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ORIGINAL RESEARCH **INTENSIVE CARE**

Prognostic significance of non-thyroidal illness syndrome in sepsis and septic shock cases: a systematic review and meta-analysis

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Abstract

Background: This study aimed to assess non-thyroidal illness syndrome (NTIS) as a prognostic determinant in patients with sepsis, severe sepsis, and septic shock by evaluating thyroid hormone (TH) levels.

Methodology: A systematic search was performed through electronic databases including PubMed, Embase, Scopus, and Medline. Following medical subject headings (MeSH) and free-text terms: "euthyroid sick syndrome" or "Euthyroid Sick Syndromes" or "non–thyroidal illness syndrome" or "non–thyroidal illness syndrome" or "sick euthyroid syndrome" or "low T3 syndrome" or "low tri-iodothyronine syndrome" AND "sepsis" or "septic shock" or "systemic inflammatory response syndrome" or "septicemia" or "bacteremia". Boolean operators' combinations were applied to broaden and narrow the search results. Investigators independently reviewed the search results. For the purpose of the meta-analysis each thyroid hormone level was converted into the same unit: nmol/L for T3, T4 and rT3; µIU/mL for TSH; and pmol/L for fT3 and fT4. Statistical analysis was performed using *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

Results: A total of 843 patients from 9 studies were included in this analysis. In septic patients, the lowest effect size of thyroid function parameter was TSH (g = 2.05; 95% CI = 1.56-2.54), while T3, fT3, and fT4 had the lowest effect size in severe septic patients (g [95%CI]: 0.83 [0.22-1.44]; 1.92 [0.57-3.27]; 1.00 [0.87-1.13]). Patients with septic shock had the highest effect size of TSH (g = 2.08; 95% CI = 1.54-2.61) and fT4 (g = 9.26; 95% CI = 0.98-17.53). Meanwhile, the lowest was T4 (g = 65.60; 95% CI = 64.63-66.57) and rT3 (g = 0.29; 95% CI = 0.24-0.34). A lower effect size of T3 (g = 0.83; 95% CI = 0.76-0.91), T4 (g = 59.48; 95% CI = 57.92-61.04), fT3 (g = 2.25; 95% CI = 1.83-2.66), and fT4 (g = 9.19; 95% CI = 1.56-16.81) were found in non-survivor groups.

Conclusion: Thyroid hormone levels differ according to the severity of sepsis in septic patients. Non-thyroidal illness syndrome is a prognostic factor in septic patients and is associated with the risk of the mortality.

Abbreviations: ESS - Euthyroid Sick Syndrome; NTIS - Non-Thyroidal Illness Syndrome; Tg - Thyroglobulin

Key words: Non-thyroidal illness syndrome; Euthyroid sick syndrome; Sepsis; Septic shock; Prognosis

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1. Introduction

During stress the body creates a metabolic response regulated by a complex combination of pathways; neuroendocrine response being one of the main components that is triggered. Within seconds to minutes, the sympathetic nervous system is stimulated, followed by activation of the hypothalamic-pituitary axis. Atypical thyroid hormone findings, as part of the hypothalamic-pituitary-thyroid axis, are frequently detected in hospitalized elderly or critically ill patients.[1, 2] This condition is often recognized as Euthyroid Sick Syndrome (ESS) or Non-Thyroidal Illness Syndrome (NTIS). ESS (or NTIS) is characterized by a decrease in triiodothyronine (T3), and thyroxine (T4) without changes in thyroid-stimulating hormone (TSH), or a history of thyroid disease.[3] This neuroendocrine response to critical illness can be seen in septic patients.[4]

Sepsis is a significant healthcare issue, with up to 300 cases per 100,000 people annually in the USA.[5] Despite many advances in both treatment and prevention, sepsis caused a substantial financial burden and remained one of the significant causes of mortality in critically ill patients.[5] Some studies suggested that thyroid hormone changes can be correlated with poor outcomes in septic patients.[4] However, we found that studies tend not to measure all thyroid functions tests, e.g., T3, T4, TSH, free T3 (fT3), free T4 (fT4), reverse T3 (rT3), and thyroglobulin (Tg); and thus their recommendations for serum tests that can be used as a prognostic factor for sepsis are inconsistent.[6,7] Although a systematic review on low thyroid hormone and sepsis has been done earlier, but that study did not categorize the outcome of sepsis and septic shock.[8]

Considering the difference in prognosis, we attempted to separate the prognostic effect of sepsis and septic shock in this review. We also evaluated the updated quantitative assessment of the clinical significance of NTIS in sepsis, severe sepsis, and septic shock patients.

2. Methodology

This systematic review and meta-analysis has been registered in the PROSPERO public database (CRD42021227931).

Database Search Strategy

We conducted this systematic review according to the Cochrane Handbook for Systematic Review of Interventions and based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements.[9,10] We systematically searched PubMed, Scopus, Embase, and Medline databases using the following medical subject headings (MeSH) and free-text terms: "euthyroid sick syndrome" or "Euthyroid Sick Syndromes" or "non–thyroidal illness syndrome" or "non–thyroidal illness syndrome" or "sick euthyroid syndrome" or "low T3 syndrome" or "low tri-iodothyronine syndrome" AND "sepsis" or "septic shock" or "systemic inflammatory response syndrome" or "septicemia" or "bacteremia". Boolean operators' combinations were applied to broaden and narrow the search results. The search was limited to human subjects and articles written in English.

Eligibility Criteria

We included all cohort (prospective or retrospective) studies, cross-sectional studies, case-control studies, or controlled trial studies. All studies with the following criteria were included in the analysis: 1) adult patients with sepsis, severe sepsis, SIRS, and septic shock, while also diagnosed with ESS or NTIS; 2) Where the primary outcome was mortality rate; 3) The secondary outcomes included the prevalence of ESS and a descriptive result of overall thyroid function. Subsequently, the exclusion criteria were as follows: case reports or case series, editorials, reviews, and animal studies, as well as patients that were given any pharmacologic agents or that had an endocrine abnormality that could have confounded the outcomes.

Data Synthesis and Quality Assessment

Multiple investigators (NY, KL, AP, NA, and DN) independently reviewed the search results. Duplicate records were removed manually by NA. Then, the primary screening was done by assessing each study's title and abstract. Then, the eligibility of each study was decided by multiple investigators. The reason for exclusion was reported. Any disagreements between authors were discussed with final decisions made by investigators who were experts in the area. Furthermore, we extracted the data regarding the author/s and the year of publication, study design and location, total sample size, ages, Thyroid Function Tests (TFT), measurement method, and mortality.

To evaluate the quality of included studies, we performed quality assessments for bias using Newcastle-Ottawa Scale (NOS) by two authors (NA and DN) collaboratively.[11] Any disagreements between investigators were adjudicated by a third investigator (KL).

Statistical Analysis

The studies in this review excluded patients with precursor thyroid diseases, endocrine abnormality, thyroid hormone therapy or replacement, and amiodarone therapy that would affect thyroid levels. All thyroid values that were calculated in the meta-analysis were extracted from the baseline characteristics (during admission or diagnosis of sepsis). Studies that had thyroid evaluation outcomes were divided into each

Table 1: Particulars of the included studies

Authors, Year	Study Design	Country	Population (n)	Age (y); Male %	Type of TFT (timing of measurement)	Study definition for ESS/NTIS/Low T3	Mortality (%)
Cornu et al., 2020 [13]	Prospective Cohort	Argentina	27 [septic shock]	55.9 ± 16; 48.9%	TSH, T3, T4 (on admission/diagnosis, day 7, day 14, day 21)	T3 < 80 ng/dL	36.7% (28-days mortality)
Gore et al., 1998 [14]	Prospective Cohort	USA	6 [severe sepsis]	45.5; N/A	TSH, fT4, fT3, T3 (on admission)	Low plasma concentrations of both total and free T3, while rT3, T4, and TSH levels were normal.	N/A
Hosny et al., 2015 [7]	Prospective Cohort	Egypt	[sepsis (36), severe sepsis (22), septic shock (22)]	55.8 ± 17; 75%	TSH, fT4, fT3 (on admission/day 1, day 5)	N/A	48.75% (ICU mortality)
Meyer et al., 2011 [6]	Prospective Cohort	Switzerland	103 [sepsis (22), SIRS (50), severe sepsis (15), septic shock (16)]	59 (46-68.5); 54.4%	fT4, T3 (on admission/day), follow up day 2)	Low triiodothyronine (below normal range)	23.3% (In hospital mortality)
Monig et al., 1999 [15]	Prospective Cohort	Germany	9 [sepsis]	61; 55.5%	TSH, fT4, T3, T4 (on admission/day 1)	N/A	N/A
Padhi et al., 2018 [16]	Prospective Cohort	India	360 [sepsis, severe sepsis, septic shock]	70 ± 13.4; 58.3%	TSH, fT4, fT3, T3, T4, rT3 (within 24h of ICU admission)	(i) Low T3 and normal or high T4, (ii) combination of low T3 and low T4	36.1% (28-days mortality)
Palazzo et al., 1991 [17]	Prospective Cohort	Switzerland	14 [septic shock]	52.92; N/A	TSH, fT4, fT3, rT3; Each morning	Low T3, normal TSH and rT3.	42.8% (In hospital mortality)
Rodriguez-Perez et al., 2008 [18]	Prospective Cohort	Netherlands	13 [septic shock]	73; 46%	TSH, fT4, fT3, rT3 (5 days after ICU admission)	N/A	N/A
Todd et al., 2012 [12]	Retrospective Cohort	USA	231 [sepsis (39), severe sepsis (131), septic shock (61)]	59 ± 3; 43%	T3, T4, TSH (on admission)	N/A	18% (In hospital mortality)

N/A = not available; SIRS = Systemic inflammatory response syndrome

population (sepsis, severe sepsis, septic shock), were measured in each subgroup in the forest plot as a one arm analysis. Otherwise, they were calculated in the survivor or non-survivor subgroups only. For the purpose of the meta-analysis each thyroid hormone level was converted into the same unit: nmol/L for T3, T4 and rT3; μIU/mL for TSH; and pmol/L for fT3 and fT4.

The estimate analysis was effect size (ES) with its 95% CI for binary and continuous outcomes. If the included studies had no or small heterogeneity ($p > 0.1$, $I^2 < 50\%$), the fixed-effects inverse-variance model was chosen to synthesize data. When the heterogeneity was found to be significant ($p < 0.1$, $I^2 > 50\%$), we chose the DerSimoian-Laird model. Statistical analysis was performed using *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

3. Results

Overview of Literature Search

During the initial search, a total of 286 studies were identified. Two additional studies were included from a previous systematic review. Of these, 138 studies were not duplicative. 110 studies were excluded based on study objectives, leaving 28 studies for eligibility assessment. Finally, nine studies were included for qualitative and quantitative analysis after excluding 19 studies. This process has been summarized in Figure 1.

Table 2: Normal thyroid function test values in different studies

Authors, Year	Measurement device	T3	T4	TSH	fT3	fT4	rT3
Cornu et al., 2020	Electro chemiluminescence	80 - 200 ng/dL (1.2 - 3.0 nmol/L)	5.1 - 14.1 µg/dL (65.6 - 181.5 nmol/L)	0.27 - 4.2 µIU/mL	N/A	0.93 - 1.7 ng/dL (11.9 - 21.8 pmol/L)	N/A
Gore et.al., 1998	Radioimmunoassay	90 - 190 ng/dl (1.3 - 2.9 nmol/L)	4.5 - 12.0 mcg/dl (58 - 154 nmol/L)	0.32 ± 5 µIU/ml	125 - 300 pg/dl (1.9 – 4.6 pmol/L)	N/A	10 - 24 ng/dL (0.15 - 0.37 nmol/L)
Hosny et.al., 2015	ELISA	N/A	N/A	0.3 - 5.50 mIU/L (0.3 - 5.50 µIU/ml)	1.7 – 4.5 pmol/L	0.8 – 2 pmol/L	N/A
Meyer et.al., 2011	Electro chemistry-luminescence immunoassay	0,3 – 10 nmol/L	N/A	N/A	N/A	0.3 – 100 pmol/L	N/A
Monig et.al., 1999	Chemiluminescence immunoassay	N/A (ng/ml)	N/A (ng/ml)	N/A (µIU/mL)	N/A	N/A (ng/dL)	N/A
Padhi et.al., 2018	IMMULITE 2000 (TSH and thyroid hormone), chemiluminescence immunoassay (rT3)	1.1 - 2.6nmol/L	65 – 130nmol/L	0.27 - 4.6µIU/mL	3.7 - 7.3 pmol/L	12-24 pmol/L	0.15 - 0.43nmol /L
Palazzo et.al., 1991	Coated tube RIA (TSH), radioimmunoassay (fT4, fT3), reverse radioimmunoassay (rT3)	N/A	N/A	0.5 - 4 µIU/mL	2.2 - 7.2 pmol/L	10 - 26 pmol/L	103 - 508 pg/ml (0.16 - 0.78 nmol/L)
Rodriguez-Perez et al., 2008	Chemiluminescence	N/A	N/A	0.41 - 4.94 mU/L (0.41 - 4.94 µIU/ml)	3.89 - 6.60 pmol/L	10.94 - 21.75 pmol/L	0.23 - 0.54 nmol/L
Todd et.al., 2012	N/A	60 - 181 ng/dL (0.9 - 2.7 nmol/l)	0.8 - 1.8 ng/dL (64 - 154 nmol/L)	0.55 - 4.78 µIU/mL	N/A	N/A	N/A

N/A = not available

Characteristics and Eligibility of Selected Studies

A total of 843 patients from 9 unique studies were included in this analysis. The detailed characteristics are displayed in Table 1. Most of the studies were prospective cohort studies, except a study by Todd *et al.* (2012).[12] The mean age of participants ranged from 45.5 to 73 y and the gender was predominately male. Thyroid function (TSH, T3, T4, fT3, or fT4) was mostly measured during admission using various methods. The studies' definition of sepsis was assembled in Supplemental Table S1. SIRS (systemic inflammatory response syndrome) was only classified in one study by Meyer et al. (2011); thus, it was not elaborated further in the forest plot subgroup.[6] The crude mortality rate of the population in this review was 23.3 - 48.75%. Measured death was limited from in–ICU death, in–hospital death to 28–day follow-up.

Each study's normal thyroid function values are listed in Table 2. Different laboratory tests for measuring TFTs have different reference ranges. The study by Meyer et al. (2011) had a very high upper range in both T3 and fT4.[6] The normal fT4 and fT3 values for Hosny et al. (2015) were relatively different from the others, as was the fT3 level from Gore et al. (1998).[7, 14] Monig et al.

Table 3: Risk of bias assessment using New-Castle Ottawa Scale (NOS)

Author	Selection			Comparability			Outcome			NOS score	Interpretation of Quality
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of cohorts on the basis of the design or analysis: Age and sex adjustment	Comparability of cohorts on the basis of the design or analysis: Additional factors adjustment	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts		
Cornu, 2020	*		*	*	*	*	*	*	*	8	Good
Gore, 1998	*		*	*			*	*	*	6	Poor
Hosny, 2015	*		*	*	*	*	*	*	*	8	Good
Meyer, 2011	*		*	*	*	*	*	*	*	8	Good
Monig, 1999	*		*	*	*	*	*	*		7	Good
Padhi, 2018	*		*	*	*	*	*	*	*	8	Good
Palazzo, 1991	*	*	*	*	*	*	*	*	*	9	Good
Rodriguez, 2008	*		*	*	*	*	*			6	Poor
Todd, 2012	*		*	*	*	*	*		*	7	Good

(1999) did not include their TFT reference ranges in their study.[15]

Quality Assessment

Based on the NOS criteria, most studies were considered to have good methodological quality as shown in Table 3. The exceptions to this were the studies by Gore *et al.* and Rodriguez *et al.* due to their inadequate quality in comparability and outcome, respectively.[14, 18]

Thyroid Function Parameter Evaluation

This single-arm meta-analysis included different total numbers of patients in each thyroid function parameter: 923 patients in T3 and TSH, 736 patients in T4, 443 patients in fT3, 540 patients in fT4, and 269 patients in rT3 (Table 4). In septic patients, the lowest effect size of thyroid function parameter was only found in TSH ($g = 2.05$; 95% CI = 1.56-2.54), while the highest was

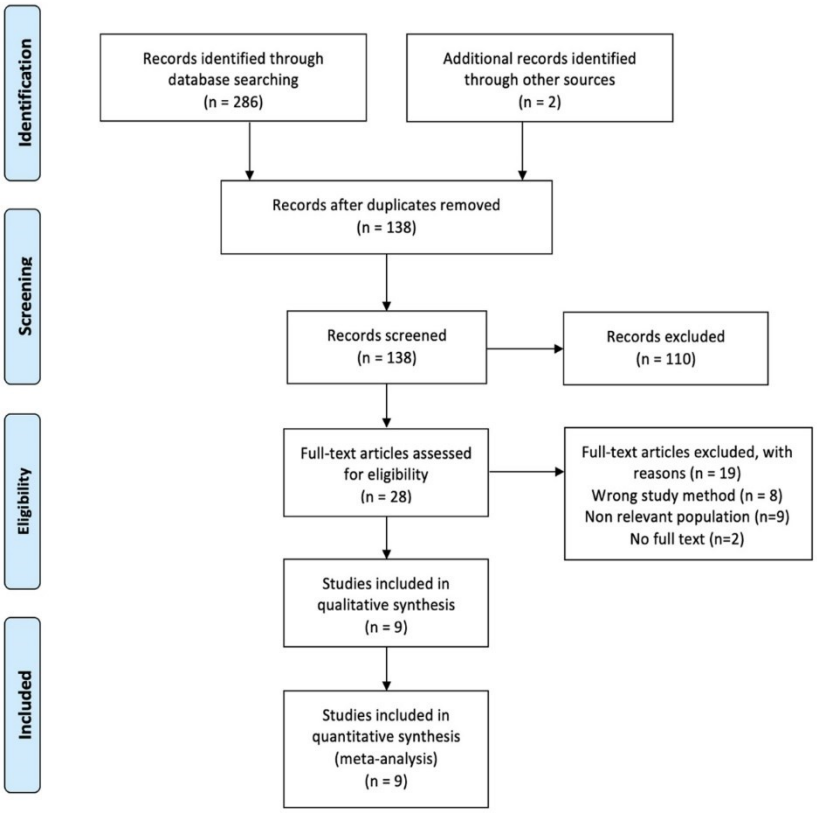

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart

Table 4: Pooled analysis of thyroid function parameters.

Thyroid Function Parameter	Study Population	Sample Size (n)	Effect Size (g)	95% CI	Heterogeneity		
					I^2 (%)	H^2	p-value
T3 (nmol/L)	Sepsis	92	1.09	0.93, 1.25	93.59	15.59	0.00
	Severe Sepsis	152	0.83	0.22, 1.44	99.58	236.31	0.00
	Septic Shock	77	0.86	0.64, 1.09	77.66	4.48	0.03
	Survivor	430	1.12	0.92, 1.32	95.35	21.52	0.00
	Non-Survivor	172	0.83	0.76, 0.91	84.73	6.55	0.00
	Overall	923	0.95	0.88, 1.02	99.38	160.49	0.00
T4 (nmol/L)	Sepsis	39	81.10	79.48, 82.72	N/A	N/A	N/A
	Severe Sepsis	137	72.10	71.66, 72.54	0.00	1.00	0.75
	Septic Shock	61	65.60	64.63, 66.57	N/A	N/A	N/A
	Survivor	351	71.02	66.05, 75.99	88.88	8.99	0.00
	Non-Survivor	148	59.48	57.92, 61.04	0.00	1.00	0.47
	Overall	736	67.88	64.69, 71.06	98.72	78.41	0.00
TSH (mcIU/mL)	Sepsis	75	2.05	1.56, 2.54	97.30	37.03	0.00
	Severe Sepsis	159	2.07	1.08, 3.06	99.00	100.25	0.00
	Septic Shock	110	2.08	1.54, 2.61	98.20	55.60	0.00
	Survivor	392	1.43	0.57, 2.28	98.36	60.93	0.00
	Non-Survivor	187	2.44	0.55, 4.33	98.77	81.45	0.00
	Overall	923	1.95	1.68, 2.22	98.34	60.07	0.00
fT3 (pmol/L)	Sepsis	36	3.68	3.08, 4.28	N/A	N/A	N/A
	Severe Sepsis	28	1.92	0.57, 3.27	99.18	122.46	0.00
	Septic Shock	49	2.78	1.11, 4.45	99.44	178.94	0.00
	Survivor	189	2.82	0.71, 4.93	99.68	311.41	0.00
	Non-Survivor	141	2.25	1.83, 2.66	85.63	6.96	0.00
	Overall	443	2.59	1.96, 3.22	99.42	131.45	0.00
fT4 (pmol/L)	Sepsis	36	1.30	1.04, 1.56	N/A	N/A	N/A
	Severe Sepsis	22	1.00	0.87, 1.13	N/A	N/A	N/A
	Septic Shock	49	9.26	0.98, 17.53	99.75	399.73	0.00
	Survivor	268	10.07	1.17, 18.97	99.89	887.12	0.00
	Non-Survivor	165	9.19	1.56, 16.81	99.45	181.96	0.00
	Overall	540	7.93	6.79, 9.06	99.71	343.51	0.00
rT3 (nmol/L)	Sepsis	N/A	N/A	N/A	N/A	N/A	N/A
	Severe Sepsis	6	0.36	0.32, 0.40	N/A	N/A	N/A
	Septic Shock	13	0.29	0.24, 0.34	N/A	N/A	N/A
	Survivor	148	0.65	0.13, 1.16	89.20	9.26	0.00
	Non-Survivor	102	1.11	-0.16, 2.39	94.00	16.66	0.00
	Overall	269	0.63	0.44, 0.82	95.03	20.10	0.00

N/A = not available

found in T3, T4, and fT3 (*g* [95% CI] = 1.09 [0.93-1.25]; 81.10 [79.48-82.72]; 3.68 [3.08-4.28]), compared to patients with severe sepsis and septic shock. However, in severe septic patients, rT3 had the highest effect size (*g* = 0.36; 95% CI = 0.32-0.40), while T3, fT3, and fT4 (*g* [95% CI] = 0.83 [0.22-1.44]; 1.92 [0.57-3.27]; 1.00 [0.87-1.13], respectively) had the lowest effect size, compared to septic and septic shock patients.

Conversely, in patients with septic shock, the highest effect size was found in TSH (*g* = 2.08; 95% CI = 1.54-2.61) and fT4 (*g* = 9.26; 95% CI = 0.98-17.53). The lowest effect size was in T4 (*g* = 65.60; 95% CI = 64.63-66.57) and rT3 (*g* = 0.29; 95% CI = 0.24-0.34). The

effect size of thyroid function parameters between survivors and non-survivors was also assessed. Survivor groups had a lower effect size in TSH and rT3 (g [95% CI] = 1.43 [0.57-2.28]; 0.65 [0.13-1.16], respectively). While the non-survivor group had a lower effect size for T3 (g = 0.83; 95% CI = 0.76-0.91), T4 (g = 59.48; 95% CI = 57.92-61.04), fT3 (g = 2.25; 95% CI = 1.83-2.66), and fT4 (g = 9.19; 95% CI = 1.56-16.81). Tests of group differences among sepsis, severe sepsis, septic shock, survivors, and non-survivors were statistically significant in T3, T4, fT3, and fT4 (p = 0.00), but not in TSH and rT3 (p = 0.72 and 0.06, respectively). With two exceptions, heterogeneity statistics were significant in all patient groups, as well as in the overall analysis, with $p < 0.05$ and I^2 ranging from 77.66% to 99.89%. These exceptions were T4 of severe septic patients (p = 0.75) and non-survivors (p = 0.47). The thorough pooled analysis is listed in supplementary material as Figure S1 to Figure S7.

4. Discussion

Over the years, the importance of TFT has shifted from identifying thyroid dysfunction to utilizing it to interpret the severity of critical illness.[19] Current pooled results in this study demonstrated a low level of T_3 and a normal level of TSH in septic patients. Both are classic forms of NTIS or low T_3 syndrome (low T_3 with low or normal TSH and high rT_3).[20] The previous systematic review and meta-analysis reported that decreased serum T3 or T4 levels are associated with adult septic patients' mortality.[8] In this meta-analysis, we will further explore NTIS's possibility as a prognostic factor in the various severity stages of sepsis, that is to say sepsis, severe sepsis, and septic shock.

NTIS is theorized as an adaptive and beneficial response in patients under severe acute illness. The syndrome occurs in response to the body's attempts to reduce energy expenditure to limit catabolism by lowering T_3 plasma level and converting it to its inactive form (rT3).[21] On the contrary, evidence has shown T_3 specific receptors tend to be higher in chronic disease patients than ICU patients; hence it seems that an adaptive state is never adequately achieved.[17] Therefore NTIS could be one part of organ-related failure and hypothalamic-pituitary-thyroid axis alteration in sepsis.[13, 22]

In this study, we found that other thyroid hormones were in the normal range and rarely changed. We also discovered that studies discussing thyroid hormones often lack adequate numbers. An important finding in our study was a low-free T_4 (fT_4) in septic patients. fT_4 is known to recuperate along with the process of the patient's recovery.[23] This highlights the importance of fT_4, where if its low persistence could indicate that there were no signs of recovery and sepsis would progress further, taking into account that reduced T_3 or fT_4 is a dynamic process, and the levels may change over time. The prognostic interpretation needs to be carefully considered given the possibility of delay in the ICU admission.[6] Decreased T_3 in the acute critical phase may indicate the severity of illness, whereas a chronic phase may portray the patient's recovery.[24]

With the evidence of thyroid hormones and their clinical correlation, NTIS in septic patients can also be explained by two different time courses. During acute critical illness, there is fewer thyroid binding globulin in the serum.[24, 25] The changes in the peripheral conversion of T_4 to T_3 during acute phase is more noticeable due to a decline in the number of active type-1 deiodinase (D1) and increases type-3 deiodinase (D3) activity.[18] These changes may explain our findings of low T_3 and elevated rT_3 in non-survivor groups. Subsequently, type-2 deiodinases (D2) which are essential for the local conversion of T_4 to T3 are altered during the prolonged phase of illness. The expression of deiodinases (*DIO2* mRNA), which is essential for the local conversion of T_4 to T_3 in human muscles, is also decreased during bacterial sepsis.[26] D2 is also expressed in tanycyte, a unique glial cell that lies in the mediobasal hypothalamus. It is hypothesized that when tanycyte D2 increases in septic patients, conversion from T_3 to T_4 will rise.[1]

Another theory suggested that when the activity of the I 5'-deiodinase enzyme is diminished, possibly due to interleukin (IL-6) and C-reactive protein (CRP) produced in the course of sepsis,[6,7,12] it could decrease the production of T_3.[12] IL-6, together with tumor necrosis factor alpha (TNF-α), interferon (IFN-γ), and other stress factors may also suppress the activity of TSH, impairing its surge.[1] Despite that, TSH levels were normal in this study. This review also discovered that T_3 levels in septic patients were the highest among severe septic and septic shock patients, which can also be observed in a study by Meyer et al.[6] It could be due to sepsis being less profound compared to severe sepsis and septic shock. Both in acute and prolonged phases, the pulsatility of the normal TSH surge pattern is altered, which ultimately results in an overall low-level thyroid hormone.[21]

There are other hypotheses though that state that NTIS in septic shock is caused by deiodinase impairment. A study regarding deiodinase activity in septic shock patients demonstrated a significant increase of skeletal muscle deiodinase-3 activity compared to control ($p < 0.01$).[18] A molecular analysis research in NTIS patients discovered a selective thyroid hormone transporter called Monocarboxylate Transporter 8 (MCT8). MCT8 is found to be significantly under-expressed in the adipose tissue. A study in lipopolysaccharides-infused septic shock pig models also showed increased

deiodinase-3 and decreased MCT8 expression along with increased NF-kB binding activity.[27] Therefore, a low number of thyroid hormone transporters besides thyroid binding protein may also contribute to NTIS development.[24]

After comparison between sepsis with severe sepsis, rT_3 levels seemed to be the lowest. This phenomenon is explained by the low level of T_4, thus reducing the final amount of converted rT_3.[27] In due course, T_4 levels tend to decrease as the critical state progresses. This is presented in our study by the low T4 level in the non-survivor group. Besides, pooled data regarding rT_3 and T_4 is derived from a single limited study, warranting a high chance of bias. This study also found that the incidence of NTIS in septic shock is high. A study of 27 septic shock patients demonstrated 26 patients (96.3%) had NTIS, and 15 were persistent at 28 days.[13] Similarly, another study of 14 septic shock patients showed that nine patients had a classic NTIS form, and three patients had low T_3 levels.[17]

Ultimately, TFT should be interpreted attentively according to each patient's clinical course. The onset, severity, and duration of the critical illness can affect TFT outcomes.[28] In this meta-analysis, we analyzed all thyroid hormones during admission or early critical state. Furthermore, there is a chance of variability in the reference range for fT4 and fT3 estimates, so it is recommended to check the method-specific normal values before interpreting the results thoroughly.

Researchers have tried replacement therapy in a setting of critical care facilities to treat NTIS in hopes of a better recovery.[2, 21] A study by Todd suggested that levothyroxine (T4) administration is fruitless because eventually, it will be converted to rT3.[12] Another study also reported that selenium, as an essential mineral that plays a crucial role in thyroid metabolism, could improve morbidity. Nevertheless, there was no direct effect on free and total thyroid hormones.[29] Hence, this thyroid hormone replacement strategy remains unclear and needs to be further investigated by large-scale randomized clinical trials to understand the benefits for critically ill patients with NTIS.[2]

5. Limitations

There were several limitations in the current meta-analysis that need to be addressed. First, the significant heterogeneity might be attributed to differing definitions of NTIS. There should be a consensus for the definition for NTIS depending on its origin.[30] Second, the included studies in this review had differences in their reference range for thyroid hormones which may affect how well differences can be interpreted across studies. Physicians should remain mindful of their normal values.

6. Conclusion

In summary, we can conclude that thyroid hormone levels differ according to the severity of sepsis. non-thyroidal illness syndrome is a prognostic factor in septic patients, and it is associated with an increased risk of mortality. Based on these findings, the measurement of serum T3 in adult septic patients could be beneficial for predicting the severity of sepsis and can potentially help prognosticate patients.

7. Conflict of interests

None declared by the authors.

8. Author's Contribution

RW/MM/SA: Conceptualization, design, supervision, analysis and/or interpretation, writing, critical review.

NAK/APW/DH/NY/KL/YPK: Materials, data collection and/or processing, analysis and/or interpretation, literature review, writing.

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