RESEARCH

Non-thyroidal illness syndrome predicts outcome in adult critically ill patients: a systematic review and meta-analysis

Josi Vidart[1,2], Paula Jaskulski[3], Ana Laura Kunzler[3], Rafael Aguiar Marschner[1], André Ferreira de Azeredo da Silva[3] and Simone Magagnin Wajner[1,3]

[1]Thyroid Section, Endocrine Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
[2]Intensive Care Unit, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil
[3]Internal Medicine Division, Hospital de Clínicas de Porto Alegre, Internal Medicine Department, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

Correspondence should be addressed to S M Wajner: simone.wajner@ufrgs.br

Abstract

We performed a systematic review and meta-analysis to comprehensively determine the prevalence and the prognostic role of non-thyroidal illness syndrome (NTIS) in critically ill patients. We included studies that assessed thyroid function by measuring the serum thyroid hormone (TH) level and in-hospital mortality in adult septic patients. Reviews, case reports, editorials, letters, animal studies, duplicate studies, and studies with irrelevant populations and inappropriate controls were excluded. A total of 6869 patients from 25 studies were included. The median prevalence rate of NTIS was 58% (IQR 33.2–63.7). In univariate analysis, triiodothyronine (T3) and free T3 (FT3) levels in non-survivors were relatively lower than that of survivors (8 studies for T3; standardized mean difference (SMD) 1.16; 95% CI, 0.41–1.92; $I^2 = 97\%$; $P < 0.01$). Free thyroxine (FT4) levels in non-survivors were also lower than that of survivors (12 studies; SMD 0.54; 95% CI, 0.31–0.78; $I^2 = 83\%$; $P < 0.01$). There were no statistically significant differences in thyrotropin levels between non-survivors and survivors. NTIS was independently associated with increased risk of mortality in critically ill patients (odds ratio (OR) = 2.21, 95% CI, 1.64–2.97, $I^2 = 65\%$ $P < 0.01$). The results favor the concept that decreased thyroid function might be associated with a worse outcome in critically ill patients. Hence, the measurement of TH could provide prognostic information on mortality in adult patients admitted to ICU.

Key Words

- thyroid hormone
- low T3 levels
- critically ill patients

Endocrine Connections (2022) **11**, **e210504**

Introduction

Thyroid hormones (TH) are essential for cellular growth, differentiation, and energetic regulation. Critical illness is frequently associated with alterations in TH metabolism not caused by abnormalities of the hypothalamic–pituitary–thyroid function. These changes, collectively known as 'non-thyroidal illness syndrome' (NTIS) or 'low T3 syndrome' are characterized by low plasma concentrations of the biologic active hormone triiodothyronine (T3), low or normal plasma concentrations of thyroxine (T4), and elevated plasma levels of the inactive hormone reverse T3 (rT3) in the presence of normal thyrotropin (TSH) levels (1). The pathophysiology of NTIS is multifactorial. In the early phase, the peripheral TH metabolism is impaired, with reduced hormonal bioavailability consequent to the consumption of carrier proteins, as acute-phase proteins, and changes in the expression of transmembrane hormone transporters. Additionally, deranged iodothyronine deiodinases function causes a decrease of T4 to T3 conversion with a further raise in the inactivation of T4 to rT3. In the chronic course of the disease, inhibition of the

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

hypothalamic–pituitary feedback loop also seems to occur, reflecting the severity of the disease (2, 3, 4). Although NTIS has been studied for decades, it is still under debate whether these changes represent an adaptive mechanism in response to the demanding circumstances of disease or if it contributes to the persistence of organ dysfunctions and adversely impacts the outcome (5).

Currently, there are some well-established prognostic scores to estimate mortality and disease severity in the intensive care unit (ICU), such as APACHE IV, Simplified Acute Physiology Score (SAPS III), and Sequential Organ Failure Assessment (SOFA) (6, 7, 8). APACHE IV score uses 12 physiological variables presented in the first 24 h of admission, evaluates chronic diseases, and the reason for admission at the ICU. SAPS III uses the worst values measured within the first 24 h of admission and reflects the severity of illness on admission. Alternatively, SOFA is based on simple measurements of organ function and was designed to track the evolution throughout the ICU stay. Although it was not designed for prognosis prediction, higher scores are associated with an increased risk of death (9). The risk-adjusted mortality provided by these prognostic scoring systems is mainly used to compare the quality of care provided by different ICUs, helping to identify institutional deficiencies in clinical outcomes and to emphasize areas for improvement. Prognostic scoring systems perform best at the cohort level due to the uncertainty concerning prediction in individual patients (10). Interestingly, some studies suggest a potential role of TH levels to predict mortality in hospitalized patients since T3 levels are lower in non-survivors than in survivors in different clinical settings (11, 12, 13, 14). Considering that most studies are underpowered and not primarily designed with this objective, whether NTIS may influence the outcome of critically ill patients admitted to ICU is still a matter of debate.

The aim of this study is to systematically review and provide evidence regarding a standardized definition, prevalence, and the association between NTIS and the outcome of critically ill patients admitted to ICU.

Methods

Protocol and registration

This systematic review adheres to the PRISMA (15) guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42020172989).

Study objectives

Our aim was to investigate the prognostic relevance of NTIS in critically ill adult patients. Particularly we focused on the following research questions:

(I) What is the prevalence of NTIS?
(II) Is NTIS associated with adverse clinical outcome?

Eligibility criteria

We included only cohort studies (either prospective or retrospective) and clinical trials which analyzed NTIS as a prognostic factor in adult patients in ICU settings.

The exclusion criteria were age younger than 18 years, animal studies, and articles that were not a cohort study or clinical trial. We considered articles written in English, Portuguese, and Spanish. No restriction to the date of publication was applied.

Search strategy and study selection

We conducted a systematic search on MEDLINE (via PubMed) and Embase databases from inception to March 2020. Comprehensive search queries included text words and descriptors (MeSH and Emtree) based on expressions 'Euthyroid Sick Syndrome', 'Non-thyroidal Illness Syndrome', and 'Low T3 Syndrome'. The complete search strategy for Embase and Pubmed is presented in Supplementary data 1 (see section on supplementary materials given at the end of this article).

Three independent reviewers (PRJ, ALK, and JV) assessed the records for inclusion based on the titles and abstracts. Abstracts that did not meet the inclusion criteria or that met the exclusion criteria were discarded. The remaining records and those abstracts that did not provide sufficient information to decide upon their exclusion were selected for full-text evaluation, which was performed by the same reviewers independently. A fourth reviewer (SW) solved the disagreements.

Data collection and extraction

Independent reviewers extracted the data using a standardized system. The following information was obtained: first author, year of publication, study design, sample size, and age distribution. Baseline values of thyroid function tests and definition of NTIS outcome used measures and main results, correlated to critical illness prognosis scores, conclusions, and limitations.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

During the process of data extraction, the individual risk of bias of each study was assessed using the SIGN checklist (Supplementary data 2) (16). The research team checked and discussed the final extraction results.

Statistical analysis

The main analysis consisted of the investigation into an association between decreased peripheral TH levels and in-hospital mortality in adult patients. To determine the strength of the association between decreased THs and death, the standardized mean differences (SMD) were derived between survivor and non-survivor groups, using a random-effect model. The effect size estimation was performed by determining the SMD with their 95% CI because the TH levels were reported with a wide variety of measurement units. SMD was calculated by the following equation: ((non-survivor group mean level – survivor group mean level)/pooled S.D.). The mean difference ± S.D. was derived from the TH levels across the comparison groups. Since various units of TH were used in our study, we converted all into the recommended standard international units: T4 (nmol/L), T3 (nmol/L), free T4 (pmol/L), fT3 (pmol/L), and TSH (μIU/mL). The odds ratio (OR) with 95% CI for all-cause mortality were pooled using a meta-analysis. For this purpose, only studies that presented results from multiregression analysis were included. In one study (17) that did not present the CI, we used a meta-analysis level imputation, based on methodologic quality and similarity of effect to estimate the missing values. This study used both the I^2 statistic and Cochran's Q statistic to evaluate the heterogeneity. I^2 higher than 40% indicated substantial heterogeneity across the included studies. Because of the difference in those included studies, we used the random-effects model to calculate the pooled prevalence of ORs. Subgroup analysis was performed by the type of admission and by quality assessment. Identification of publication bias was performed by the R packages 'meta' (R version 3.3.2). The assessment of publication bias was by funnel plot and Egger's test. The asymmetry of the funnel plot and *P*-value (<0.05) using Egger's test indicated that bias was present.

Results

Trials identified through the search strategy

Our search identified 3038 titles and abstracts of potentially eligible studies through database searching. After duplicate removal, 2078 records were screened and 38 full texts were assessed for eligibility. Of these, 13 did not provide information about the outcome of interest. Twenty-five studies with 6869 patients in total were included in the analysis (Fig. 1).

Study characteristics and risk of bias

Most of the records were from a small sample size, single-center studies including heterogeneous adult medical or mixed medical/surgical ICUs. Studies were conducted between 2001 and 2020. There was a high risk of bias (Table 1) resulting from the observational (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41) and retrospective study design (17, 18, 22, 30, 31, 37) used in the studies. The absence of statistical control for known confounders (17, 23, 25, 26, 34, 37) and for covariance with severity scores (24, 35) was also identified. Additionally, some trials did not deal with NTIS as the main research aspect and did not exclude patients with previous thyroid disease (18, 30).

Diagnostic criteria and prevalence rates for NTIS

Among the 25 studies, 16 reported the use of strict diagnostic criteria, while other studies used 'decreased

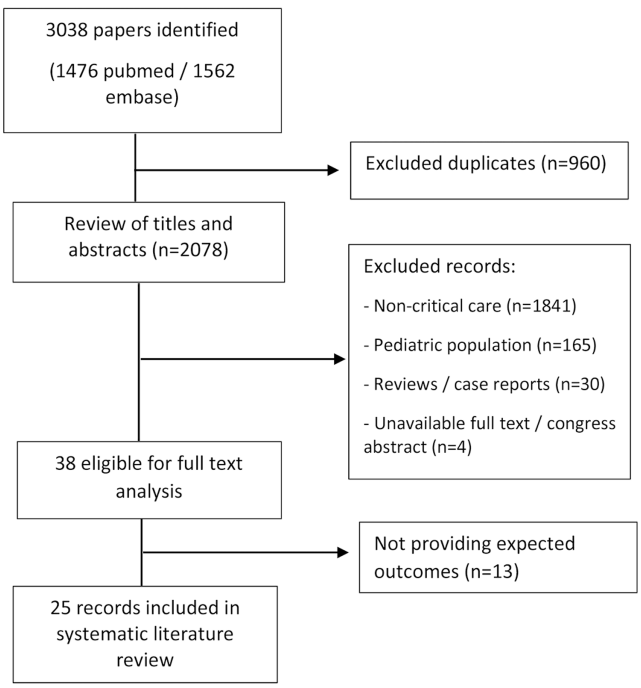

Figure 1
Flowchart of study selection.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Table 1 SIGN quality assessment.

Study	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	1.11	1.12	1.13	1.14	2.1	2.2	2.3	2.4
Bayarri, 2001 (17)	Y	N	N	Y	30%	N	N	N	N	Y	Y	N	N	N	+	N	N	Heterogeneous population, not controled for confounders
Scoscia, 2004 (18)	Y	Y	N	Y	0%	NA	Y	N	N	Y	Y	Y	N	Y	+	NA	Y	Small sample size, single center trial, no covariance analysis
Peeters, 2005 (19)	Y	Y	N	Y	0	NA	Y	N	Y	Y	Y	Y	N	Y	+	NA	Y	Study was not designed for the clinical outcomes, prior thyroid disease not excluded
Plikat, 2006 (20)	Y	Y	Y	Y	0%	NA	Y	NA	N	Y	Y	N	Y	Y	+	Y	Y	Retrospective
Gangemi, 2007 (21)	Y	Y	Y	Y	0%	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	
Sahana, 2008 (22)	Y	N	Y	Y	0%	NA	Y	N	Y	Y	Y	Y	N	Y	+	Y	Y	Not controled for confounders
Bello, 2009 (23)	Y	Y	Y	Y	0%	NA	Y	N	N	Y	Y	Y	Y	Y	+	N	N	Retrospective, thyroid hormones only tested when clinical suspicion for thyroid dysfunction
Meyer, 2011 (24)	Y	N	Y	NA	0%	NA	Y	N	Y	Y	Y	Y	N	Y	+	Y	Y	Not controled for confounders
Tas, 2012 (25)	Y	N	Y	NA	0%	NA	Y	Y	Y	Y	Y	N	Y	Y	+	Y	Y	Significant correlation with APACHE score. No analysis of covariance.
Todd, 2012 (26)	Y	Y	N	Y	0%	NA	Y	N	Y	Y	Y	N	N	Y	+	Y	Y	
Wang, 2012 (27)	Y	Y	N	Y	0%	NA	Y	N	Y	Y	Y	N	Y	N	++	Y	Y	
Nafae, 2013 (28)	Y	Y	N	N	0%	NA	Y	N	N	Y	Y	Y	Y	Y	+	Y	Y	

concentrations of T3 or FT3 or elevated concentrations of rT3' as the diagnostic criteria of NTIS, not considering the changes in TSH. As to the prevalence rate, only three studies did not describe the results of their samples. The median prevalence rate was 58% (IQR 33.2–63.7). Four studies also described the prevalence of the combination of low T3 and T4 levels (median rate 26.1% IRQ 13.6–32.3), pointing to a more severe form of the disease. Most studies (16/25) collected blood samples for TH measurements on the first day of admission, as the timing of sampling may interfere with the results (Table 2).

Prognostic role of NTIS

In Table 3, we present the characteristics of the 25 included studies and the data on the association between serum TH levels and the outcome of critically ill patients. As to types of diseases, 14 studies presented information from patients admitted to ICU with non-specified clinical and surgical critical illness, 4 studies included patients admitted for cardiovascular causes – 2 from patients undergoing CABG (19, 39) and 2 from decompensated heart failure (17, 20), 3 studies included patients with sepsis (24, 29, 37), 1 study was on patients with polytrauma (21) and 1 study was from a burning trauma center (22). Mortality rates varied greatly since they derived from a heterogeneous population with different follow-up periods.

Studies that reported differences between survivors and non-survivors according to four different serum TH levels (FT3, FT4, T3, and TSH) were included in the meta-analysis (Fig. 2). T3 and FT3 levels in non-survivors were lower than that of survivors (eight studies for T3: SMD 1.16; 95% CI, 0.41–1.92; $I^2 = 97\%$; $P < 0.001$; 11 studies for FT3; SMD, 1.03; 95% CI, 0.57–1.5; $I^2 = 95\%$; $P < 0.01$). FT4 levels in non-survivors were also lower than that of survivors (12 studies; SMD 0.54; 95% CI, 0.31–0.78; $I^2 = 83\%$; $P < 0.01$). There were no statistically significant differences in TSH levels between non-survivors and survivors. Substantial heterogeneity was present in the results, so we performed an additional stratified analysis of studies according to methodologic quality assessment, finding that there was no significant decrease in heterogeneity in each subgroup.

Studies that reported OR for adverse outcome were pooled in a meta-analysis (Fig. 3). Data from 12 studies on outcome showed that NTIS was independently associated with increased risk of mortality in critically ill patients (OR = 2.21, 95% CI, 1.64.-2.97, $I^2 = 65\%$ $P < 0.01$). Subgroup analyses of patients admitted for cardiovascular causes or all other causes for admission suggested that NTIS was

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Table 2 Diagnostic criteria and prevalence rate for NTIS.

Reference	Definition of NTIS	Prevalence	Sampling time
Bayarri, 2001 (17)	Type 1: FT3 < 2.3 μg/mL, rT3 > 0.50 ng/mL with normal T4; Type 2: FT3 <2.3 μg/mL, FT4 <0.9 ng/dL, rT3 >0.50 ng/mL, and TSH <0.35 μIU/L; Type 3: FT4 >1.8 ng/dL and rT3 >0,.50 ng/mL, T3 within normal limit	Type 1: 55.4% Type 2: 10.9% Type 3: 1%	3°Day
Scoscia, 2004 (18)	Reduced T3, T4 range from reduced to slightly elevated, with either normal or slightly suppressed TSH levels	53%	Within 24 h of admission
Peeters, 2005 (19)	Low serum T3 and high rT3.	Not described	On day 1, 5, 15, and last day
Plikat, 2006 (20)	Low serum levels of T3, normal or low serum levels of T4, and normal or low serum levels of TSH.	44% low T3 22% low T3 and low T4	Not described
Gangemi, 2007 (21)	Low serum levels of fT3 with increase of rT3 and normal-to-low serum concentrations of fT4 and TSH.	Not described	1–3 days after admission
Sahana, 2008 (22)	Decreased serum T3 and increased TSH, followed by a decrease in T4.	80%	On admission and on day 7
Bello, 2009 (23)	Low serum levels of T3, normal or low serum levels of T4, and normal or low serum levels of TSH.	78% for low FT3 30.3 % for low FT3 and low FT4	In the first 4 days after admission, and consecutively every 8 days after
Meyer, 2011 (24)	Low T3 levels, increased rT3 levels, and/or low T4 levels with normal fT4 levels in the absence of an obvious thyroid disease	65%	During the first 24 h, on day 2, and at discharge from the ICU or death
Tas, 2012 (25)	Low fT3 levels, although decreases in fT3, fT4, and TSH may occur in varying combinations	77.2%	Blood samples were obtained 24 h after admission
Todd, 2012 (26)	Low T3	Not described	Blood samples colected when sepsis were dianosed
Nafae, 2013 (27)	Low serum levels of T3 and high levels of rT3, with normal or low levels of T4 and normal or low levels of TSH.	31% at the firsst day 79.6% at the thirrd day 43.7% at the tenth day	On day 1, 3, and 10
Cerillo, 2014 (28)	Low circulating T3 levels in the absence of an intrinsic thyroid disease	9.8%	On admission
Chuang, 2014 (29)	Total T3 cutoff of 52.3 ng/dL (reference range 84 to 172 ng/dL)	42%	Within 48 h of admission
Naby, 2014 (30)	Low serum levels of free and total T3 and high levels of rT3 accompanied by normal or low levels of T4 and TSH	40%	On admission and discharge
Galusova, 2015 (31)	Low T3 levels, increased reverse T3 levels, and/or low total T4 levels with normal fT4 levels in the absence of an obvious thyroid disease	T3 levels were lower in 20%, and fT3 levels were lower in 33% patients	First, second, third, and seventh day after admission
Quari, 2015 (32)	Low FT4, FT3, and TSH levels.	16% of medical ICU patients and 19.3% of surgical ICU cases	On the first to third days after ICU admission.
Yasar, 2015 (33)	FT3 levels below the lower limit, and/or fT4 within the normal or low limits and TSH levels within the normal or low limits	51.2%	In the first 24 h
Hosny, 2015 (34)	Low serum levels of T3 and high levels of rT3 accompanied by normal or low levels of T4 and TSH	48.8 on admission and 61.3% on the fifth day	On the day of admission (D1) and fifth day after admission (D5)
Gutch, 2018 (35)	Low levels T3 and high levels of rT3 with variable values of T4 and TSH in the low to normal range.	Not described	On admission
Padhi, 2018 (36)	Group A: low T3 and normal or high T4. Group B: low T3 and low T4.	67%	On admission
Wang, 2019 (37)	High rT3 levels	Decreased fT3 or fT4 group: 33% Decreased TSH group: 41%	On the second day.
Rothberger, 2019 (38)	FT3 <2.3 pg/mL	60%	On the day of initiation of MV
Wang, 2019 (39)	Decrease in levels of T3 and increase in levels of rT3	58.7%	1–3 days after CABG
Asai, 2020 (40)	Low FT3 (<1.88 μL/mL)	53%	Most underwent measurements at days 1 (77.8%) and 2 (13.4%)

CABG, coronary artery bypass grafting; fT3, free triiodothyronine; fT4, free thyroxine; ICU, intensive care unit; MV, mechanical ventilation; rT3, reverse triiodothyronine; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Table 3 Characteristics of the studies and data on the association between serum TH levels and outcome. Thyroid hormone levels are presented as median (IQI) or mean ± s.d.

Reference	Study design	Population	Age in years mean (range)	Sex (male/ total)	TFT reference values	Mortality (%)	Comparison between favorable and unfavorable groups, n	Univariate analysis			Other analysis	Conclusions
								Main results favorable	Main results unfavorable	*P*		
Bayarri, 2001 (17)	PCS	Ninety-one patients admitted to ICU	58.3 ± 14.2	56/91		Type 1: 38.5% Tipe 2: 87.9%	NTIS type I (56) × NTIS type II (11)	Mortality: 38.5%	87.9%	0.004	NA	Thyroid hormone disfunction associated with mortality
Scoscia, 2004 (18)	PCS	Thirty-two patients with acute or acute on-chronic respiratory failure requiring MV	75.5 (43–90)	18/32	FT3: 3.5–6.45 pmol/L	12.5%	Survivors (*n* = 28) × non-survivors (*n* = 4)	FT3 3.68 (2.01–5.37)	FT3 2.15 (1.53–2.78)	0.002	Correlation between plasma T3 and PO2/FiO2 ρ 0.64 *P* < 0.001 Univariate analysis OR = 64.23 (1.78–2316.1 *P* = 0.023)	FT3 as a marker of disease severity and prognostic marker
Peeters, 2005 (19)	RCS	451 critically ill patients who received intensive care for more than 5 days	61.3 ± 15.7	308/451	TSH 0.4– 4.3 mU/mL T4 4.51–9.95 mg/dL T3: 1,42–2.5 nmol/L rT3 9.1–2.1 ng/dL	15.7%	Survivors (380) × non survivors (71)	TSH D1: 0.5 (0.16–1.17) TSH D5: 1.22 (0.49–2.27) T4 D1: 4.62 (3.65–5.87) T4 D5: 5.66 (4.09–7.2) T3 D1: 0.96 (0.74–1.21) T3 D5: 1.13 (0.9–1.41) rT3 D1: 38.3 (26.–57.1 rT3 D5: 40.9 (27.9–65.6)	TSH D1: 0.39 (0.13–1.28) TSH D5: 0.42 (0.12–1.32) T4 D1: 4.37 (3.43–5.74) T4 D5: 3.35 (2.46–5.29) T3 D1: 0.88 (0.72–1.16) T3 D5: 0.82 (0.64– 1.08) rT3 D1: 55.2 (31.2–91.5) rT3 D5: 59.1 (35.0 –97.4)	0.46 <0.001 0.19 <0.001 0.32 <0.001 <0.001 <0.001	OR for survival of the highest vs the lowest quartile was 0.3 for rT3 and 2.9 for T3/rT3	rT3 and T3/rT3 were already prognostic for survival on D1. On D5, T4, T3, but also TSH levels are higher in patients who will survive.
Plikat, 2006 (20)	RCS	220 patients admitted to ICU	57.8 ± 18.5	49.4%		Euthyroid 12.7% Low fT3 17.6% Low fT3 and low FT4 45.8%	Euthyroid (*n* = 79) Low T3 (*n* = 73) Low FT3 and low FT4 (*n* = 24)				NTIS with reduced FT4 was significantly associated with reduced survival in a MRA (OR = 2.57; 95% CI 1.19–5.52; *P* = .016)	Reduction of FT4 together with FT3 is associated with an increase in mortality
Gangemi, 2007 (21)	RCS	295 patients admitted to a Burn Center	55 (38–74)	202/295	FT3: 3.1–7.5 pmol/L; FT4: 10.6–21.0 pmol/L TSH, 0.41–4.01 mIU/L.	19.3%	survivors (*n* = 238) x Non-survivors (*n* = 57)	FT3 3.3 (2.72–3.8) FT4 13.5 (11.41–15.63) TSH 1.33 (0.63–2.22)	FT3 2.71 (2.02–3.28) FT4 13.02 (10.59–16.08) TSH 0.61 (0.29–1.31)	0.001 0.396 <0.001	MRA adjusted for total burn surface area burnt OR = 1.1 (0.63–1.93) *P* > 0.05	Low FT3 correlated with worse clinical presentation

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Sahana, 2008 (22)	PCS	80 Patients admitted to ICU with APACHE II score >10	Men: 48.6 ± 16 and women 42.6 ± 17.5	50/80	T3 inferior range :0.92 nmol/L FT4 inferior range:11.45 pmol/L T4 inferior range: 4 μg/dL)	32.5% at day 7 and 47.5% at 6 weeks	Survivors (42) × non-survivors (38)	T3 1.05 ± 0.52 T4 8.62 ± 4.57 FT4 14.28 = 3.6 TSH 10.47 ± 16.10	T3 0.73 ± 0.46 T4 6.9 ± 4.03 FT4 11.06=3.8 TSH 5.45 ± 6.20	<0.005 <0.05 <0.001 <0.05	Serum T4, FT4, and T3 concentrations were significantly lower with more severe illness (comparison between APACHE score <15 and >20) $P < 0.05$	Low T3, low T4, and low FT4 are associated with increased mortality.
Bello, 2009 (23)	RSC	264 Patients admitted to a general ICU who had undergone MV	71 (60–77)	135/264	FT3: 3.6–6.45 pmol/L FT4: 10.94–19.95 TSH, 0.35–2.8 mIU/mL	30%	Euthyroid (n = 56) x low FT3 (n = 208)	FT3 3.07 (2.6–3.68) FT4 14.28 (12.09–16.73 TSH 1.20 (0.78–1.89)	FT3 1.84 (1.38–2.45) FT4 12.09 (9.26–14.54 TSH 1.1 (0.63–1.71)	<0.001 <0.001 0.264	MRA for prolonged MV – OR = 2.25 IC 1.18–4.29 $P <$ 0.001	NTIS represents a risk factor for prolonged MV in critically ill patients admitted to the ICU.
Meyer, 2011 (24)	PCS	103 critically ill patients in the medical ICU	59 (46–68)	56/103	T3: lower reference range 1.2 nmol/L FT4: 11.6–22.0 pmol/L	23.3	Survivors (79) × non-survivors (24)	T3 D1 1.0 (0.7–1.3) fT4 D1 14.6 (11.7–16.5) T3 D2 1.1 (0.8–1.3) fT4 on day two 14.7 (11.6–17.1) T3 death/ discharge 1.0 (0.7–1.3) FT4 death or discharge 15.3 (12.3–18.3)	T3 D1 0.9 (0.7–1.1) FT4 D1 13.6 (11–17.3) T3 D2 0.9 (0.8–1.1) FT4 D2 11.8 (9.8–17) T3 death/ discharge 0.8 (0.7–0.9) FT4 death or discharge 11.9 (6.9–15.8)	0.3 0.66 0.08 0.2 0.004 0.02	na	T3 and fT4 levels on admission were not prognostic in septic and non-septic critically ill patients
Tas, 2012 (25)	PCS	417 ICU patients	58.92 ± 11.20 for survivors and 60.28 ± 11.52 for non-survivors	235/417	fT3: 3.5–6.45 pmol/L fT4: 11.45–23.17 pmol/L TSH :0.35–5.5 mIU/L	40%	Survivors (250) × non-survivors (167)	FT3 3.22 ±1.05 FT4 15.57± 4.37 TSH 1.50 ± 1.36	fT3 2.71 ± 1.01 fT4 13.51± 5.4 TSH 1.06 ± 1.26	<0.001 <0.001 0.001	Correlation between APACHE II and fT3 (r = 0.364, $P < 0.001$)	Suppression of either of the three hormones, fT3, fT4, or TSH, was associated with an increased likelihood of mortality when compared to patients with normal thyroid function tests
Todd, 2012 (26)	RCS	231 Patients admited to a surgical ICU who developed sepsis	59 ±3	43%	T3: 0.92–2.78 nmol/L TSH: 0.55–4.78 mIU/L	21.5%	Survivors (190) × non-survivors (41)	T4 58 ± 0.2 T3 1.1 ± 0.03 TSH 2.4 ± 0.6	T4 46 ± 0.6 T3 0.88 ± 0.07 TSH 5.1 ± 1.6	0.01 0.01 0.06		Decreased T3 levels at baseline are associated with mortality
Wang, 2012 (27)	PCS	480 Patients admitted to ICU	71.71 ± 15.52	59.7%	FT3, 3.5–6.5 pmol/L; TT3, 0.92–2.78 nmol/L; FT4, 11.5–22.7 pmol/L; TT4, 57.9–140.3 nmol/L; TSH, 0.35–5.50 mIU/L; rT3, 0.16–0.95 ng/mL	23.7%	Survivors (388) × non-survivors (92)	TT3 1.16 ± 0.32 TT4 73.92 ± 20.88 FT3 3.53 ± 0.60 FT4 15.80 ± 3.29 TSH 0.87 (0.04–23.87)	TT3 0.89 ± 0.30 TT4 59.52 ± 21.92 FT3 2.95 ± 0.57 FT4 14.48 ± 3.66 TSH 0.60 (0.05–12.73)	<0.001 <0.001 <0.001 0.0008 0.0022	FT3 AUC of 0.762 ± 0.028 for mortality	FT3 was the only independente predictor of ICU mortality among the complete thyroid hormone indicators

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Table 3 Continued.

Reference	Study design	Population	Age in years mean (range)	Sex (male/ total)	TFT reference values	Mortality (%)	Comparison between favorable and unfavorable groups, n	Univariate analysis			Other analysis	Conclusions
								Main results favorable	Main results unfavorable	*P*		
Cerillo, 2014 (29)	PCS	806 consecutive patients undergoing CABG	67.5 ± 9.6	76.9 %		2.3%	Low T3 vs normal T3				OR 6.093 IC 2.862–12.971 $P < 0.0001$ for low CO OR = 12.539; 95% CI, 4.656–32.373; $P < 0.0001$ for death	Low T3 syndrome at admission is associated with an increased risk of postoperative myocardial dysfunction and death in patients undergoing CABG.
Chuang, 2014 (30)	PCS	106 Acute decompensated or severe heart failure in ICU	71 ± 13	54/106	FT3: 2.41 – 7.23 pmol/L FT4: 11.45–22.65 pmol/L T3: 1.29–2.64 nmol/L TSH: 0.4 to 4.0 mIU/L	50.9%	Survivors (52) × non-survivors (54)	FT3 2.59 = 0.95 FT4 16.6 = 4.63 T3 0.96 ± 0.35 TSH 0.93 ± 0.89	FT3 2.48=0.92 FT4 15.44 = 5.14 T3 0.81 ± 0.26 TSH 1.10 ± 1.36	0.56 0.22 0.01 0.44	HR for death in the low T3 group 2.97, 95% CI 1.67 to 5.26 $P = 0.0003$	T3 levels provided adicional prognostic information to classical heart failure biomarkers
Naby, 2014 (31)	PCS	40 mechanically ventilated patients with acute respiratory failure secondary to pulmonary disease	64.33 ± 5.96	24/40	FT3: 2.15–6.45 pmol/L FT4: 8.36–25.35 TSH 0.4–7.0 mIU/L	14.2%	Survivors (35) × non-survivors (5)	FT3 3.84 ± 2.25 FT4 12.09 ± 6.43 TSH 0.560 ± 0.88	FT3 3.02 ± 1.67 FT4 9.12 ± 4.37 TSH 0.794 ± 0.84	0.346 0.304 0.294		TH levels were not significantly correlated to the type of MV, its duration, and the length of ICU stay and survival
Galusova, 2015 (32)	PCS	24 critically ill patients with polytrauma	38.9 ± 13.8	20/24		12%					PTS was positively associated with fT3 (r = 0.582, $P = 0.004$)	Alterations of TH are dependent of trauma severity
Quari, 2015 (33)	PCS	340 medical ICU 162 surgical patients admited to ICU	56.2 (19.9)	47%		36.4	Euthyroid (303) × NTIS (86)				Mortality: OR = 1.32 (0.73, 2.40) $P = 0.72$ in clinical patients and OR = 2.7 (1.2, 6.2) $P = 0.085$ for surgical patients	Throid function has no association with mortality
Yasar, 2015 (34)	PCS	125 patients with COPD admitted to ICU who had undergone MV	65 ± 11	101/125	Not described	Not described	Prolonged weaning vs regular weaning	FT3 (pmol/L) 3.36 (2.45–3.9) FT4 (pmol/L) 15 (12.7–19.9) TSH (mIU/mL) 0.51 (0.29–1.70)	FT3 (pmol/L) 2.61 (1.55–3.17) FT4 (pmol/L) 13 (9.01–16.9) TSH (mIU/mL) 0.68 (0.24–1.62)	$P < 0.001$ $P = 0.06$ $P = 0.94$	OR = 3.21 IC = 1.31–7.83 $P = 0.01$ for prolonged weaning	NTIS may be an Independent predictor for prolonged weaning in intubated COPD patients

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Hosny, 2015 (35)	PCS	80 patients admitted to ICU with sepsis	55.8 ± 17.0	60/80	FT3 = 1.7–4.5 pmol/L, FT4 = 0.8–2 pmol/L, TSH = 0.3–5.50 mIU/L.	48.7%	Survivors (41) × non-survivors (39)	FT3 D1 2.00 ± 0.87 FT3 D5 2.9 ± 1.03 FT4 D1 1.15 ± 0.39 FT4 D5 1.12 ± 0.41 TSH D1 0.92 ± 0.90 TSH D5 1.01 ± 0.96	FT3 D1 1.9 ± 0.98 FT3 D5 1.0 ± 0.65 FT4 D1 1.13 ± 0.42 FT4 D5 1.13 ± 0.42 TSH D1 0.91 ± 1.08 TSH D5 0.91 ± 0.96	0.7 <0.001 0.2 1 1 0.7	FT3 D5 correlates with APACHE r = −0.359 P = 0.025 and SOFA r = −0.427 P = 0.007	TH levels on admission failed to provide prognostic information
Gutch, 2018 (36)	PCS	270 ICU-admitted patients	38.99 ± 18.3	138/270	T3 (1.2–2 nmol/L) T4 (70–150 nmol/L) TSH (0.3–4.5 µIU/L), FT3 (3.5–6.5 pmol/L) FT4 (11.5–23 pmol/L	30%	Survivors (63) × non-survivors (27)	T3 0.95 ± 0.38 T4 72.89 ± 34.1 TSH 3.69 ± 13.99 FT3 3.57 ± 0.19 FT4 15.6 ± 0.42	T3 1.23 ± 0.56 T4 75.54 ± 36.2 TSH 2.41 ± 3.58 FT3 2.94 ± 0.15 FT4 13.44 ± 1.4	0.007 0.742 0.64 <0.001 <0.001	AUC (0.990 ± 0.007 for mortality with fT3 cut-off value of 3.19	FT3 was the strongest predictor of ICU mortality
Padhi, 2018 (37)	PCS	360 patients with sepsis in ICU	70.0 ± 13.4 years,	58.3%	T3 1.1–2.6 nmol/L FT3 3.70–7.30 pmol/L T4 65–130 nmol/L FT4 12–24 pmol/L rT3 0.15–0.43 nmol/L	36.1	Survivors (144) vs non-survivors (97)	T3 1.58 (0.91–2.13) FT3 4.15 (3.98–5.17); T4 69.35 (53.7–75.5) FT4 14.73 (11.60–17.11) rT3 0.37 (0.05–2.45)	T3 0.74 (0.56–1.17) FT3 2.08 (1.74–2.98); T4 59.95 (51.78–65.98) FT4 11.8,4 (9.80–171) rT3 0.39 (0.45–3.76)	<0.001 <0.001 0.088 0.073 0.147	HR for 28 day mortality 1.66 (1.00–2.76) P = 0.49	Non-survivors had lower FT3 and T3 compared to survivors. Among patients with NTIS, groups with a combination of low T3 and T4 had worse prognosis compared to those with isolated low T3 levels
Wang, 2019 (38)	PCS	51 patients admitted to ICU	60.39 ± 19.32	38/51		Not described	Euthyroid × low T3 and low T4 × low TSH				mean (±S.D.) APACHE II score for the euthyroid, decreased FT3 or FT4, and decreased TSH groups were 13.23 (±3.56), 14.12 (±7.42), and 16.19 (±5.15), respectively (P > 0.05)	Correlation between rT3 and severity scores
Rothberger, 2019 (39)	PCS	162 patients who underwent MV	66.9 + 16.8	105/162		39%	Low × normal FT3				Patients with low FT3 had a significantly higher mortality rate (52% vs 19%, P < 0.001) Adjusted OR = 3.68 (1.43–9.45)	NTIS predicted higher mortality and less ventilation free days at day 28 in critically ill patients and can be used for risk stratification

(Continued)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

Table 3 Continued.

Reference	Study design	Population	Age in years mean (range)	Sex (male/total)	TFT reference values	Mortality (%)	Comparison between favorable and unfavorable groups, n	Univariate analysis			Other analysis	Conclusions
								Main results favorable	Main results unfavorable	*P*		
Asai, 2020 (41)	RCS	956 Acute heart failure in ICU	74 (65–81)	627/956		6.3%	Normal tyroid function (n = 445) × Low FT3 (n = 511)				HR for 365-day mortality 1.429, 95% CI 1.013–2.015 P = 0.042	Adverse outcome associated with low T3 syndrome only in patients with old age or maltrution

Thyroid hormone levels are presented as median (IQI) or mean ± s.d.
APACHE, acute physiology and chronic health evaluation; CABG, coronary artery bypass grafting; CI, CI; CO, cardiac output; D, day; FT3, free triiodothyronine; FT4, free thyroxine; HR, hazard ratio; ICU, intensive care unit; MACCE, major adverse cardiovascular and cerebral events; MRA, multivariate regression analysis; MV, mechanical ventilation; NTIS, non-thyroidal illness syndrome; OR, odds ratio; PCS, prospective cohort study; PTS, polytrauma score; RCS, retrospective cohort study; rT3, reverse triiodothyronine; TFT, thyroid function tests; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin.

associated with increased mortality risk in both groups, with reduced heterogeneity in patients admitted for non-cardiovascular causes (Fig. 4).

Publication bias

Funnel plot suggested a tendency of publication bias on the metanalysis on mortality risk (P Egger's test = 0.05, Fig. 5). To adjust for funnel plot asymmetry, we used the trim and fill method for sensitivity analysis, finding increased mortality risk associated with NTIS (random-effects model: OR 1.6049; 95% CI, 1.16–2.21; P = 0.004).

Discussion

This study is the first systematic review and meta-analysis to evaluate the prevalence and prognostic relevance of NTIS in critically ill patients. According to our results, decreased TH levels, either T3 or T4, are highly prevalent and are associated with an unfavorable outcome in adult patients admitted to ICU. Additionally, the independent mortality risk associated with NTIS suggests the possibility of using TH measurements as a prognostic factor in this setting.

For decades, NTIS was regarded as an adaptive mechanism to prevent catabolic changes during critical illness (42). Our findings are in accordance with other studies (13, 14, 43, 44, 45, 46) that consistently suggest no survival advantage and question the generally accepted idea of preservation associated with decreased TH metabolism. Systematic reviews evaluating patients with acute neurologic events (43, 44), cardiovascular disease (14), sepsis (13), and chronic renal failure (45, 46) point to an incremental risk of unfavorable outcomes in patients with NTIS. Experimental and clinical studies support the hypothesis that reduced serum and tissue concentrations of T3 may be implicated in organic dysfunction commonly related to the critically ill as diminished cognitive status with lethargy (47), altered cardiac inotropism and chronotropism, altered vasoactive properties (48, 49), inability to control bacterial infections due to reduced response of the innate immune system (50), respiratory muscle weakness (51), reduced synthesis of pulmonary surfactant, and decrease of lung compliance resulting in the impairment of lung function (52). The significant correlation between decreased TH and organic dysfunctions indicates the possibility of the use of TH as a prognostic factor for the critically ill, as multiple organ

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

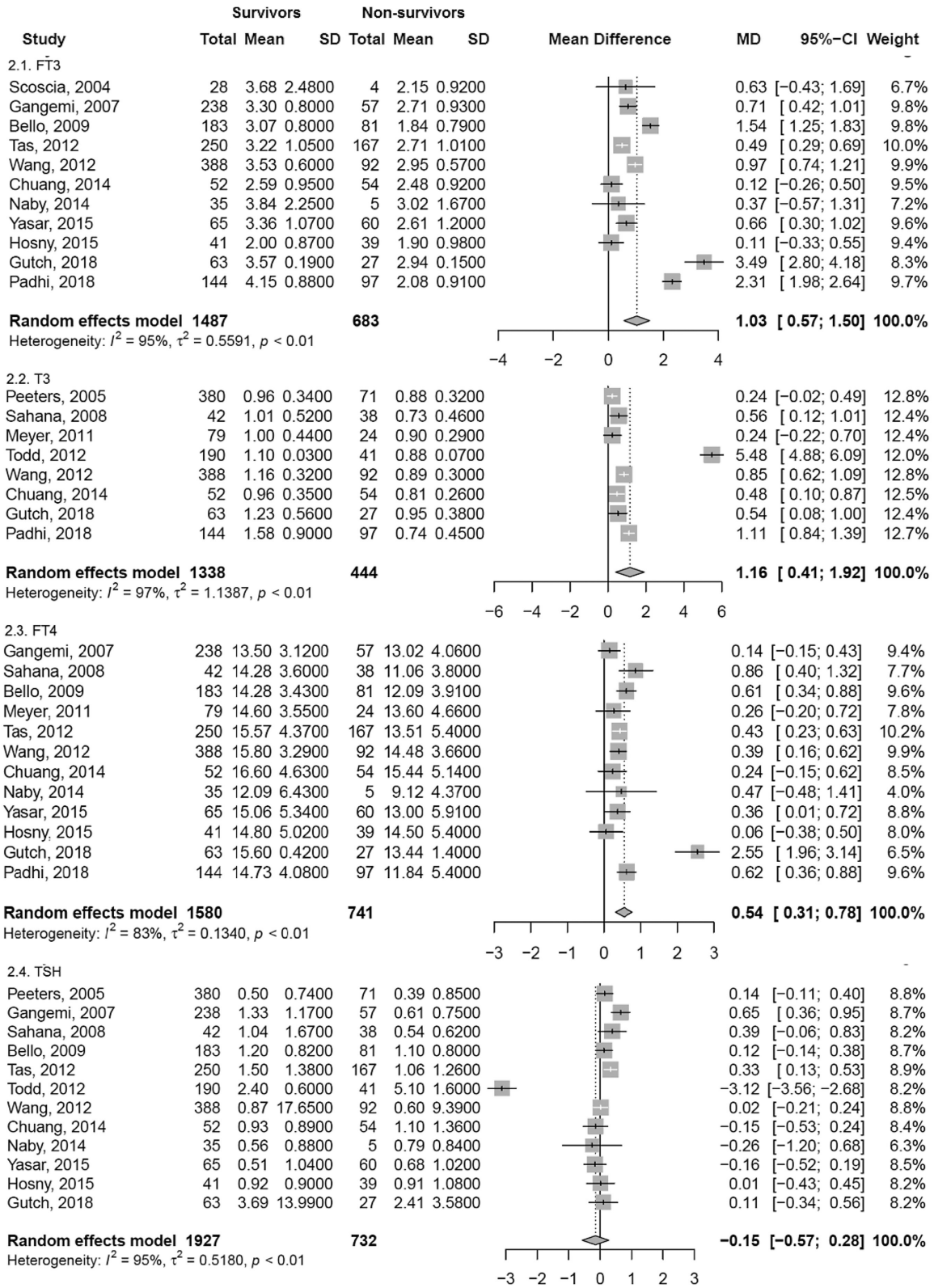

Figure 2
Forest plot of the effect of low thyroid hormone level and mortality.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

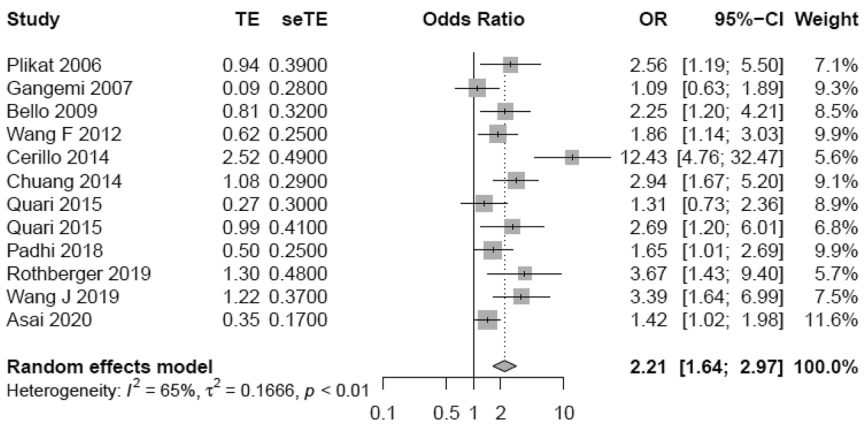

Figure 3
Forest plot of the OR for mortality associated with NTIS.

dysfunction syndrome is the most frequent cause of death in the ICU (53).

Whether replacing TH can help to improve the outcomes of NITS patients is still unknown. While some studies are inconclusive regarding the effectiveness of TH therapy in the outcome of patients with NTIS (54, 55) with risks associated with overdosage and delayed recovery of the neuroendocrine feedback axis (56), others have shown benefit on secondary endpoints, as reduced protein degradation associated with restoration of plasma TH levels (57) and increment of cardiac stroke volume (58). Importantly, no of manuscripts here had patients receiving any kind of treatment to NTIS. Nevertheless, it is important to remember that normalization of deranged physiologic parameters in ICU patients has repeatedly proved to be ineffective in improving outcomes when the causal stimulus is not addressed (59).

There were some limitations in this meta-analysis. Firstly, we found high heterogeneities in the statistical results. To address this issue, we performed a pre-specified stratified analysis for confounding factors, such as main diagnosis and methodological quality, which reduced the heterogeneity (I^2 from 65 to 21%), showing more reliable results in the risk assessment for mortality in the general admission of ICU patients. Still, we were unable to control for other causes of heterogeneities, like the severity of disease and inconsistence of TH ample sizes, because of insufficient data. Also, data were primarily derived from single-center studies. Although from a geographically diverse population, they might lack the necessary external validity support. Finally, it is unclear if the presence of patients with protracted disease prior to acute illness may influence the results and for this matter we need more studies in the future.

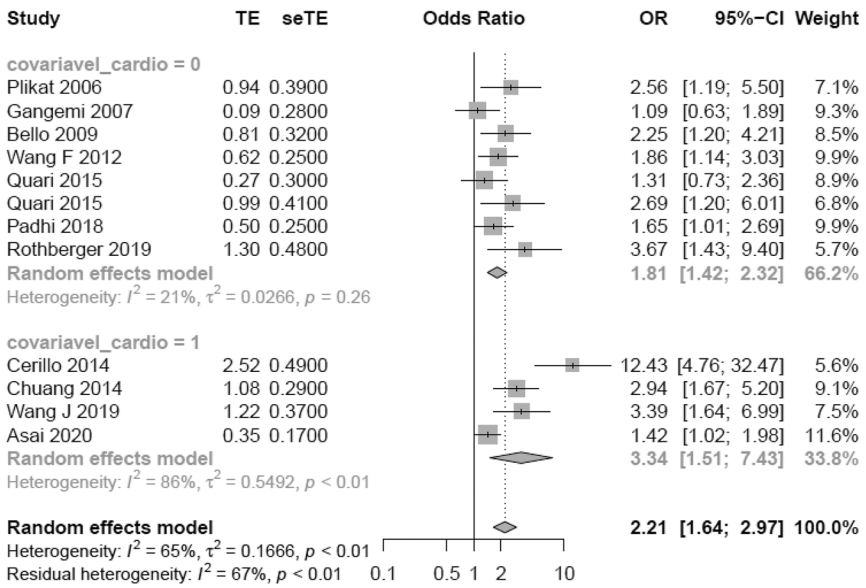

Figure 4
Forest plot of the OR for mortality in a stratified analysis for cause of admission.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-21-0504

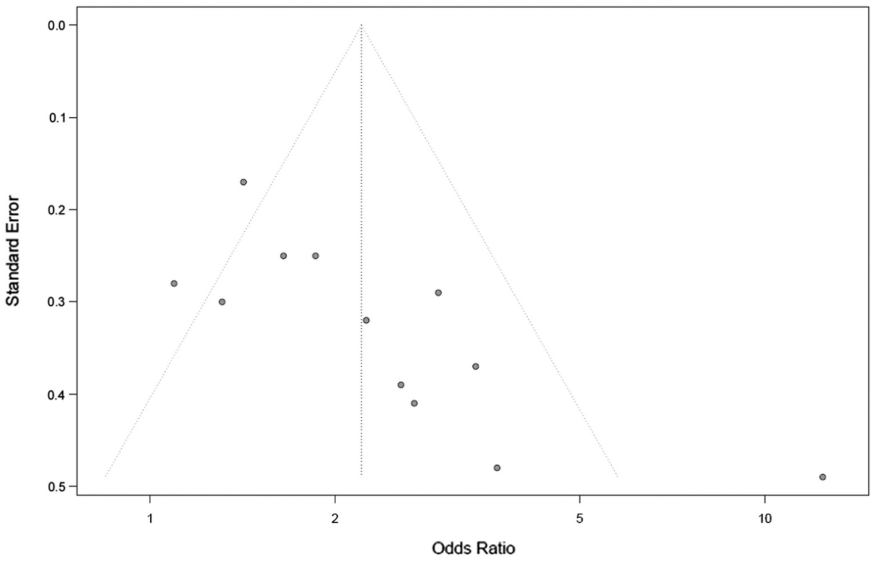

Figure 5
Funnel plot of publication bias.

Conclusion

The findings of this systematic review and meta-analysis suggest that NTIS is highly prevalent in the critically ill population and that decreased serum T3 or T4 levels are associated with mortality in adult ICU patients. Based on these findings, the measurement of serum T3 or T4 levels could provide better information-related prognosis in this setting.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0504.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work was supported by FIPE/HCPA – Hospital de Clínicas de Porto Alegre Research Incentive Fund (0170492) and CNPq – National Council for Scientific and Technological development (301585/2018-0).

References

1 Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid* 2014 **24** 1456–1465. (https://doi.org/10.1089/thy.2014.0201)
2 Kaptein EM, Robinson WJ, Grieb DA & Nicoloff JT. Peripheral serum thyroxine, triiodothyronine and reverse triiodothyronine kinetics in the low thyroxine state of acute nonthyroidal illnesses. A noncompartmental analysis. *Journal of Clinical Investigation* 1982 **69** 526–535. (https://doi.org/10.1172/jci110478)
3 Maia AL, Goemann IM, Meyer EL & Wajner SM. Deiodinases: the balance of thyroid hormone: type 1 iodothyronine deiodinase in human physiology and disease. *Journal of Endocrinology* 2011 **209** 283–297. (https://doi.org/10.1530/JOE-10-0481)
4 Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ & Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3202–3211. (https://doi.org/10.1210/jc.2002-022013)
5 De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 151–164. (https://doi.org/10.1210/jcem.84.1.5364)
6 Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, Lapichino G, Edbrooke D, Capuzzo M, Le Gall JR, *et al.* SAPS 3-from evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Medicine* 2005 **31** 1345–1355. (https://doi.org/10.1007/s00134-005-2763-5)
7 Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F & Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on 'sepsis-related problems' of the European Society of Intensive Care Medicine. *Critical Care Medicine* 1998 **26** 1793–1800.
8 Zimmerman JE, Kramer AA, McNair DS & Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Critical Care Medicine* 2006 **34** 1297–1310. (https://doi.org/10.1097/01.CCM.0000215112.84523.F0)
9 Ferreira FL, Bota DP, Bross A, Melot C & Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001 **286** 1754–1758. (https://doi.org/10.1001/jama.286.14.1754)
10 Keegan MT & Soares M. What every intensivist should know about prognostic scoring systems and risk-adjusted mortality. *Revista Brasileira de Terapia Intensiva* 2016 **28** 264–269. (https://doi.org/10.5935/0103-507X.20160052)
11 Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A & Donato L. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. *Circulation* 2003 **107** 708–713. (https://doi.org/10.1161/01.cir.0000048124.64204.3f)
12 Iglesias P, Muñoz A, Prado F, Guerrero MT, Macías MC, Ridruejo E, Tajada P & Díez JJ. Alterations in thyroid function tests in aged hospitalized patients: prevalence, aetiology and clinical outcome.

Clinical Endocrinology 2009 **70** 961–967. (https://doi.org/10.1111/j.1365-2265.2008.03421.x)
13 Kim JG, Shin H, Kim W, Lim TH, Jang B, Cho Y, Choi KS, Ahn C, Lee J & Na MK. The value of decreased thyroid hormone for predicting mortality in adult septic patients: a systematic review and meta-analysis. *Scientific Reports* 2018 **8** 14137.
14 Wang B, Liu S, Li L, Yao Q, Song R, Shao X, Li Q, Shi X & Zhang JA. Non-thyroidal illness syndrome in patients with cardiovascular diseases: a systematic review and meta-analysis. *International Journal of Cardiology* 2017 **226** 1–10. (https://doi.org/10.1016/j.ijcard.2016.10.039)
15 Moher D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009 **62** 1006–1012. (https://doi.org/10.1016/j.jclinepi.2009.06.005)
16 SIGN. *SIGN 50: A Guideline Developer's Handbook*. Edinburgh, UK: SIGN, 2015. (available at: https://www.sign.ac.uk/media/1644/sign50_2015.pdf)
17 Asai K, Shirakabe A, Kiuchi K, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, Goda H, Shigihara S, Asano K, *et al.* Relation of low triiodothyronine syndrome associated with aging and malnutrition to adverse outcome in patients with acute heart failure. *American Journal of Cardiology* 2020 **125** 427–435. (https://doi.org/10.1016/j.amjcard.2019.10.051)
18 Bello G, Pennisi MA, Montini L, Silva S, Maviglia R, Cavallaro F, Bianchi A, De Marinis L & Antonelli M. Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. *Chest* 2009 **135** 1448–1454. (https://doi.org/10.1378/chest.08-1816)
19 Cerillo AG, Storti S, Kallushi E, Haxhiademi D, Miceli A, Murzi M, Berti S, Glauber M, Clerico A & Iervasi G. The low triiodothyronine syndrome: a strong predictor of low cardiac output and death in patients undergoing coronary artery bypass grafting. *Annals of Thoracic Surgery* 2014 **97** 2089–2095. (https://doi.org/10.1016/j.athoracsur.2014.01.049)
20 Chuang CP, Jong YS, Wu CY & Lo HM. Impact of triiodothyronine and N-terminal pro-B-type natriuretic peptide on the long-term survival of critically ill patients with acute heart failure. *American Journal of Cardiology* 2014 **113** 845–850. (https://doi.org/10.1016/j.amjcard.2013.11.039)
21 Galusova A, Pauliny M, Majek M, Mackova J, Meskova M, Vlcek M, Imrich R & Penesova A. Dynamic neuroendocrine changes in critically ill patients with polytrauma. *Neuro Endocrinology Letters* 2015 **36** 498–503.
22 Gangemi EN, Garino F, Berchialla P, Martinese M, Arecco F, Orlandi F & Stella M. Low triiodothyronine serum levels as a predictor of poor prognosis in burn patients. *Burns* 2008 **34** 817–824. (https://doi.org/10.1016/j.burns.2007.10.002)
23 Gutch M, Kumar S & Gupta KK. Prognostic value of thyroid profile in critical care condition. *Indian Journal of Endocrinology and Metabolism* 2018 **22** 387–391. (https://doi.org/10.4103/ijem.IJEM_20_18)
24 Hosny M, Rashad R, Atef D & Abed N. Predictive value of thyroid hormone assessment in septic patients in comparison with C-reactive protein. *Egyptian Journal of Critical Care Medicine* 2015 **3** 55–61.
25 Meyer S, Schuetz P, Wieland M, Nusbaumer C, Mueller B & Christ-Crain M. Low triiodothyronine syndrome: a prognostic marker for outcome in sepsis? *Endocrine* 2011 **39** 167–174. (https://doi.org/10.1007/s12020-010-9431-4)
26 Miguel Bayarri V, Borrás Palle S, Murcia Llácer B, Sancho Chinesta S, Málaga López A, Solá Izquierdo E, Pérez Bermúdez B & Hernández Mijares A. Prevalence and prognosis significance of euthyroid sick syndrome in critical illness. *Revista Clínica Española* 2001 **201** 572–574. (https://doi.org/10.1016/s0014-2565(01)70916-2)
27 Naby EAA, Selim S, Mohsen M & Helmy M. Thyroid function in mechanically ventilated patients with acute respiratory failure: prognostic value and its relation to high-sensitivity C-reactive protein. *Egyptian Journal of Chest Diseases and Tuberculosis* 2015 **64** 175–181.
28 Nafae RM, Mohammed MA, Morsi AF & Ibrahim DA. Thyroid function in respiratory failure patients. *Egyptian Journal of Chest Diseases and Tuberculosis* 2014 **63** 513–521. (https://doi.org/10.1016/j.ejcdt.2013.12.009)
29 Padhi R, Kabi S, Panda BN & Jagati S. Prognostic significance of nonthyroidal illness syndrome in critically ill adult patients with sepsis. *International Journal of Critical Illness and Injury Science* 2018 **8** 165–172. (https://doi.org/10.4103/IJCIIS.IJCIIS_29_17)
30 Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ & Van den Berghe G. Serum 3,3',5'-triiodothyronine (rT3) and 3,5,3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4559–4565. (https://doi.org/10.1210/jc.2005-0535)
31 Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Schölmerich J & Wrede CE. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. *Metabolism: Clinical and Experimental* 2007 **56** 239–244. (https://doi.org/10.1016/j.metabol.2006.09.020)
32 Qari FA. Thyroid function status and its impact on clinical outcome in patients admitted to critical care. *Pakistan Journal of Medical Sciences* 2015 **31** 915–919. (https://doi.org/10.12669/pjms.314.7497)
33 Rothberger GD, Valestra PK, Knight K, Desai AK, Calixte R & Shapiro LE. Low free T3 is associated with worse outcomes in patients in the ICU requiring invasive mechanical ventilation. *Journal of Intensive Care Medicine* 2021 **36** 313–318. (https://doi.org/10.1177/0885066619890822)
34 Sahana PK, Ghosh A, Mukhopadhyay P, Pandit K, Chowdhury BR & Chowdhury S. A study on endocrine changes in patients in intensive care unit. *Journal of the Indian Medical Association* 2008 **106** 362–364.
35 Scoscia E, Baglioni S, Eslami A, Iervasi G, Monti S & Todisco T. Low triiodothyronine (T3) state: a predictor of outcome in respiratory failure? Results of a clinical pilot study. *European Journal of Endocrinology* 2004 **151** 557–560. (https://doi.org/10.1530/eje.0.1510557)
36 Tas A, Tetiker T, Beyazit Y, Celik H & Yesil Y. Thyroid hormone levels as a predictor of mortality in intensive care patients: a comparative prospective study. *Wiener Klinische Wochenschrift* 2012 **124** 154–159. (https://doi.org/10.1007/s00508-012-0125-1)
37 Todd SR, Sim V, Moore LJ, Turner KL, Sucher JF & Moore FA. The identification of thyroid dysfunction in surgical sepsis. *Journal of Trauma and Acute Care Surgery* 2012 **73** 1457–1460. (https://doi.org/10.1097/TA.0b013e318270db2c)
38 Wang F, Pan W, Wang H, Wang S, Pan S & Ge J. Relationship between thyroid function and ICU mortality: a prospective observation study. *Critical Care* 2012 **16** R11. (https://doi.org/10.1186/cc11151)
39 Wang J, Yuan W, Dong R, Liu N, Liu D & Zhou Y. Predictors for euthyroid sick syndrome and its impact on in-hospital clinical outcomes in high-risk patients undergoing coronary artery bypass grafting. *Perfusion* 2019 **34** 679–688. (https://doi.org/10.1177/0267659119846789)
40 Wang YF, Heng JF, Yan J & Dong L. LRelationship between disease severity and thyroid function in Chinese patients with euthyroid sick syndrome. *Medicine* 2018 **97** e11756. (https://doi.org/10.1097/MD.0000000000011756)
41 Yasar Z, Kirakli C, Cimen P, Ucar ZZ, Talay F & Tibet G. Is non-thyroidal illness syndrome a predictor for prolonged weaning in intubated chronic obstructive pulmonary disease patients? *International Journal of Clinical and Experimental Medicine* 2015 **8** 10114–10121.
42 Van den Berghe G. The neuroendocrine response to stress is a dynamic process. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2001 **15** 405–419. (https://doi.org/10.1053/beem.2001.0160)
43 Jiang X, Xing H, Wu J, Du R, Liu H, Chen J, Wang J, Wang C & Wu Y. Prognostic value of thyroid hormones in acute ischemic stroke – a meta analysis. *Scientific Reports* 2017 **7** 16256.
44 Lamba N, Liu C, Zaidi H, Broekman MLD , Simjian T, Shi C, Doucette J, Ren S, Smith TR, Mekary RA, *et al.* A prognostic role for low tri-

iodothyronine syndrome in acute stroke patients: a systematic review and meta-analysis. *Clinical Neurology and Neurosurgery* 2018 **169** 55–63. (https://doi.org/10.1016/j.clineuro.2018.03.025)

45 Schultheiss UT, Steinbrenner I, Nauck M , Schneider MP, Kotsis F, Baid-Agrawal S, Schaeffner E, Eckardt K-U, Köttgen A, Sekula P, *et al.* Thyroid function, renal events and mortality in chronic kidney disease patients: the German Chronic Kidney Disease study. *Clinical Kidney Journal* 2021 **14** 959–968. (https://doi.org/10.1093/ckj/sfaa052)

46 Xu H, Brusselaers N, Lindholm B, Zoccali C & Carrero JJ. Thyroid function test derangements and mortality in dialysis patients: a systematic review and meta-analysis. *American Journal of Kidney Diseases* 2016 **68** 923–932. (https://doi.org/10.1053/j.ajkd.2016.06.023)

47 Vaughan GM, Mason AD, Jr, McManus WF & Pruitt BA, Jr. Alterations of mental status and thyroid hormones after thermal injury. *Journal of Clinical Endocrinology and Metabolism* 1985 **60** 1221–1225. (https://doi.org/10.1210/jcem-60-6-1221)

48 Kim BB, Ku YH, Han JY, Ha JM, Park G, Choi DH & Song H. Relation of triiodothyronine to subclinical myocardial injury in patients with chest pain. *American Journal of Cardiology* 2013 **111** 1087–1091. (https://doi.org/10.1016/j.amjcard.2012.12.039)

49 Pol CJ, Muller A, Zuidwijk MJ, van Deel ED, Kaptein E, Saba A, Marchini M, Zucchi R, Visser TJ, Paulus WJ, *et al.* Left-ventricular remodeling after myocardial infarction is associated with a cardiomyocyte-specific hypothyroid condition. *Endocrinology* 2011 **152** 669–679. (https://doi.org/10.1210/en.2010-0431)

50 Boelen A, Boorsma J, Kwakkel J, Wieland CW, Renckens R, Visser TJ, Fliers E & Wiersinga WM. Type 3 deiodinase is highly expressed in infiltrating neutrophilic granulocytes in response to acute bacterial infection. *Thyroid* 2008 **18** 1095–1103. (https://doi.org/10.1089/thy.2008.0090)

51 Siafakas NM, Salesiotou V, Filaditaki V, Tzanakis N, Thalassinos N & Bouros D. Respiratory muscle strength in hypothyroidism. *Chest* 1992 **102** 189–194. (https://doi.org/10.1378/chest.102.1.189)

52 Dulchavsky SA, Kennedy PR, Geller ER, Maitra SR, Foster WM & Langenbeck EG. T3 preserves respiratory function in sepsis. *Journal of Trauma* 1991 **31** 753–758; discussion 8–9. (https://doi.org/10.1097/00005373-199106000-00004)

53 Mayr VD, Dunser MW, Greil V, Jochberger S, Luckner G, Ulmer H, Friesenecker BE, Takala J & Hasibeder WR. Causes of death and determinants of outcome in critically ill patients. *Critical Care* 2006 **10** R154. (https://doi.org/10.1186/cc5086)

54 Kaptein EM, Beale E & Chan LS. Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3663–3675. (https://doi.org/10.1210/jc.2009-0899)

55 Kaptein EM, Sanchez A, Beale E & Chan LS. Clinical review: Thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review and synthesis. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4526–4534. (https://doi.org/10.1210/jc.2010-1052)

56 Brent GA & Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *Journal of Clinical Endocrinology and Metabolism* 1986 **63** 1–8. (https://doi.org/10.1210/jcem-63-1-1)

57 Van den Berghe G, de Zegher F & Bouillon R. Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 1827–1834. (https://doi.org/10.1210/jcem.83.6.4763)

58 Pingitore A, Mastorci F, Piaggi P, Donato Aquaro GD, Molinaro S, Ravani M, De Caterina A, Trianni G, Ndreu R, Berti S, *et al.* Usefulness of triiodothyronine replacement therapy in patients with ST elevation myocardial infarction and borderline/reduced triiodothyronine levels (from the THIRST Study). *American Journal of Cardiology* 2019 **123** 905–912. (https://doi.org/10.1016/j.amjcard.2018.12.020)

59 Kavanagh BP & Meyer LJ. Normalizing physiological variables in acute illness: five reasons for caution. *Intensive Care Medicine* 2005 **31** 1161–1167. (https://doi.org/10.1007/s00134-005-2729-7)

Received in final form 20 December 2021
Accepted 11 January 2022
Accepted Manuscript published online 11 January 2022