216
BAS% (0–1%)	0.20(0–0.40)	0.20(0.10–0.40)	0.10(0–0.30)	0.954	0.45(0.38–0.75)	0.610
RBC (4.3–5.8×10^{12}/L)	4.60(4.32–4.96)	4.62(4.30–5.02)	4.56(4.30–4.99)	0.705	4.80(4.53–4.96)	0.662
Hb (130–175g/L)	142.00(133.00–154.75)	141.50(132.75–157.25)	142.00(132.00–152.50)	0.325	144.50(138.75–156.25)	0.571
PLT (125–350×10^9/L)	76.00(55.00–94.00)	84.50(55.75–108.50)	75.00(54.25–88.25)	0.190	79.50(54.00–115.50)	0.576
ALT (9–50U/L)	72.00(45.40–155.05)	63.00(36.83–113.60)	72.00(44.30–151.35)	0.429	139.75(60.23–258.1)	0.130
AST (15–40U/L)	147.80(77.68–303.00)	85.60(54.53–115.13)	161.65(85.70–320.13)	0.001*	193.6(87.4–867.8)	0.168
ALB (35–53g/L)	34.15(34.43–36.38)	34.30(30.98–36.38)	34.30(31.80–36.43)	0.642	32.20(28.35–34.88)	0.423
TBIL (0.1–21umol/L)	9.70(7.55–12.72)	10.85(9.57–14.04)	8.98(7.49–12.64)	0.749	7.97(5.43–10.39)	0.027*
CK (0–190U/L)	386.50(165.75–1160.50)	171.00(53.00–510.50)	473.00(237.00–1489.00)	0.335	218.00(69.00–599.75)	0.649
LDH (80–285U/L)	526.50(395.50–900.75)	407.00(324.00–577.00)	603.00(412.50–993.50)	0.001*	426.00(301.25–1318.75)	0.397
α-HBDH (72–182U/L)	363.78(227.30–587.50)	292.86(224.49–400.52)	437.76(285.71–631.12)	0.003*	288.78(227.30–758.16)	0.477
PT (11–14.5S)	12.75(12.30–13.38)	12.50(11.90–12.95)	12.80(12.40–13.45)	0.578	12.65(12.18–13.35)	0.704
APTT (28–43.5S)	48.55(41.43–56.90)	38.00(33.35–44.00)	50.00(45.10–60.80)	0.005*	46.60(34.38–57.83)	0.178
FIB (2–4g/L)	2.51(2.25–3.02)	3.58(2.91–3.90)	2.44(2.20–2.70)	0.303	2.74(2.41–3.24)	0.203
D-Dimer (0–0.5ug/mL)	2.46(1.36–3.73)	1.10(0.51–1.78)	2.68(1.76–5.33)	<0.001*	1.34(0.61–2.36)	0.809
CRP (0–5mg/L)	4.01(1.43–8.87)	2.31(0.38–7.15)	4.91(1.70–10.90)	0.286	1.64(0.29–8.78)	0.645

(*Continued*)

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Table 1 (Continued).

Characteristics	Total	Euthyroid	NTIS	*P* value	Others	*P* value
PCT (0–0.06ng/mL)	0.19(0.11–0.47)	0.14(0.09–0.33)	0.22(0.13–0.56)	0.290	0.09(0.06–0.26)	0.514
Sodium (136–146mmol/L)	134.10(131.00–136.68)	136.65(133.43–139.10)	133.40(130.43–136.33)	0.044*	134.15(133.28–138.63)	0.869
Potassium (3.5–5.1mmol/L)	3.67(3.36–4.02)	3.52(3.22–3.93)	3.67(3.38–4.00)	0.712	3.91(3.37–4.07)	0.817
Calcium (2.2–2.55mmol/L)	2.03(1.93–2.14)	2.05(1.93–2.15)	2.02(1.92–2.12)	0.652	2.12(2.06–2.16)	0.385

Notes: Data are presented as median (interquartile range) and number (percentage) as appropriate. * indicates *P* value < 0.05, which is statistically significant.
Abbreviations: SP, Systolic pressure; DP, Diastolic pressure; TFTs, Thyroid function tests; FT3, Free triiodothyronine; FT4, Free thyroxine; TSH, thyroid-stimulating hormones; ICU, Intensive care unit; WBC, White blood cell count; NEUT, Neutrophil count; LYM, Lymphocyte count; MONO, Monocyte count; EOS, Eosinophil count; BAS, Basophil count; RBC, Red blood cell count; Hb, Hemoglobin; PLT, Platelet; ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALB, Albumin; TBIL, Total bilirubin; CRP, C-reactive protein; PCT, Procalcitonin; CK, Creatine kinase; LDH, Lactate dehydrogenase; PT, Prothrombin time; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen.

Table 2 The Thyroid Hormones Characteristics of Different Types NTIS

Thyroid Function	Euthyroid (n=16)	NTIS type1 (n=22)	NTIS type2 (n=4)	NTIS type3 (n=35)	NTIS type4 (n=1)
FT3, pmo/L	3.57(3.06–4.19)	2.21(1.83–2.52)	2.22(1.35–2.52)	1.90(1.67–2.08)	1.74(1.74–1.74)
FT4, pmo/L	14.23(13.11–16.04)	12.45(11.54–13.49)	12.72(11.74–14.16)	9.75(8.79–10.52)	10.27(10.27–10.27)
TSH, ulU/mL	2.07(1.41–3.79)	1.05(0.78–1.79)	0.29(0.26–0.31)	1.17(0.70–1.96)	0.21(0.21–0.21)

Abbreviations: FT3, Free triiodothyronine; FT4, Free thyroxine; TSH, thyroid-stimulating hormones.

NTIS type 3 (low fT3, fT4, normal TSH) had the highest mortality rate (28.57%). Patients with NTIS type 1 and type 3 also showed significantly higher mortality rates compared to euthyroid patients (HR=1.896, CI 1.055–3.409, $P = 0.033$).

Effects of NTIS on Lymphocytes and Their Subsets

Notably, the median lymphocyte count at admission among NTIS patients was 0.39×10^9/L (IQR: 0.26–0.76), with 83.3% of this cohort presenting with lymphopenia (Table 1). We further analyzed the characteristics of lymphocyte subsets among euthyroid and NTIS patients (Table 3). Compared to patients with normal thyroid function, NTIS patients showed significantly lower counts of CD3+ T cells (312cell/ul vs 85cell/ul, $P < 0.001$), Ts cells (127cell/ul vs 479cell/ul, $P = 0.037$), and Ts% (22.76% vs 32.03%, $P = 0.035$), while NK% was notably elevated (25.62% vs.15.93%, $P = 0.019$).

Correlation Among Immune Cells and FT3, FT4, and TSH

Spearman correlation analysis revealed that FT3 was positively correlated with LYM ($r = 0.389$, $p < 0.001$), LYM% ($r = 0.375$, $p < 0.001$), MONO ($r = 0.318$, $p = 0.003$), MONO% ($r = 0.276$, $p = 0.011$), BAS ($r = 0.236$, $p = 0.031$), CD3+T ($r = 0.329$, $p = 0.019$), CD3+T% ($r = 0.349$, $p = 0.012$), Th ($r = 0.379$, $p = 0.006$), and Th% ($r = 0.327$, $p = 0.019$). Conversely, FT3 was negatively correlated with NEUT% ($r = 0.361$, $p = 0.001$), and NK% ($r = 0.328$, $p = 0.019$). FT4 was positively correlated with MONO ($r = 0.266$, $p = 0.014$), MONO% ($r = 0.295$, $p = 0.007$), and CD3+T% ($r = 0.277$, $p = 0.049$), while negatively correlated with NK% ($r = 0.282$, $p = 0.045$) and B% ($r = 0.318$, $p = 0.023$). TSH was positively correlated with LYM% ($r = 0.226$, $p = 0.039$), and CD3+T% ($r = 0.288$, $p = 0.040$) (Figure 3, Supplement Table 2).

Discussion

This study is the first retrospective analysis to evaluate the prognostic significance of NTIS in SFTS patients. Our results show that viral load, NTIS type, FT3, and FT4 were associated with mortality, with adjusted hazard ratios (aHRs) of 12.288, 0.002, 0.004, and 0.063, respectively. Notably, viral load was the strongest predictor of poor outcomes, consistent with previous studies that identified high viral load as a risk factor for fatal outcomes in SFTS patients.[18]

NTIS, first described in the 1970s, has long been considered a predictor of unfavorable outcomes in various severe illnesses.[6,7] The adverse effects of NTIS have been demonstrated in patients with conditions such as COVID-19, septic, stroke,

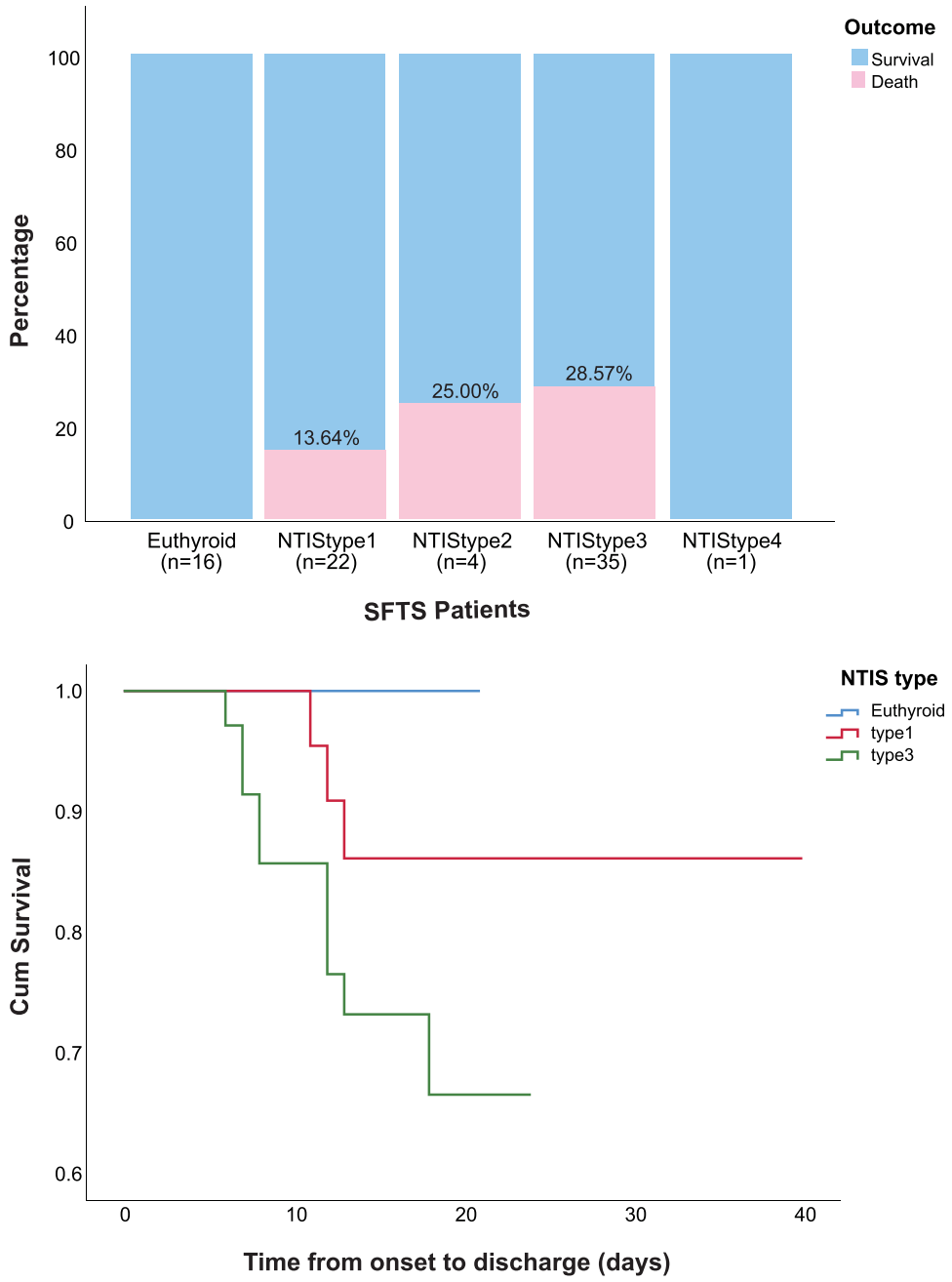

Figure 2 Mortality and risk assessment of patients with different NTIS types.

acute liver failure, Crohn's disease, and heart failure.[16,19–24] However, there has been little research on the impact of NTIS in SFTS patients. Previous studies have shown that low serum FT3 levels are associated with high mortality in SFTS patients.[15] In this study, we found that both decreased serum FT3 and FT4 levels are independent risk predictors for SFTS, aligning with previous research.[6,25] Another important finding of our study is that the mortality rate in SFTS patients with NTIS is higher than in those with normal thyroid function. Moreover, the different NTIS subtypes significantly impact mortality, suggesting that the specific classification of NTIS should be considered in clinical practice. Due to the small number of patients with NTIS type 2 and type 4, we only performed survival analysis on NTIS type 1 and type 3 patients. We found that the mortality rate of NTIS type 3 was higher, consistent with a study by Ning et al, which reported that NTIS type 4 had the highest mortality rate, followed by type 2, type 3, type 1, and euthyroid patients.[6]

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Table 3 Characteristics of Lymphocyte Subsets in Patients With NTIS

Characteristics	Total (n=47)	Euthyroid (n=5)	NTIS (n=42)	*P* value
T (848–1759cells/ul)	329.00(203.00–537.00)	875.00(569–1137.50)	312.00(175.75–455.75)	<0.001*
T % (60.8–75.4%)	52.76(42.70–62.13)	64.00(48.76–73.43)	52.31(41.09–61.45)	0.096
Th (417–986cells/ul)	148.00(99.00–256.00)	363.00(141.00–611.50)	140.50(95.50–253.25)	0.147
Th% (29.4–45.8%)	23.50(16.13–33.36)	20.73(13.60–38.76)	23.68(16.19–32.66)	0.824
Ts (266–660cells/ul)	140.00(81.00–268.00)	479.00(253.50–676.50)	127.00(78.50–236.75)	0.037*
Ts% (18.2–32.8%)	23.60(18.10–32.72)	32.03(24.90–45.79)	22.76(17.15–31.93)	0.035*
Th/Ts (1.05–2.03%)	1.09(0.65–1.47)	0.65(0.36–1.40)	1.10(0.67–1.50)	0.579
B (5–18cells/ul)	123.50(61.50–254.25)	231.00(84.00–294.75)	111.00(60.00–261.00)	0.984
B% (5–18%)	17.50(13.77–25.54)	12.60(9.53–30.82)	17.60(13.97–25.57)	0.758
NK (74–254cells/ul)	187.00(109.00–356.00)	223.00(126.00–333.00)	179.50(107.25–358.50)	0.696
NK% (9.5–23.5%)	25.12(18.89–33.66)	15.93(9.96–21.97)	25.62(19.43–36.21)	0.019*

Notes: * indicates *P* value < 0.05, which is statistically significant.
Abbreviations: T, CD3+ T cell count; T%, CD3+ T cell count%; Th, CD3+CD4+ T cell count; Th%, CD3+CD4+ T cell%; Ts, CD3+CD8+ T cell count; Ts%, CD3+CD8+ T cell%; B, CD3-CD19+ cells count; B%, CD3-CD19+ cells%; NK, Natural Killer cell; (CD3-CD56+ cells), CD3-CD56+ cells.

NTIS has remained an intriguing phenomenon, especially with the recent findings on the role of thyroid hormone metabolism in innate immune cells, including neutrophiles (NEUT), monocytes (MONO), and macrophages.[7] In our study, SFTS patients with NTIS exhibited contrasting trends in most innate and adaptive immune cells at admission compared to euthyroid patients. Specifically, elevated NEUT%, Natural Killer cell% (NK%) and decreased Lymphocyte (LYM), LYM%, MONO%, T lymphocyte, Suppressor T cell (Ts), and Ts% were observed in NTIS patients. Spearman correlation analysis revealed that LYM, LYM%, MONO, MONO%, BAS, CD3+T, CD3+T%, Th, Th% were positively correlated with FT3, FT4, or TSH. There is a bilateral interaction between the immune system and thyroid hormones, both in physiological and pathological conditions.[11] Immune cells are targets for THs, and FT3 and FT4 modulate specific immune responses, such as cell-mediated immunity, NK cell activity, the antiviral action of interferon (IFN), and the proliferation of T- and B- lymphocytes,[26] influencing inflammation-related processes.[27,28] Inflammatory cytokines produced by immune cells enhance the negative feedback of THs to the hypothalamus by unregulating the local expression of iodothyronine deiodinase II (DIO2), thereby reducing the secretion of thyrotropin-releasing hormone (TRH) and TSH. Inflammatory stimuli also affect peripheral TH metabolism, limiting the expression of iodothyronine deiodinase I (DIO1) in the liver, further reducing serum FT3 and/or FT4 levels.[12] Our findings suggest that when NTIS occurs, the HPT axis is suppressed due to the disease state, leading to reduced THs levels and affecting immune cells activation. Additionally, this may be influenced by the direct impact of the virus on immune cells, bone marrow dysfunction, and thymic suppression.[14] The increased neutrophil ratio may be due to the presence of infection, while elevated NK % and B% might reflect their crucial role in immune responses in SFTS patients with NTIS, acting as a stress response to the disease. However, the exact mechanism remain unclear, and further research is needed to elucidate this.

Thyroid hormone levels typically normalize as patients recover, although there have been reports of permanent thyroid hormone defects due to subacute thyroiditis following viral infection.[29] Due to the lack of follow-up data, our study could not analyze the recovery of thyroid function in discharged patients. The question of whether thyroid hormone treatment should be considered for patients with NTIS, espically critically ill patients, remains unanswered.[30] While some clinical studies had been conducted, only a few small randomized controlled trials (RCTs) have assessed the effects

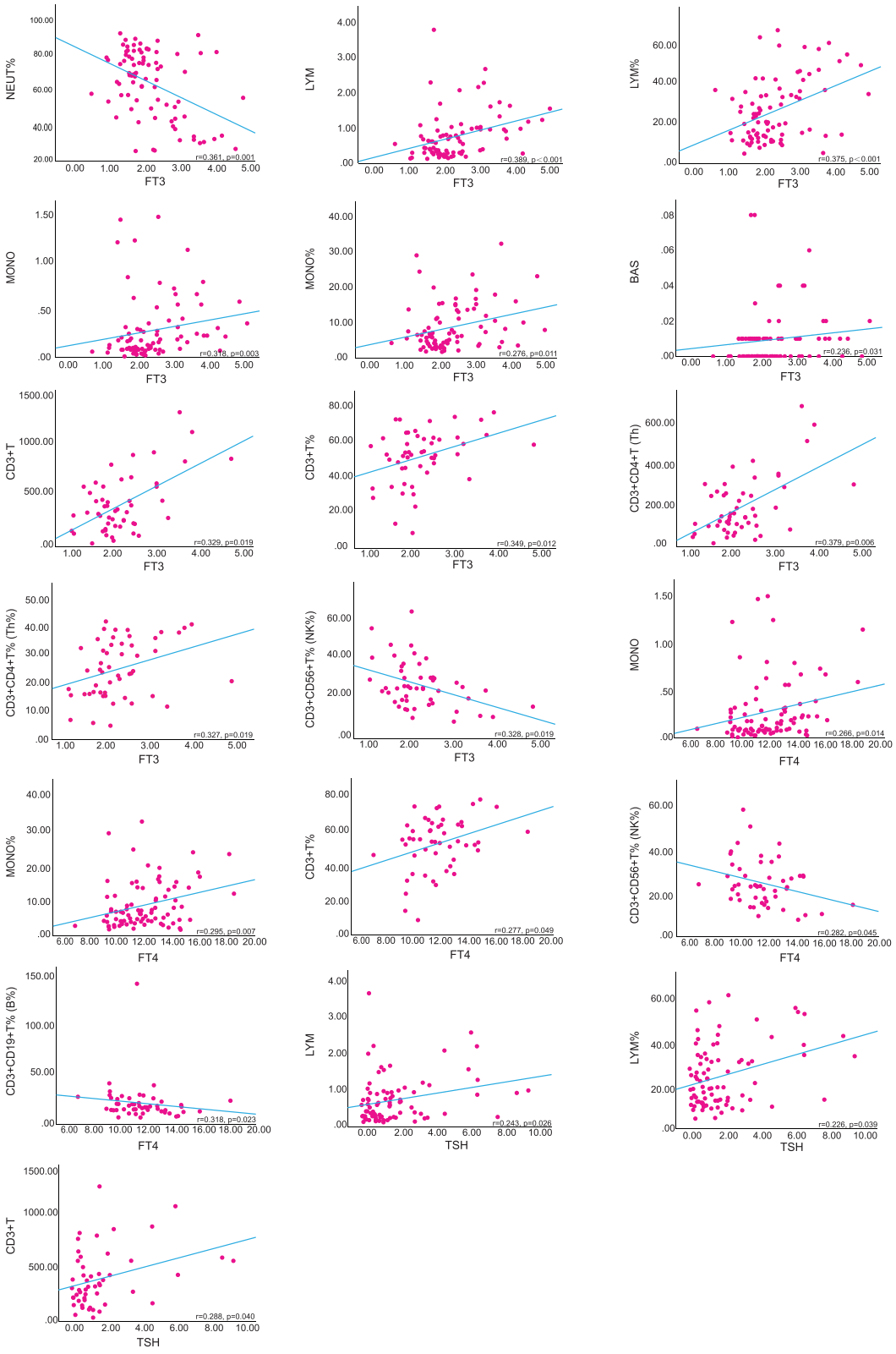

Figure 3 Linear correlation between FT3, FT4, and TSH and different immune cells.

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of thyroid hormones treatment in NTIS patients, and the results have been inconclusive.[31–33] However, some research suggests that treatment like N-acetyl-cysteine (NAC) or sodium bicarbonate (SB) may offer benefits for NTIS patients, warranting further investigation.[31,34]

There are several limitations to this study. First, the data were retrospectively collected, and missing data is inevitable Second, the THs levels fluctuate dynamically during the course of SFTS, and longitudinal measurement of thyroid hormone, as well as follow-up after discharge, were not available. Third, our study was conducted at a single center and focused on the Chinese population. Nevertheless, to our knowledge, this is the first study to comprehensively analyzed the relationship among NTIS and prognosis in SFTS patients. Our findings may provide valuable insights for selecting treatment strategies for SFTS patients, especially those who are critically ill, in future clinical trials.

Conclusion

In summary, more than half of SFTS patients develop NTIS, with a higher incidence observed in more severe cases. NTIS patients have a lower survival rate compared to those with normal thyroid function. Additionally, the mortality risk in NTIS type 3 is higher than that in NTIS type 1. Specific NTIS subtypes should be taken into account when enrolling participants or selecting treatment strategies in future clinical practice.

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Disclosure

The author(s) report no conflicts of interest in this work.

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