

# Association Between Nonthyroidal Illness Syndrome and Disseminated Intravascular Coagulation in Sepsis

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**Purpose:** Both nonthyroidal illness syndrome (NTIS) and disseminated intravascular coagulation (DIC) are commonly occurred in sepsis. The objective of this study is to evaluate the association between NTIS and DIC, as well as their impacts on the mortality in adults with sepsis.

**Patients and methods:** A total of 1219 septic patients in two Chinese academic centers from October 2012 and October 2022 were enrolled in analysis. We conduct logistic regression models to analyze the independent risk factors for DIC. Modified Poisson regression models are used to estimate the relative risk (RR) of NTIS on the 28 days mortality in septic patients with DIC. Correlation analysis between thyroid function parameters and coagulation parameters is performed with Pearson coefficient be reported.

**Results:** DIC is diagnosed on 388 (31.8%) of all the 1219 enrolled septic patients within 72 hours after admission. In multivariate logistic regression models, NTIS (OR 3.19; CI 2.31–4.46;  $p < 0.001$ ) is a statistically significant independent risk factor for DIC after adjustment for potential confounders. Twenty-eight days mortality is significantly higher in DIC patients complicated with NTIS compared with the other DIC patients (23.2% vs 14.0%,  $p = 0.024$ ). This result is also robust in different modified Poisson regression models (Model 1: RR 1.46; CI 1.25–1.70;  $p < 0.001$ ; Model 2: RR 1.35; CI 1.14–1.60;  $p < 0.001$ ; Model 3: RR 1.18; CI 1.02–1.37;  $p = 0.026$ ). Correlation analysis reveals that the thyroid function parameters of FT3, FT4 and TSH only have weak correlations with coagulation parameters of platelet count, fibrinogen, FDP, D-dimers, PT, APTT and INR in sepsis.

**Conclusion:** NTIS is an independent risk factor for DIC in adults with sepsis. DIC patients complicated with NTIS have significantly higher severity and higher rate of mortality.

**Keywords:** sepsis, low T3 syndrome, nonthyroidal illness syndrome, thyroid function, disseminated intravascular coagulation

## Introduction

Sepsis is an infection induced life-threatening syndrome, which impacts millions of people around the world each year. Sepsis accounts for about 6% of adult hospitalization in high-income countries, and the overall mortality rate remains as high as 15%–23%.<sup>1,2</sup>

Sepsis is a systemic illness that involves, but not limited to circulatory, respiratory, coagulation or endocrine system. The dysregulated inflammatory processes induced by infection compromise multiple systems leading to multiple organ dysfunction syndrome (MODS) and potentially life-threatening consequences.<sup>3</sup> Disseminated intravascular coagulation (DIC) in sepsis, defined as a coagulation disorder induced by infection, is characterized by endothelial dysfunction and systemic thrombin generation.<sup>4</sup> The prevalence of DIC in septic patients is as about 30%–50%. The percentage is relatively high because the inflammatory reaction and coagulation process closely interact with each other. Complication with DIC indicates unfavorable prognosis and higher mortality for septic patients.<sup>5,6</sup>

Current precision medicine in the field of intensive care medicine highlights stratifying patients and finding phenotypes with best host-response patterns.<sup>7,8</sup> This concept is of great importance in identification and management of DIC in septic patients. For example, anticoagulation treatment is very important but is also controversial in the treatment of DIC, because conflicting conclusions were obtained from a series of clinical studies.<sup>9,10</sup> Further analysis suggests that treatment for DIC should concentrate on the very severely ill patients,<sup>11</sup> which emphasizes the precise stratification for DIC patients. Risk stratification is of particular importance, because high-risk patients may get benefit from earlier treatment, whereas low-risk patients may get benefit from avoiding unnecessary interventions. Although coagulation markers such as platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimers have been widely acknowledged to diagnose DIC on sepsis, these biomarker are not satisfied in severity stratification. Nonthyroidal illness syndrome (NTIS), also called “low T3 syndrome” or “euthyroid sick syndrome”, is the most common endocrine dysfunction in sepsis with a reported rate of about 42% and well known as a negative predictor for outcomes.<sup>12</sup> The conclusion of a meta-analysis revealed that either low triiodothyronine or thyroxine was associated with the increased in-hospital mortality in adult septic patients.<sup>13</sup> This conclusion was also supported in another study using data from a large critical care database.<sup>14</sup> However, even though thyroid function is commonly tested for septic patients, the association between NTIS and DIC in sepsis was not taken seriously in previous studies.

Given that NTIS represents a specific group of patients with higher illness severity and unique pathophysiological characteristics, the objective of the study is therefore to evaluate the association between NTIS and DIC, as well as its impact on the outcomes in adult septic patients, in order to provide evidence for precise intervention in future studies.

## Methods

### Participants

This retrospective study was conducted in Ruijin Hospital, Shanghai Jiaotong University School of Medicine, and Xinhua Hospital, Shanghai Jiaotong University School of Medicine. The protocol was approved by the institutional ethics board of each hospital, and the informed consent was waived because of the non-interventional, retrospective design of the study. Data analysis was performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Consecutive adult patients (age $\geq$ 18 years) with a diagnosis of sepsis on admission between May 2015 and May 2022 (Ruijin Hospital, Shanghai Jiaotong University School of Medicine), and between October 2012 and October 2022 (Xinhua Hospital, Shanghai Jiaotong University School of Medicine) were screened. Patients exclusion criteria included: (1) incomplete coagulation function test; (2) without thyroid function test on admission; (3) history of hematological or coagulation system diseases; (4) history of cirrhosis; (5) using anticoagulants before coagulation function test.

### Data Collection

The clinical variables are extracted from the paper-based or electronic medical records for each patient. Baseline demographic information includes age, sex, comorbidities (hypertension, diabetes, and chronic kidney diseases). Infection source is classified into respiratory system source, gastrointestinal tract source, urogenital tract source, and others (including skin and soft tissue infection, bone and joint infection, and meningitis). Laboratory indicators collected within 24 hours after admission include white blood cell count, alanine aminotransferase, total bilirubin, creatinine, lactate, C-reactive protein, procalcitonin, free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH). Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and Sequential Organ Failure Assessment (SOFA) scores are collected within 24 hours after admission. Coagulation parameters (including fibrinogen, fibrin/fibrinogen degradation products (FDP), D-dimers, PT, APTT, and international normalized ratio (INR)) are obtained within 72 hours and DIC is diagnosed on the worst results. Thyroid dysfunctions are classified into euthyroid, history of hypothyroidism, history of hyperthyroidism, NTIS, and others. The rate of 28 days in-hospital mortality is reported. Patients discharged any earlier than 28 days were considered survivors.

## Definition

The diagnosis of sepsis is defined as (SOFA) score  $\geq 2$  points consequent to the infection (Sepsis-3). Septic shock is defined as sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure  $\geq 65$  mm Hg and having a serum lactate level  $>2$  mmol/L despite adequate volume resuscitation.<sup>15</sup> The diagnosis of DIC is defined according to the International Society on Thrombosis and Haemostasis (ISTH) diagnostic criteria for overt DIC.<sup>16</sup> Patients with ISTH overt DIC scores  $\geq 5$  is diagnosed of DIC. NTIS in this study is defined as a low serum FT3 level ( $<2.63$  pmol/L) without an elevated TSH level ( $<4.94$  mIU/mL).<sup>17</sup>

## Data Statistics

Categorical data will be described in terms of frequency or ratio. Continuous variables will be described using median and interquartile range. Categorical variables will be compared using  $\chi^2$  test or Fisher's exact test. Continuous variables will be compared using the *t*-test for normally distributed variables or Wilcoxon rank-sum test for non-normally distributed variables. We implement multiple predictive mean matching imputations using chained equation and created 5 independent datasets to compute missing data. Variables with missing data more than 20% are deleted.

Survival curve between septic patients with or without DIC is plotted using the Kaplan–Meier method. The associations between NTIS and DIC are estimated using logistic regression models. Variables in univariate logistic regression model with  $p < 0.15$  are included in multivariate logistic regression model. The effect of NTIS on the 28 days mortality in septic patients with DIC is analyzed. Considering the high 28 days mortality in septic patients with DIC, we used modified Poisson regression model with robust (sandwich) estimation of variance to calculate the relative risk (RR), instead of logistic regression model with odds ratio (OR). Baseline information includes age, sex, and comorbidities are adjusted. Moreover, total bilirubin represents liver function; creatinine represents renal function; lactate represents oxygen debt; C-reactive protein represents inflammation reaction degree; procalcitonin represents infection severity, and APACHE II score represent the overall condition. These variables are also adjusted in the models. The correlations between thyroid function parameters and coagulation parameters are reported as Pearson correlation coefficients and shown in correlation-based heatmap. Sensitivity analysis is conducted on the raw data to evaluate the associations between NTIS and DIC, and the effect of NTIS on the 28 days mortality in septic patients with DIC. Statistical analyses are performed using R software (version 4.2.1). A two-sided significance level less than 0.05 is defined as statistical significance.

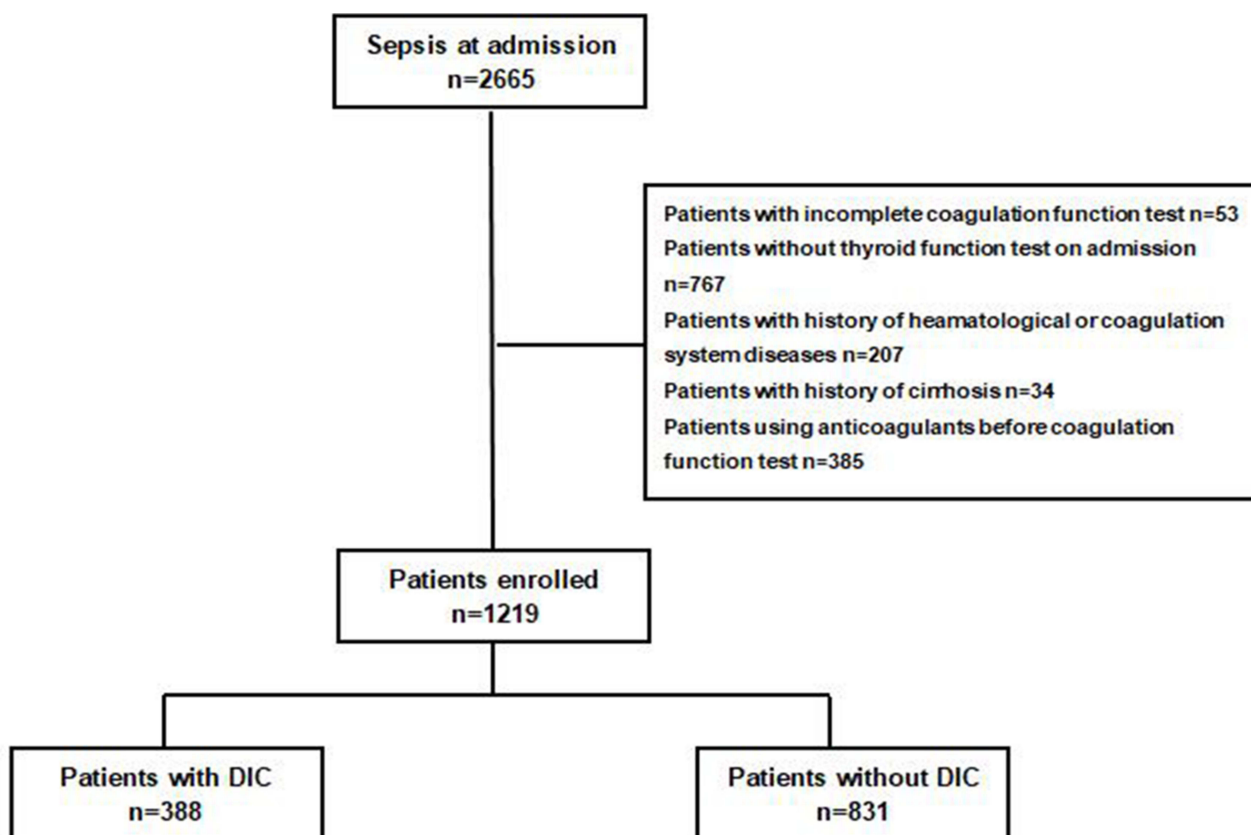
## Results

### Patients' Characteristics

A total of 2665 patients diagnosed with sepsis on admission in two centers are included. After screening, 1219 septic patients are enrolled. [Figure 1](#) shows the screening flowchart. Among them, DIC is diagnosed in 388 (31.8%) patients within 72 hours after admission, and 165 (13.5%) patients died within 28 days. Remarkable laboratory differences are found at the levels of alanine aminotransferase, creatinine, C-reactive protein and procalcitonin. All the coagulation parameters are significantly worse in patients with DIC, except for INR (median 1.2 vs 1.2,  $p=0.082$ ). Patients with DIC have a significantly lower FT3 level (median 2.1 pmol/L vs 2.7 pmol/L,  $p<0.001$ ), and FT4 level (median 12.1 pmol/L vs 13.9 pmol/L,  $p<0.001$ ), but no difference on TSH level (median 0.9  $\mu$ IU/mL vs 1.1  $\mu$ IU/mL,  $p=0.944$ ). APACHEII scores are higher (median 13 vs 11,  $p<0.001$ ), more patients suffer septic shock (37.4% vs 22.0%,  $p<0.001$ ), and more patients dies within 28 days (19.3% vs 10.8%,  $p<0.001$ ) in DIC group ([Supplementary Figure 1](#)). There is no difference on the history of hypothyroidism (3.4% vs 5.7%,  $p=0.083$ ) or hyperthyroidism (3.1% vs 3.0%,  $p=0.936$ ) between groups, but much more patients suffer NTIS in DIC group (57.7% vs 27.9%,  $p<0.001$ ) ([Table 1](#)).

### Association Between NTIS and DIC in Sepsis

Of all the 1219 patients, the distribution of ISTH overt DIC scores is as follows: 330 of them score between 0 and 2; 501 of them score between 3 and 4; 350 of them score between 5 and 6; and 38 of them score between 7 and 8. [Figure 2](#) shows the incidence of NTIS in the groups with different DIC scores. The NTIS percentage is increasing gradually with



**Figure 1** Screening flowchart.

**Abbreviation:** DIC, disseminated intravascular coagulation.

the DIC scores (15.4%, 36.1%, 55.7% and 76.3%, respectively). Logistic regression model is developed to estimate the risk factors for DIC. Variables in univariate logistic regression model with  $p < 0.15$  are included in multivariate logistic regression model. Finally, in multivariate logistic regression model, the following confounders are included: age, sex, hypertension, chronic kidney diseases, infection source classified as others, white blood cell count, alanine aminotransferase, total bilirubin, creatinine, C-reactive protein, procalcitonin, APACHE II score, and thyroid dysfunctions. In multivariate model, NTIS (OR 3.19; CI 2.31–4.46;  $p < 0.001$ ) is a statistically significant independent risk factor for DIC

**Table 1** Characteristics Between Septic Patients with or Without DIC

Characteristics	Total n = 1219	With DIC n = 388	Without DIC n = 831	p value
Age, years	70(61–81)	71(60–81)	70(61–81)	0.377
Sex (male%)	744(61.0)	221(57.0)	523(62.9)	0.046*
<b>Comorbidities</b>				
Hypertension	603(49.5)	175(45.1)	428(51.5)	0.037*
Diabetes	417(34.2)	131(33.8)	286(34.4)	0.823
Chronic kidney diseases	255(20.9)	96(24.7)	159(19.1)	0.025*
<b>Infection sources</b>				
Respiratory system	801(65.7)	254(65.5)	547(65.8)	0.902
Gastrointestinal tract	330(27.1)	103(26.5)	227(27.3)	0.778
Urogenital tract	251(20.6)	81(20.9)	170(20.5)	0.866
Others	145(11.9)	60(15.5)	85(10.2)	0.009*

(Continued)

Table 1 (Continued).

Characteristics	Total n = 1219	With DIC n = 388	Without DIC n = 831	p value
<b>Laboratory indicators</b>				
White blood cell, ×10 <sup>9</sup> /L	10.1(6.7–14.8)	10.4(6.7–15.5)	9.8(6.8–14.6)	0.094
Alanine aminotransferase, IU/L	28(16–59)	35(19–90)	26(15–48)	<0.001*
Total bilirubin, μmol/L	14.8(9.6–23.6)	16.4(10.5–29.3)	14.0(9.2–21.9)	0.085
Creatinine, μmol/L	85(63–134)	102(67–186)	81(61–119)	<0.001*
Lactate, mmol/L	1.8(1.4–2.6)	1.8(1.4–2.7)	1.8(1.4–2.5)	0.604
C-reactive protein, mg/L	106(42–160)	124(58–165)	98(37–160)	<0.001*
Procalcitonin, ng/mL	1.6(0.2–12.8)	4.6(0.7–35.2)	1.0(0.2–7.4)	<0.001
FT3, pmol/L	2.5(2.0–3.1)	2.1(1.6–2.7)	2.7(2.1–3.3)	<0.001*
FT4, pmol/L	13.4(11.3–15.5)	12.1(10.3–14.2)	13.9(12.0–16.3)	<0.001*
TSH, μIU/mL	1.0(0.5–1.9)	0.9(0.4–1.8)	1.1(0.5–2.1)	0.944
<b>Coagulation parameters</b>				
Platelet count, ×10 <sup>9</sup> /L	152(100–207)	85(57–134)	176(134–223)	<0.001*
Fibrinogen, g/L	4.3(3.3–5.3)	4.0(2.9–5.1)	4.4(3.5–5.3)	<0.001*
FDP, mg/L	8.3(4.1–17.2)	22.2(13.3–41.2)	5.4(3.1–9.3)	<0.001*
D-dimers, mg/L	1.7(0.8–4.2)	6.4(2.8–11.4)	1.1(0.6–2.2)	<0.001*
PT, seconds	13(12–15)	14(12–16)	13(12–14)	<0.001*
APTT, seconds	32(29–36)	33(29–39)	32(28–35)	<0.001*
INR	1.2(1.1–1.3)	1.2(1.1–1.4)	1.2(1.1–1.3)	0.082
APACHEII score	12(8–17)	13(9–19)	11(8–16)	<0.001*
Septic shock	328(26.9)	145(37.4)	183(22.0)	<0.001*
<b>Thyroid dysfunctions</b>				
Euthyroid	497(40.8)	96(24.7)	401(48.3)	<0.001*
History of hypothyroidism	60(4.9)	13(3.4)	47(5.7)	0.083
History of hyperthyroidism	37(3.0)	12(3.1)	25(3.0)	0.936
NTIS	456(37.4)	224(57.7)	232(27.9)	<0.001*
Others	169(13.9)	43(11.1)	126(15.2)	0.055
28 days mortality	165(13.5)	75(19.3)	90(10.8)	<0.001*

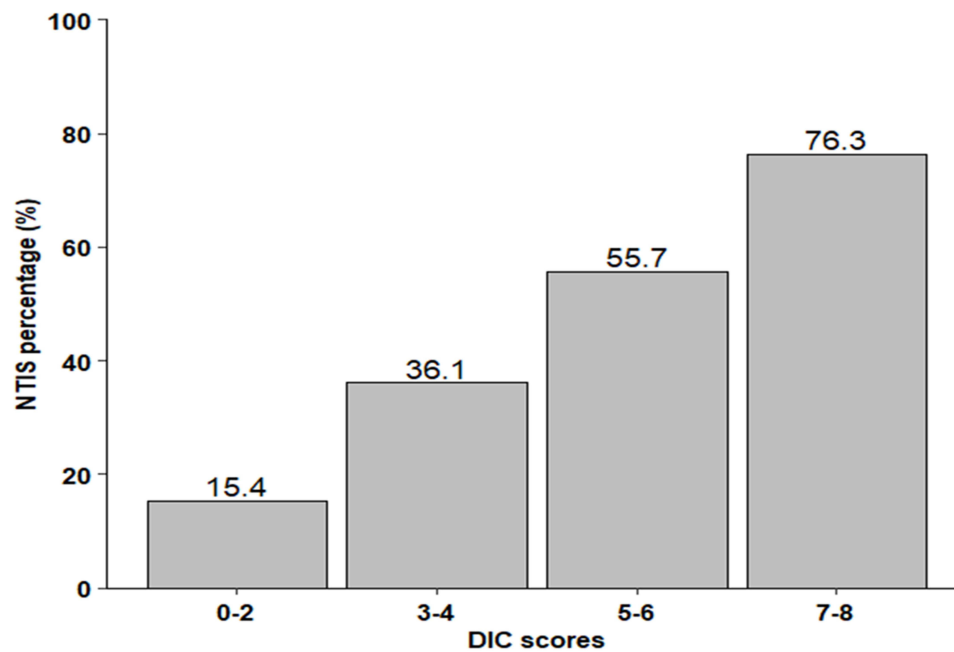
Notes: Data are presented as median and interquartile range or number (percentage). \*p < 0.05.

Abbreviations: DIC, disseminated intravascular coagulation; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; FDP, fibrin/fibrinogen degradation products; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; NTIS, nonthyroidal illness syndrome.

compared with euthyroid or the other thyroidal dysfunctions (Table 2). The results are similar in sensitivity analysis on raw data (Supplementary Table 2).

## Impact of NTIS on the 28 Days Mortality in Septic Patients with DIC

A total of 388 patients with DIC are divided into two groups: patients with both NTIS and DIC (n=224); and patients with DIC, but without NTIS (n=164). The patients' characteristics between two groups are shown in Supplementary Table 1. DIC patients with NTIS have higher APACHEII score (median 15 vs 11, p<0.001) and 28 days mortality rate (23.2% vs 14.0%, p=0.024) compared with the DIC patients without NTIS. Modified Poisson regression models are adjusted for several risk factors, including age, sex, comorbidities, total bilirubin, creatinine, lactate, C-reactive protein, procalcitonin, and APACHE II score. The results in different models reveal that after adjustment for potential confounders, the 28 days mortality is still significantly higher in NTIS group (Model 1: RR 1.46; CI 1.25–1.70; p<0.001; Model 2: RR 1.35; CI 1.14–1.60; p<0.001; Model 3: RR 1.18; CI 1.02–1.37; p=0.026) (Table 3). The results are similar in sensitivity analysis on raw data (Supplementary Table 3).



**Figure 2** Association between NTIS and DIC in sepsis.

**Abbreviations:** DIC, disseminated intravascular coagulation; NTIS, nonthyroidal illness syndrome.

## Correlations Between Thyroid Function Parameters and Coagulation Parameters in Sepsis

The correlation analysis between thyroid function parameters and coagulation parameters in sepsis are shown in [Figure 3](#). The thyroid function parameters of FT3, FT4 and TSH do not have strong correlations with coagulation parameters of platelet count, fibrinogen, FDP, D-dimers, PT, APTT and INR in sepsis. There is only significantly weak correlation

**Table 2** Analysis of Risk Factors for DIC in Sepsis Using Logistic Regression Models

Variables	Univariate Logistic Model		Multivariate Logistic Model	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.996(0.989–1.004)	0.377	0.997(0.987–1.006)	0.518
Sex	0.78(0.61–0.99)	0.046	0.68(0.52–0.90)	0.007*
Hypertension	0.77(0.60–0.98)	0.037	0.66(0.49–0.88)	0.005*
Diabetes	0.97(0.75–1.25)	0.882		
Chronic kidney diseases	1.39(1.04–1.85)	0.025	1.06(0.73–1.53)	0.736
Infection sources				
Respiratory system	0.98(0.76–1.26)	0.901		
Gastrointestinal tract	0.96(0.73–1.26)	0.778		
Urogenital tract	1.02(0.76–1.38)	0.866		
Others	1.60(1.12–2.29)	0.009	1.63(1.08–2.44)	0.017*
White blood cell	1.015(0.998–1.032)	0.071	0.978(0.958–0.999)	0.034*
Alanine aminotransferase	1.001(1.001–1.002)	<0.001	1.001(1.000–1.002)	<0.001*
Total bilirubin	1.003(0.999–1.006)	0.088	0.999(0.995–1.003)	0.682
Creatinine	1.003(1.002–1.004)	<0.001	1.002(1.001–1.003)	<0.001*
Lactate	1.014(0.978–1.052)	0.445		
C-reactive protein	1.004(1.002–1.005)	<0.001	1.001(0.999–1.003)	0.127
Procalcitonin	1.020(1.015–1.025)	<0.001	1.017(1.012–1.023)	<0.001*
APACHEII score	1.053(1.034–1.072)	<0.001	1.020(0.997–1.044)	0.076

(Continued)

**Table 2** (Continued).

Variables	Univariate Logistic Model		Multivariate Logistic Model	
	OR (95% CI)	p value	OR (95% CI)	p value
<b>Thyroidal dysfunctions</b>				
<b>Euthyroid</b>	I (ref.)		I (ref.)	
<b>Hypothyroidism</b>	0.58(0.31–1.08)	0.0865	0.92(0.44–1.80)	0.811
<b>Hyperthyroidism</b>	1.03(0.51–2.07)	0.936	1.59(0.69–3.45)	0.247
<b>NTIS</b>	3.52(2.74–4.53)	<0.001	3.19(2.31–4.46)	<0.001*
<b>Others</b>	0.69(0.48–1.00)	0.055	1.16(0.74–1.82)	0.502

Note: \*p < 0.05.

Abbreviations: OR, odds ratio; DIC, disseminated intravascular coagulation; APACHE II, Acute Physiology and Chronic Health Evaluation II; NTIS, nonthyroidal illness syndrome.

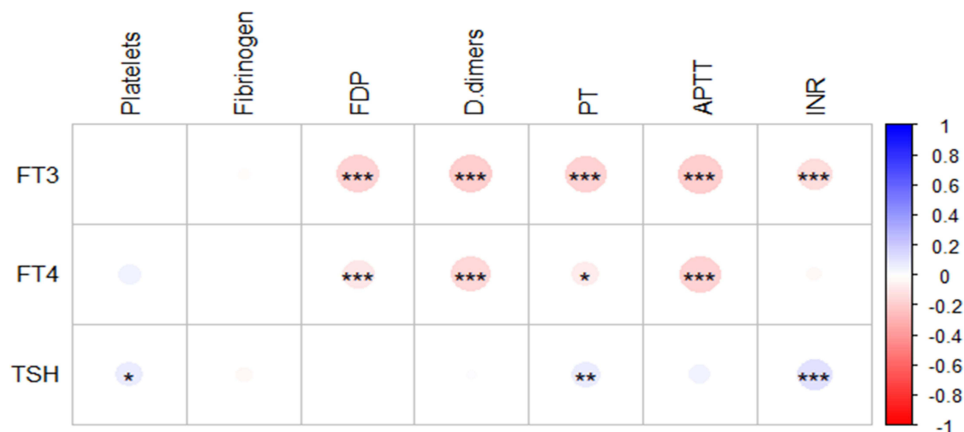
**Table 3** Impact of NTIS on the 28 Days Mortality in Septic Patients with DIC Estimated Using Modified Poisson Regression Models

	RR (CI)	p value
<b>With NTIS vs without NTIS</b>		
<b>Crude</b>	1.45 (1.24–1.70)	<0.001*
<b>Model 1</b>	1.46 (1.25–1.70)	<0.001*
<b>Model 2</b>	1.35 (1.14–1.60)	<0.001*
<b>Model 3</b>	1.18 (1.02–1.37)	0.026*

Notes: Data are presented as relative risk (RR) and 95% confidence intervals. Model 1 adjusted for age, sex, and comorbidities (hypertension, diabetes, and chronic kidney diseases). Model 2 adjusted for model 1, plus total bilirubin, creatinine, lactate, C-reactive protein, and procalcitonin. Model 3 adjusted for model 2, plus APACHE II score. \*p < 0.05.

Abbreviations: DIC, disseminated intravascular coagulation; NTIS, nonthyroidal illness syndrome.

between FT3 and FDP (Pearson coefficient  $-0.17$ ); FT3 and D-dimers (Pearson coefficient  $-0.18$ ); FT3 and PT (Pearson coefficient  $-0.16$ ); FT3 and APTT (Pearson coefficient  $-0.19$ ); and weak correlation between FT4 and D-dimers (Pearson coefficient  $-0.15$ ); FT4 and APTT (Pearson coefficient  $-0.16$ ).



**Figure 3** Correlation matrix between thyroid function parameters and coagulation parameters. The correlations are reported as Pearson correlation coefficients. The negatively relation is represented in red, and positive relation is represented in blue. The darker the colour, the higher the correlation is. \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001. Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; FDP, fibrin/fibrinogen degradation products; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

## Discussion

To our knowledge, this is the first study to investigate the association between NTIS and DIC in sepsis. It is found that, after adjustment for potential confounders, NTIS is an independent risk factor for DIC in sepsis. Moreover, DIC patients with NTIS have higher incidence of death than those without NTIS, which indicates the higher severity and worse prognosis in this subgroup.

NTIS was first described in 1970s and manifested as changes in the level of serum thyroid hormones without concomitant thyroid diseases.<sup>18</sup> In previous reports, it was estimated about 40% critical illnesses in ICU complicated with NTIS.<sup>19</sup> This number is close in our study that, 37.4% of all the enrolled septic patients are diagnosed with NTIS on admission. It was well known that NTIS has a negative impact on the prognosis of the disease with a relevant increased risk of death. However, even though the underlying pathophysiological mechanism has been clarified, the question that whether the NTIS represents a beneficial adaptive response to stress or a maladaptive response to illness that requires treatment remains unanswered.<sup>20</sup> In this study, NTIS is an independent risk factor for DIC after adjustment for confounders. DIC is an acquired thrombohemorrhagic syndrome marked by extensive uncontrolled activation of coagulation with intravascular micro-thrombosis and progressive depletion of coagulation factor. Generally, patients suffer more severe illnesses have higher chance to be complicated with DIC. In previous studies, it was reported that liver function, specific infection site and delayed use of antibiotics are risk factors for DIC in septic patients.<sup>21</sup> The association between DIC and specific hematological cancer or metabolic diseases were also described in some studies but not in septic population.<sup>22,23</sup> In this study, we adjusted factors including demographic characteristics, severity, infection indicators and organ function indicators in the multivariate logistic regression model, and found that NTIS is an independent risk factor for DIC in sepsis. Other risk factors include sex, history of hypertension, specific infection site, white blood cell count, alanine aminotransferase level, creatinine level and procalcitonin level. The influence of thyroid function on the coagulation-fibrinolytic system has been appreciated in previous study. Overt hypothyroidism is reported to have an increased risk of bleeding, and overt hyperthyroidism is reported to have an increased risk of thrombosis.<sup>24</sup> In a prospective cohort study, Sevim et al reported that bleeding time, PT, APTT and clotting time are increased in patients with overt hypothyroidism compared with euthyroid controls. Moreover, the bleeding time, PT, APTT and clotting time are decreased after overt hypothyroidism was treated with levothyroxine.<sup>25</sup> As a contrast, in another retrospective study, patients with overt hyperthyroidism have shortened APTT and higher fibrinogen level.<sup>26</sup> However, in our study, thyroid hormone levels are only weakly associated with coagulation parameters such as PT, APTT, and D-dimers. It seems unlikely that the impact of thyroid hormones in “low T3 syndrome” status has a direct impact on coagulation process in sepsis. Another explanation may be the changed fibrinolytic system in NTIS. The fibrinolytic system could automatically counteract the thrombosis as the clot starts to form. However, the activity of antifibrinolytic factors such as PAI-1, thrombin activatable fibrinolysis inhibitor (TAFI) or other prothrombotic mediators may be impaired in sepsis.<sup>27</sup> Thyroid hormones are reported to be associated with the activity of PAI-1 and TAFI.<sup>28,29</sup> Anti-thrombin III is a potent inhibitor of the coagulation cascade and takes part in the anticoagulatory process in septic patients. Anti-thrombin III level is significantly decreased in the septic animal model, and supplement of T3 could protect septic rats from DIC through increasing level of anti-thrombin III,<sup>30</sup> which may be one explanation for the increased risk of DIC in septic patients with NTIS in this study.

It is well recognized that DIC is associated with worse outcomes in septic patients. In our study, DIC patients have significantly higher 28 days mortality compared with those septic patients without DIC (19.3% vs 10.8%). Given that coagulation processes contribute to the thrombotic events in sepsis, it is logical that drugs that could modulate the coagulation processes might influence outcomes. A series of randomized controlled trials with anticoagulant treatment or coagulation inhibitors treatment solely were conducted but failed to prove benefits in sepsis. Vincent et al reported the results of the SCARLET trial, in which septic patients diagnosed with sepsis-associated coagulopathy were treated with recombinant human soluble thrombomodulin, but the difference of 28 days mortality is not significantly different between groups.<sup>31</sup> In 2009, Jaimes et al reported the trial results of the effect of heparin on the 28 days mortality in sepsis, but there was no difference on the outcome.<sup>10</sup> Meta-analyses and systematic reviews have been published, and interestingly, Wang et al reported that heparin may have therapeutic effects in patients with severe sepsis, but it has no effect on patients with non-severe sepsis.<sup>32</sup> Similarly, in the analysis of a multicenter nationwide retrospective cohort study, anticoagulant treatment could effectively reduce mortality only in subgroups of patients with very severely ill.<sup>11</sup> In our study, DIC patients with NTIS have both higher APACHEII score (median 15 vs 11) and higher



mortality (23.2% vs 14.0%) compared with the other DIC patients. If this specific group of patients could get benefit from anticoagulants or the combination treatment of endocrine and coagulation treatment, it is worth to be considered in future studies.

There are several limitations in this study. First, although the data in this study were prospectively collected, this remains a retrospective study, and missing data is inevitable. Even though we do our best to fill the missing value with multiple imputations, the bias still exists. Second, there are several scoring systems to diagnose DIC, but there is no gold standard so that misdiagnosis of DIC is probably inevitable. We choose ISTH diagnostic criteria for diagnosing DIC in this study, because it provides high specificity in diagnosing DIC comparing with the other scoring systems.<sup>33</sup> Third, there are many drugs that could influence the thyroid function test results in sepsis, such as dopamine and glucocorticoids, which could reduce TSH levels and the peripheral conversion of FT4 to FT3.<sup>34</sup> We did not exclude patients using these drugs when diagnosing NTIS, because these drugs are necessary for patients with severe sepsis. So the patients diagnosed with NTIS in this study may not definitely satisfy the diagnosis of NTIS, but reflect the real situation in real world. Fourth, the long-term survival data is absent in this study.

## Conclusions

In conclusion, this is the first study that reports NTIS as an independent risk factor for DIC in adults with sepsis. DIC patients with NTIS have higher rate of 28 days mortality than those without NTIS. Future study on DIC should pay attention on this subgroup of patients for severity stratification or precise treatment.

## Data Sharing Statement

The data will be shared upon request from the corresponding authors.

## Ethics Approval and Consent to Participate

This study was approved by the institutional ethics board of Ruijin Hospital, Shanghai Jiaotong University School of Medicine and Xinhua Hospital, Shanghai Jiaotong University School of Medicine. As a non-interventional retrospective study, informed consent was waived by the Ethical committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine and Xinhua Hospital, Shanghai Jiaotong University School of Medicine. The study was performed in accordance with the 1964 Helsinki Declaration and its later amendments.

## 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.

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

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