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PREVALÊNCIA E IMPLICAÇÕES PROGNÓSTICAS DA SÍNDROME DO T3 BAIXO EM PACIENTES COM SEPSE E CHOQUE SÉPTICO

TESE DE DOUTORADO

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Para meus pais.

“Certa vez olhamos para o mundo, na infância.
O resto é memória.”
Louise Glück

Esta tese segue o formato proposto pelo Programa de Pós- Graduação em Ciências Médicas: Endocrinologia, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul. Ela será constituída de: 1) Introdução; 2) Artigo original: *Nonthyroidal Illness syndrome predicts outcome in adult critically ill patients – a systematic review and meta-analysis*; 3) Artigo original *Low T3 levels independently predict outcome in patients with sepsis and septic shock admitted to an intensive care unit: a prospective cohort study;* 4) Perspectivas

RESUMO

A síndrome do T3 baixo refere-se a alterações dos níveis séricos dos hormônios tireoidianos em pacientes com doenças sistêmicas e ausência de disfunção primária do eixo hipotálamo-hipófise-tireoide. Sabe-se que os hormônios da tireoide têm função importante na adaptação metabólica à doença crítica e ao estresse, no entanto pacientes criticamente enfermos frequentemente apresentam redução dos níveis destes hornônios. As mudanças no metabolismo dos hormônios tireoidianos que ocorrem na fase aguda da doença crítica são consideradas benéficas, pois reduziriam o gasto energético e o consumo de proteínas, porém o aumento da morbidade e mortalidade associadas à síndrome do T3 baixo e a persistência de alterações na fase crônica da doença, em que o catabolismo é deletério, tem colocado em dúvida o caráter adaptativo dessas alterações.

Dessa forma, o primeiro estudo dessa tese consiste em uma revisão sistemática e metanálise que avalia o prognóstico de pacientes internados em unidades de terapia intensiva que desenvolveram alterações dos hormônios tireoidianos. Essa revisão incluiu um total de 25 estudos e 3260 pacientes. A despeito de limitações na qualidade dos estudos incluídos, os resultados sugerem que alterações dos hormônios tireoidianos estão associados a pior desfecho em pacientes críticos.

O segundo estudo dessa tese consiste em uma coorte que avaliou o influencia prognóstica da síndrome do T3 baixo em pacientes com sepse e choque séptico internados em unidade de terapia intensiva. O estudo demonstrou que a redução dos níveis séricos de T3 é preditor independente de mortalidade intra-hospitalar e evolução para doença crítica persistente nesta população.

Palavras-chave: Síndrome do T3 baixo. Doença não tireoidiana. Sepse. Doença crítica crônica.

ABSTRACT

Nonthyroidal illness syndrome refers to alterations in serum thyroid hormones levels in patients with systemic diseases and absence of primary dysfunction of the hypothalamic-pituitary-thyroid axis. Thyroid hormones are known to play an important role in metabolic adaptation to critical illness and stress, however critically ill patients often present with reduced thyroid hormone levels. Changes in thyroid hormones metabolism that occur in the acute phase of critical illness are considered beneficial, as they would reduce energy expenditure and protein consumption, but the increase in morbidity and mortality associated with nonthyroidal illness syndrome and the persistence of changes in the chronic phase of disease, in which catabolism is harmful, cast doubt on the adaptive nature of these changes.

Thus, the first study of this thesis consists of a systematic review and meta-analysis that assesses the prognosis of patients admitted to intensive care units who have developed changes in thyroid hormones. This review included a total of 25 studies and 6869 patients. Despite limitations in the quality of the included studies, our results suggest that changes in thyroid hormones are associated with a worse outcome in critically ill patients.

The second study of this thesis consists of a cohort that evaluated the prognostic influence of non thyroidal illness syndrome in patients with sepsis and septic shock admitted to an intensive care unit. The study demonstrated that the reduction in serum T3 levels is an independent predictor of in-hospital mortality and progression to persistent critical illness in this population.

Keywords: Low T3 syndrome. Nonthyroid disease. Sepsis. Chronic critical illness.

LISTA DE ABREVIATURAS E SIGLAS

%	por cento; percentual
ACTH	*Adrenocorticotropic hormone*
APACHE	*Simplified Acute Physiology Score*
AUC	Area under the curve
CABG	*Coronary artery bypass grafting*
CCI	*Chronic Critical Illness*
CI	*Confidence interval*
CO	*Cardiac output*
D1	Iodotironina desiodase tipo 1 / *deiodinase type 1*
D2	Iodotironina desiodase tipo 2 / *deiodinase type 2*
D3	Iodotironina desiodase tipo 3 / *deiodinase type 3*
HHA	Hipotálamo-hopófise-adrenal
HT	Hormônios tireoidianos
HHT	Hipotálamo-hipófise-tireoide
HR	*Hazard ratio*
FT3	*Free triiodothyronine*
FT4	*Free thyroxine*
GSH	*Glutathione*
ICU	*Intensive care Unit*
IQR	*Interquartile*
IL	*Interleukine*
LOS	*Length of stay*
LT3S	*Low T3 Syndrome*
MACCE	*Major adverse cardiovascular and cerebral events*
Mesh	*Medical Subject Heading*
MRA	*Multivariate regression analysis*
MV	*Mechanical ventilation*
NAC	*N-acetylcysteine*
NTIS	*Non thyroidal illness syndrome*
OR	*Odds ratio*
PCS	*Prospective coohort study*
PICO	*Patient or Population Intervention Comparison Outcome*

PICS	*Persistent inflammation, immunosuppression, and catabolism syndrome*
PRISMA	*Preferred reporting Items for Systematic reviews and meta-analysis*
PROSPERO	*Prospective Register of Systematic Reviews*
PTS	*Politrauma score*
RCS	*Retrospective cohort study*
ROC	*Receiver operating characteristic*
ROS	*Reactive oxygen species*
rT3	*Reverse triiodothyronine*
SAPS	*Simplified Acute Physiology Score*
SD	*Standard deviation*
SMD	*Standardized mean differences*
SOFA	*Sequential Organ Failure Assessment*
SPSS	*Statistical package for the social sciences*
ST3B	Síndrome do T3 Baixo
T3	Triiodotironina / *Triiodothyronine*
T3L	Triiodotironina livre
T4	Tiroxina / *thyroxine*
TBG	Globulina ligadora de tiroxina
TFT	*Thyroid function tests*
TH	*Thyroid hormones*
TNF	Tumor necrosis factor
TSH	Tireotrofina / *thyrotropin*
UTI	Unidade de terapa intensiva

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INTRODUÇÃO

Os hormônios da tireoide (HT) são essenciais para o desenvolvimento celular e metabolismo energético. Sob estímulo do eixo hipotálamo-hipofisário, a tireoide produz tiroxina (T4) e triiodotironina (T3). Embora o T4 seja o principal produto da tireoide, o T3 é o hormônio biologicamente ativo. Mais de 99% do T4 e T3 circulam ligados a proteínas, sendo as mais importantes a globulina ligadora da tiroxina (TBG), a transtirretina e a albumina. A maior parte da produção e inativação do T3 (80-90 %) ocorre nos tecidos periféricos através da ação das iodotironinas desiodases tipos 1, 2 e 3 (D1, D2 e D3) (1). Os HT são transportados para o interior da célula por transportadores específicos e se ligam aos receptores nucleares capazes de ativar ou inibir a transcrição gênica (2). A ação não genômica, por mecanismos diretos, também é descrita (3). A regulação da produção hormonal ocorre por mecanismo de retroalimentação negativa pelos níveis circulantes de T3 (4).

A síndrome do T3 baixo (ST3B), também conhecida como doença não tireoidiana, refere-se a alterações nos níveis séricos dos HT que ocorre em resposta a doenças sistêmicas, na ausência de disfunção primária do eixo hipotálamo-hipófise-tireoide (HHT) (5). É caracterizada por níveis baixos de T3 e T3 livre (T3L) e níveis elevados da forma inativa T3 reverso (rT3). Os níveis séricos de T4 podem ser normais ou reduzidos. A redução dos níveis de T4 está associada com a gravidade da doença, enquanto níveis baixos de T3L são um marcador de mau prognóstico (6, 7). Embora os níveis do hormônio estimulante da tireoide (TSH) permaneçam dentro dos limites normais, o pico noturno de TSH observado no estado fisiológico está ausente (8). A gênese da ST3B é multifatorial (9), contribuindo para a síndrome: a) redução das proteínas carreadoras, consumidas como proteínas de fase aguda (10); b) alterações na expressão de transportadores hormonais trans-membrana celular (11); e) redução da biodisponibilidade hormonal periférica por alterações na expressão e atividade das desiodases, (12, 13). c) alteração na expressão dos receptores nucleares (14) d) inibição da alça de retroalimentação positiva hipotálamo-hipofisária (15).

A doença crítica está frequentemente associada a alterações do eixo HHT. O papel das citocinas nesse contexto tem sido foco de interesse, visto que estão envolvidas na fisiopatogênese da ST3B (16). Estudo que comparou pacientes com sepse a pacientes pós-infarto agudo do miocárdio quanto ao nível de citocinas, a alterações no eixo hipotálamo-hipófise-adrenal (HHA) e no eixo HHT, demonstrou-se que, apesar de ambos os grupos apresentarem ativação do eixo HHA, com elevação dos níveis de cortisol e ACTH semelhantes,

os níveis de hormônios tireoidianos e TSH foram significativamente inferiores no grupo de pacientes com sepse quando comparados ao grupo controle. Os níveis elevados de citocinas inflamatórias presentes na sepse a diferencia das demais patologias e corrobora a influência desses mediadores na ST3B (17).

Sabe-se que a mortalidade relacionada a sepse apresenta forma bifásica. O pico inicial de mortalidade apresentou redução expressiva ao longo dos últimos anos, devido a evolução do tratamento em unidades de terapia intensiva (UTI). O uso de suporte mecânico e farmacológico, o reconhecimento precoce e a aderência a protocolos permitiram que pacientes sobrevivam a fase aguda da sepse (18-20). No entanto, a possibilidade de sobreviver à doença aguda criou uma população crescente dependente de cuidados intensivos, com necessidade de internações prolongadas, aumento da vulnerabilidade a infecções nosocomiais, dificuldade na cicatrização de feridas, caquexia progressiva e disfunções orgânicas manejáveis, com consequente aumento de mortalidade a médio e longo prazo (21-24).

Nesse contexto, a relevância clínica da ST3B necessita ser adequadamente elucidada. Acredita-se que as mudanças no metabolismo dos HT que ocorrem na fase aguda da doença crítica são benéficas, pois reduziriam o gasto energético e o consumo de proteínas. Porém, o aumento da morbidade e mortalidade associadas à ST3B e a persistência de alterações na fase crônica da doença, em que o catabolismo é deletério, tem colocado em dúvida o caráter adaptativo dessas alterações. Adicionalmente, os avanços no entendimento da patogênese da sepse e o conhecimento do papel das citocinas nas alterações hormonais faz com que uma classificação embasada apenas na temporalidade (agudo vs crônico) seja falha, visto que não considera a heterogeneidade da resposta imune na evolução dos pacientes.

Diante do exposto, os dois artigos que compõe essa tese de doutorado abordam:

- Revisão sistemática com meta-análise da literatura disponível, sobre a influência prognóstica da ST3B em doentes criticamente enfermos.

- O impacto da alteração precoce dos HT em pacientes admitidos na UTI por sepse e choque séptico sobre a mortalidade intra-hospitalar e evolução para doença crítica crônica, através de um estudo coorte prospectivo realizado em um hospital universitário de Porto Alegre.

CAPÍTULO 1

NONTHYROIDAL ILLNESS SYNDROME PREDICTS OUTCOME IN ADULT CRITICALLY ILL PATIENTS – A SYSTEMATIC REVIEW AND META-ANALYSIS

Nonthyroidal Illness syndrome predicts outcome in adult critically ill patients – a systematic review and meta-analysis

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ABSTRACT

Introduction: Critical illness is associated with various patterns of thyroid hormone (TH) abnormalities. This study aimed to evaluate the prevalence and prognostic impact of decreased TH in patients during intensive care unit (ICU) admission.

Methods: We performed a systematic review and meta-analysis to comprehensively determine the prevalence and the prognostic role of nonthyroidal illness syndrome (NTIS) in critically ill patients. We included studies that assessed thyroid function by measuring the serum thyroid hormone 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.

Results: A total of 6869 patients in 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% confidence interval (CI), 0.41–1.92; I2 = 97%; P <0.001; 11 studies for FT3; SMD, 1.03; 95% CI, 0.57–1.5; I2 = 95%; P < 0.01). Free thryroxine (FT4) levels in non-survivors were also lower than that of survivors (12 studies; SMD 0.54; 95% CI, 0.31–0.78; I2 = 83%; P < 0.01). There were no statistically significant differences in TSH levels between non-survivors and survivors. NTIS was independently associated with increased risk of mortality in critically ill patients (OR = 2.21, 95% CI 1.64.-2.97, I2 = 65% p < 0.01)

Discussion: 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 admited to ICU.

1. INTRODUCTION

Thyroid hormones (TH) are essential for cellular growth, differentiation and energetic regulation. Critical illness is frequently associated with alterations in TH metabolism that are not caused by primary abnormality of hypothalamic–pituitary–thyroid function. These changes, collectively known as ‘‘non-thyroidal illness syndrome” (NTIS) or ‘‘low T3 syndrome’’ (LT3S) 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, iodothyronine deiodinases function is deranged, causing decrease of T4 to T3 conversion with a further raise in the inactivation of T4 to rT3. In the chronic course of disease, inhibition of the hypothalamic-pituitary feedback loop also seems to occur, reflecting severity of disease (2-4). 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 impact 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, SAPS III (Simplified Acute Physiology Score) and SOFA (Sequential Organ Failure Assessment) (6-8). APACHE IV score uses twelve physiological variables presented in the first 24 hours of admission, evaluates chronic diseases and the reason to be admitted at the ICU. SAPS III uses the worst values measured within the first 24 hours 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 ICU stay. Although it was not designed for prognosis prediction, higher scores are associated with 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 outcome and to emphasize areas for improvement. Prognostic scoring systems perform best at 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 (11-14). Considering that most studies are underpowered and not primarily designed with this objective, whether NTIS may influence outcome of critically ill patients admitted to ICU is still not settled.

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

2. METHODS

2.1. 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).

2.2. 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?

2.3. Eligibility criteria

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

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

2.4. 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”, “Nonthyroidal Illness Syndrome” and “Low T3 Syndrome”. The complete search strategy for Embase and Pubmed is presented in Appendix 1.

Three independent reviewers (PRJ, ALK and JV) assessed records for inclusion based on 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 disagreements.

2.5. Data collection and extraction

Data was extracted using a standardized system by independent reviewers. 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 used, outcome measures and main results, correlation to critical illness prognosis scores, conclusions and limitations. During the process of data extraction, the individual risk of bias of each study was assessed using the SIGN checklist (Appendix 2) (16). Final extraction results were checked and discussed among the research team.

2.6. Statistical Analysis.

The main analysis consisted of an investigation into the association between decreased peripheral thyroid hormone levels and in-hospital mortality in adult patients. To determine the strength of the association between decreased thyroid hormones and death, the standardized mean differences (SMD) was 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% confidence interval (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

SD]. The mean difference ± SD were derived from the TH levels across comparison groups. Since various units of TH were used in our study; hence, we converted all these different TH units into recommended standard international units: T4 (nmol/L), T3 (nmol/L), Free T4 (pmol/L), Free T3 (pmol/L), TSH (μIU/mL). The odds ratio (OR) with 95% confidence interval (CI) for all-cause mortality were pooled using meta-analysis. For this purpose, only studies which 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 I2 statistic and the Cochran's Q statistic to evaluate heterogeneity. I2 higher than 40% indicated substantial heterogeneity across included studies. Since there was difference in those included studies, random-effects model was used to calculate the pooled prevalence of ORs. Subgroup analysis was performed by type of admission and by quality assessment. Identification of publication bias were also performed by the R packages 'meta' (R version 3.3.2). Publication bias was assessed 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.

3. RESULTS

3.1. 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 provided information about the outcome of interest. A total of 25 studies with a total of 6869 patients were included in the analysis (Figure 1).

3.2. Study characteristics and risk of bias

Most of the records were from small sample size, single-center studies including heterogeneous adult medical or mixed medical/surgical ICUs. Studies were conducted between 2001 and 2020. In regard to bias assessment (Table 1), there was a high risk of bias resulting from the observational (18-41) / retrospective study design (20, 21, 22, 24,

27, 41) used in the studies. The absence of statistical control for known confounders (18, 23, 25, 27, 36, 41) and for covariance with severity scores (19, 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 (20, 24).

3.3. Diagnostic criteria and prevalence rates for NTIS

Among the 25 studies, 16 reported the use of strict diagnostic criteria, while other studies used "decreased concentrations of T3 or FT3 or elevated concentrations of rT3" as the diagnostic criteria of NTIS, not taking into account changes in TSH. As to the prevalence rate, only 3 studies did not describe the results in their samples. Median prevalence rate was 58% (IQR 33.2-63.7). Four studies also described the prevalence of the combination of low T3 and low 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).

3.4. Prognostic role of NTIS

In Table 3, we present the characteristics of the 25 included studies and data on the association between serum TH levels and outcome of critically ill patients. As to the 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 coronary artery bypass graft (29,40) and 2 from decompensated heart failure (30, 41), 3 studies included patients with sepsis (27, 35, 37), 1 study was on patients with polytrauma (32) and 1 study was from a burning center (22). Mortality rates varied greatly since they were 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 (figure 2). T3 and FT3 levels in non-survivors were lower than that of survivors (8 studies for T3: SMD 1.16; 95% CI, 0.41–1.92; I2 = 97%; P <0.001; 11 studies for FT3; SMD, 1.03; 95% CI, 0.57–1.5; I2 = 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; I2 = 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 there was no significant decrease in heterogeneity in each subgroup.

Studies that reported OR for adverse outcome were pooled in a meta-analysis (Figure 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, I2 = 65% p < 0.01). Subgroup analyses of patients admitted for cardiovascular causes or all other causes suggested that NTIS was associated with increased mortality risk in both groups, with reduced heterogeneity in patients admitted for non-cardiovascular causes (Figure 4).

3.5. Publication Bias

Funnel plot suggested tendency of publication bias on the metanalysis on mortality risk (P Egger's test=0.05, Figure 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).

4. 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 recent systematic reviews evaluating patients with acute neurologic events (43-44), cardiovascular disease (45), sepsis (46) and chronic renal failure (47-48) that point to an incremental risk of unfavorable outcomes in patients with NTIS. Data derived from these diverse population (43-48) consistently suggest no survival advantage and question the

generally accepted idea that a reduced availability of T3 and consequently reduced metabolism are beneficial in the acute phase of disease. Experimental and clinical studies support the hypothesis that reduced serum and tissue concentrations of T3 may be implicated in organic disfunction commonly related to the critically ill as diminished cognitive status with lethargy (49), altered cardiac inotropism and chronotropism, altered vasoactive properties (50, 51), inability to control bacterial infections due to reduced response of the innate immune system (52), respiratory muscle weakness (53), reduced synthesis of pulmonary surfactant and decrease of lung compliance, resulting in the impairment of lung function (54). The significant correlation between decreased TH and organic dysfunctions indicates the possibility of use of TH as a prognostic factor for the critically ill, as multiple organ dysfunction syndrome is the most frequent cause of death in the ICU (55).

Whether replacing TH can help to improve the outcomes of NITS patients is still unknown. While some studies are inconclusive regarding effectiveness of TH therapy in outcome of patients with NTIS (56-57) with risks associated with overdosage and delayed recovery of the neuroendocrine feedback axis (58), others have shown benefit on secondary end-points, as reduced protein degradation associated with restoration of plasma TH levels (59) and increment of cardiac stroke volume (60). Nevertheless, it is important to remember that normalization of other deranged physiologic parameters in ICU patients has repeatedly proved to be ineffective in improving outcome when the causal stimulus is not addressed (61).

There were several 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 general admission of ICU patients. Still, we were unable to control for other causes of heterogeneities, like severity of disease and inconsistence of TH sampling time, 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.

5. CONCLUSION

The present systematic review and meta-analysis suggests 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 to prognosis in this setting.

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Appendix 1. Search strategy

Search terms

It was utilized Medical Subject Heading (MeSH) for Pubmed and Embase search, which

were the following:

Pubmed
Exposition:
"Euthyroid Sick Syndromes"[Mesh] OR "Euthyroid Sick Syndromes" OR "Euthyroid Sick Syndrome" OR "Sick Euthyroid Syndrome" OR "Syndrome, Sick Euthyroid" OR "Non-Thyroidal Illness Syndrome" OR "Non Thyroidal Illness Syndrome" OR "Syndrome, Non-Thyroidal Illness" OR "Syndromes, Non-Thyroidal Illness" OR "Low T3-Low T4 Syndrome" OR "Low T3 Low T4 Syndrome" OR "Low T3 and Low T4 Syndrome" OR "Low T3-High T4 Syndrome" OR "Low T3 High T4 Syndrome" OR "High T4 Syndrome" OR "High T4 Syndromes" OR "Low T3 Syndrome" OR "low T3"

Embase
Exposition:
'euthyroid sick syndrome'/exp OR 'euthyroid sick syndrome' OR 'sick euthyroid syndrome' OR 'Syndrome, Sick Euthyroid' OR 'Non-Thyroidal Illness Syndrome' OR 'Non Thyroidal Illness Syndrome' OR 'Syndrome, Non-Thyroidal Illness' OR 'Syndromes, Non-Thyroidal Illness' OR 'Low T3-Low T4 Syndrome' OR 'Low T3 Low T4 Syndrome' OR 'Low T3 and Low T4 Syndrome' OR 'Low T3-High T4 Syndrome' OR 'Low T3 High T4 Syndrome' OR 'High T4 Syndrome' OR 'High T4 Syndromes' OR 'Low T3 Syndrome' OR 'Low T3'

Appendix 2. Methodology Checklist

SIGN	**1 METHODOLOGY CHECKLIST 3: COHORT STUDIES**

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

1.1.1.1.1 Section 1: Internal validity

In a well conducted cohort study:		***1.1.1.2 Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ No □ Does not apply □

1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes □ Can't say □	No □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.		
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ Can't say □	No □ Does not apply □

ASSESSMENT			
1.7	The outcomes are clearly defined.	Yes □ Can't say □	No □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ Can't say □	No □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ Can't say □	No □ □
1.10	The method of assessment of exposure is reliable.	Yes □ Can't say □	No □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ Can't say □	No □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ Can't say □	No □ Does not apply □
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ Can't say □	No □
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes □	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			

2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

Table 1. SIGN Quality Assesment

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 (18)	Y	N	N	Y	30%	N	N	N	N	Y	Y	N	N	N	+	N	N	Heterogeneous population, not controled for confounders
Scoscia, 2004 (19)	Y	Y	N	Y	0%	NA	Y	N	N	Y	Y	Y	N	Y	+	NA	Y	small sample size, single centre trial, no covariance analysis
Peeters, 2005 (20)	Y	Y	N	Y	0	NA	Y	N	Y	Y	Y	Y	N	Y	+	NA	Y	Study was not designed for the clinical outcomes, patients with prior thyroid disease were not excluded
Plikat, 2006 (21)	Y	Y	Y	Y	0%	NA	Y	NA	N	Y	Y	N	Y	Y	+	Y	Y	retrospective
Gangemi, 2007 (22)	Y	Y	Y	Y	0%	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	
Sahana, 2008 (23)	Y	N	Y	Y	0%	NA	Y	N	Y	Y	Y	Y	N	Y	+	Y	Y	Not controled for confounders
Bello, 2009 (24)	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 disfunction
Meyer, 2011 (25)	Y	N	Y	NA	0%	NA	Y	N	Y	Y	Y	Y	N	Y	+	Y	Y	not controled for confounders
Tas, 2012 (26)	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 (27)	Y	Y	N	Y	0%	NA	Y	N	Y	Y	Y	N	N	Y	+	Y	Y	
Wang, 2012 (17)	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	
Cerillo, 2014 (29)	Y	Y	N	Y	0%	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	
Chuang, 2014 (30)	Y	Y	N	Y	0%	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	Single measurement in a long term follow up. Cutoff diagnostic value of T3 is way below inferior range
Naby, 2014 (31)	Y	Y	N	Y	0%	NA	Y	N	N	Y	Y	Y	Y	Y	+	Y	Y	
Galusova, 2015 (32)	Y	Y	N	Y	0%	NA	N	CS	N	Y	Y	Y	Y	Y	+	CS	Y	Small sample size

Qari, 2015 (33)	Y	Y	N	Y	0%	NA	Y	NA	N	Y	Y	N	Y	Y	+	Y	Y	Described conclusion is not statistically significant
Yasar, 2015 (34)	Y	Y	N	Y	0%	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	
Hosny, 2015 (35)	Y	N	N	Y	0%	NA	Y	N	Y	Y	Y	Y	Y	Y	+	CS	Y	Association to severity scores.
Gutch, 2018 (36)	Y	N	N	Y	0%	NA	Y	N	N	CS	CS	Y	N	N	+	N	N	Described results are inconsistent or not presented in a comprehensive way
Padhi, 2018 (37)	Y	N	N	Y	0%	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	
Wang, 2019 (38)	Y	Y	N	Y	0	NA	Y	N	N	Y	Y	N	Y	Y	+	Y	Y	Small and heterogeneous sample size
Rothberger, 2019 (39)	Y	Y	Y	Y	0%	NA	Y	NA	Y	Y	Y	N	Y	Y	++	Y	Y	Single center
Wang, 2019 (40)	Y	Y	N	Y	0	NA	Y	N	Y	Y	Y	N	Y	Y	++	Y	Y	
Asai, 2020 (41)	Y	Y	Y	Y	0%	NA	Y	NA	Y	Y	Y	N	Y	Y	+	N	Y	Retrospective, Old age and maltrution as confounders

Table 2. Diagnostic criteria and prevalence rate for NTIS

Reference	Definition of NTIS	Prevalence	Sampling time
Bayarri, 2001 (18)	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 μU/ml; 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 (19)	Reduced T3, T4 range from reduced to slightly elevated, with either normal or slightly suppressed TSH levels	53%	Within 24hs of admission
Peeters, 2005 (20)	low serum T3 and high rT3.	Not described	On day 1, 5, 15, and last day
Plikat, 2006 (21)	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 (22)	low serum levels of FT3 with increase of rT3 and normal-to-low serum concentrations of fT4 and TSH.	Not described	1 to 3 days after admission
Sahana, 2008 (23)	Decreased serum T3 and increased TSH, followed by a decrease in T4.	80%	On admission and on day 7
Bello, 2009 (24)	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 four days after admission, and consecutively every 8 days after
Meyer, 2011 (25)	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 (26)	low FT3 levels, although decreases in FT3, free T4 (FT4) and thyroid stimulating hormone (TSH) may occur in varying combinations	77.2%	Blood samples were obtained 24 hours after admission
Todd, 2012 (27)	Low T3	Not described	Blood samples colected when sepsis was dianosed
Nafae, 2013 (28)	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 1st day 79.6% at the 3rd day 43.7% at the 10th day	On day 1, 3 and 10
Cerillo, 2014 (29)	low circulating T3 levels in the absence of an intrinsic thyroid disease	9.8%	On admission
Chuang, 2014 (30)	Total T3 cutoff of 52,3 ng/dL (reference range 84 to 172 ng/dl)	42%	Within 48hs of admission
Naby, 2014 (31)	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 (32)	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	1st, 2nd, 3rd and 7th day after admission
Quari, 2015 (33)	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 (34)	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 hrs
Hosny, 2015 (35)	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 5th day	On the day of admission (D1) and fifth day after admission (D5

Gutch, 2018 (36)	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 (37)	Group A: low T3 and normal or high T4. Group B: low T3 and low T4.	67%	On admission
Wang, 2019 (38)	High rT3 levels	Decreased fT3 or fT4 group: 33% Decreased TSH group: 41%	On the second day.
Rothberger, 2019 (39)	FT3 <2.3 pg/mL	60%	On the day of initiation of MV
Wang, 2019 (40)	decrease in levels of T3 and increase in levels of rT3	58.7%	1 to 3 days after CABG
Asai, 2020 (41)	Low FT3 (<1.88 uI/mL)	53%	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, rT3 = reverse triiodothyronine, T3 = triiodothyronine, T4 = thyroxine, TSH = thyrotropin

Table 3: Characteristics of the studies and data on the association between serum TH levels and outcome.

Reference	Study design	Population	Age in years mean (range)	Sex (males/total	TFT Reference values	Mortality (%)	Comparison between favorable and unfavorable groups, n	Univariete analysis			Other analysis	Conclusions
								Main results Favorable	Main results unfavorable	p		
Bayarri, 2001 (18)	PCS	91 patients admitted to ICU	58.3±14.2	56/91		Type 1: 38.5% Tipe 2: 87.9%	NTIS type I (56) x NTIS type II (11)	Mortality: 38.5%	87.9%	.004	NA	Thyroid hormone disfunction associated with mortality
Scoscia 2004 (19)	PCS	32 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) x non survivors (n=4)	FT3 3.68 (2.01-5.37)	FT3 2.15 (1.53–2.78)	.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 (20)	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 9.1–22.1 ng/dl	15.7%	Survivors (380) x 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)	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]	.46 <.001 .19 <.001 0.32 <.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.

								rT3 D1: 38.3 (26.-57.1 rT3 D5: 40.9 (27.9-65.6)	rT3 D1 :55.2 [31.2–91.5] rT3 D5 :59.1 [35.0 –97.4]	<.001 <.001		
Plikat, 2006 (21)	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 (22)	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)	.001 .396 <.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
Sahana, 2008 (23)	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 six weeks	Survivors (42) x 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	<.005 <.05 <.001 <.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 (24)	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 to 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	FT3 1.84 (1.38-2.45) FT4 12.09 (9.26-14.54 TSH	< .001 < .001 .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.

								TSH 1.20 (0.78-1.89)	1.1 (0.63-1.71)			
Meyer, 2011 (25)	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) x 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 2 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)	.3 .66 .08 .2 .004 .02	na	T3 and fT4 levels on admission were not prognostic in septic and non-septic critically ill patients
Tas, 2012 (26)	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) x 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	<.001 <.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 (27)	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) x non survivors (41)	T4 58 ± 0.2 T3 1.1 ± 0.03 TSH	T4 46 ± 0.6 T3 0.88 ± 0.07 TSH	0.01 0.01		Decreased T3 levels at baseline are associated with mortality

								2.4 ± 0.6	5.1 ± 1.6	0.06		
Wang, 2012 (17)	PCS	480 Patients admitted to ICU	71.71 ± 15.52	59.7%	FT3, 3.5 to 6.5 pmol/L; TT3, 0.92 to 2.78 nmol/L; FT4, 11.5 to 22.7 pmol/L; TT4, 57.9 to 140.3 nmol/L; TSH, 0.35 to 5.50 mIU/L; and rT3, 0.16 to 0.95 ng/ml	23.7%	Survivors (388) x 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 to 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 to 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
Nafae, 2013 (28)	PCS	64 Patients admitted to ICU with respiratory failure	59.5 ±6.4	46%		14%	NTIS X euthyroid				Duration of MV and thyroid hormones at day 3: FT3: r = -0.57 p<.001 FT4: r = -0.24 p>0.05 TSH: r = -0.56 p <.001 Lenght of ICU stay and Thyroid hormones at day 3: FT3: r =-0.50 p <.001 FT4: r= -0.35 p <.001 TSH: r= -0.49 p <.001	Moderate negative correlation between FT3 and TSH at 3rd day of study and duration of MV and lengh of ICU stay
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 to 32.373; p < .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) x 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	.56 .22 .01 .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) X 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	.346 .304 .294		TH levels were not significantly correlated to the type of MV, its duration, 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) x 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 (mUI/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 (mUi/mL) 0.68 (0.24-1.62)	P<.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

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) x 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 (3.5–6.5pmol/L) FT4 (11.5–23 pmol/L	30%	Survivors (63) x 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 cutoff 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)	T3 0.74 (0.56-1.17) FT3 2.08 (1.74-2.98) T4 59.95 (51.78-65.98) FT4 11.84 (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	Nonsurvivors 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

								rT3 0.37 (0.05-2.45)				
Wang, 2019 (38)	PCS	51 Patients admitted to ICU	60.39 ± 19.32	38/51		Not described	Euthyroid X low T3 and low T4 X low TSH				mean (±SD) 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 x normal FT3				Patients with low FT3 had a significantly higher mortality rate (52% vs 19%, P <.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
Wang, 2019 (40)	PCS	659 high-risk patients undergoing isolated CABG	NTIS 65.9 (7.5) Non NTIS 60.9 (9.6)	412/659		1.5%	NTIS (387) x non NTIS (272)				MRA for MACCE - OR = 3.40, 95% CI = 1.64-7.02, p = 0.001	Patients with NTIS were at a higher risk of in-hospital MACCE, post-infection, acute renal injury, non-invasive ventilator, delirium, and hypoxemia compared with the control group
Asai, 2020 (41)	RCS	956 Acute heart failure in ICU	74 (65-81)	627/956		6.3%	Normal tyroid function (n=445) x 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

APACHE = acute physiology and chronic health evaluation, CABG = coronary artery bypass grafting, CI = confidence interval, 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. Thyroid hormone levels are presented as median (IQI) or mean ± SD

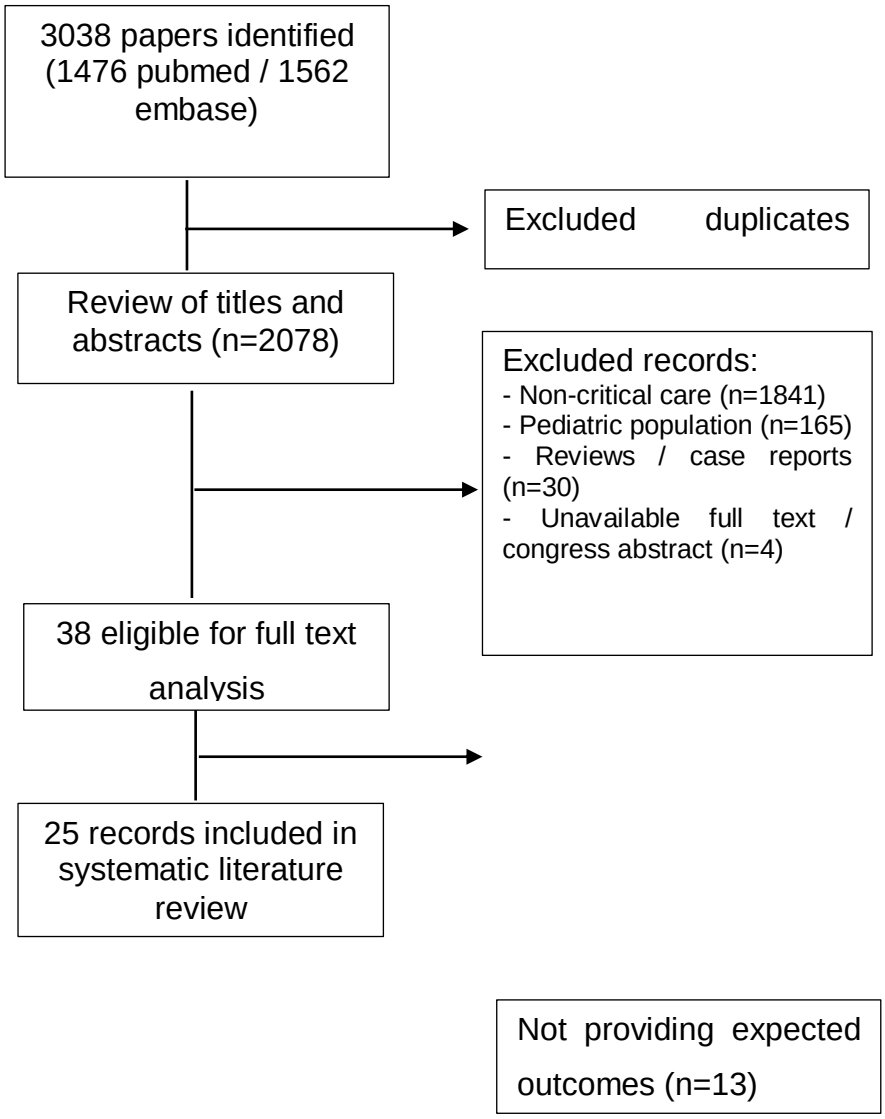


Fig. 1: Flow chart of study selection.

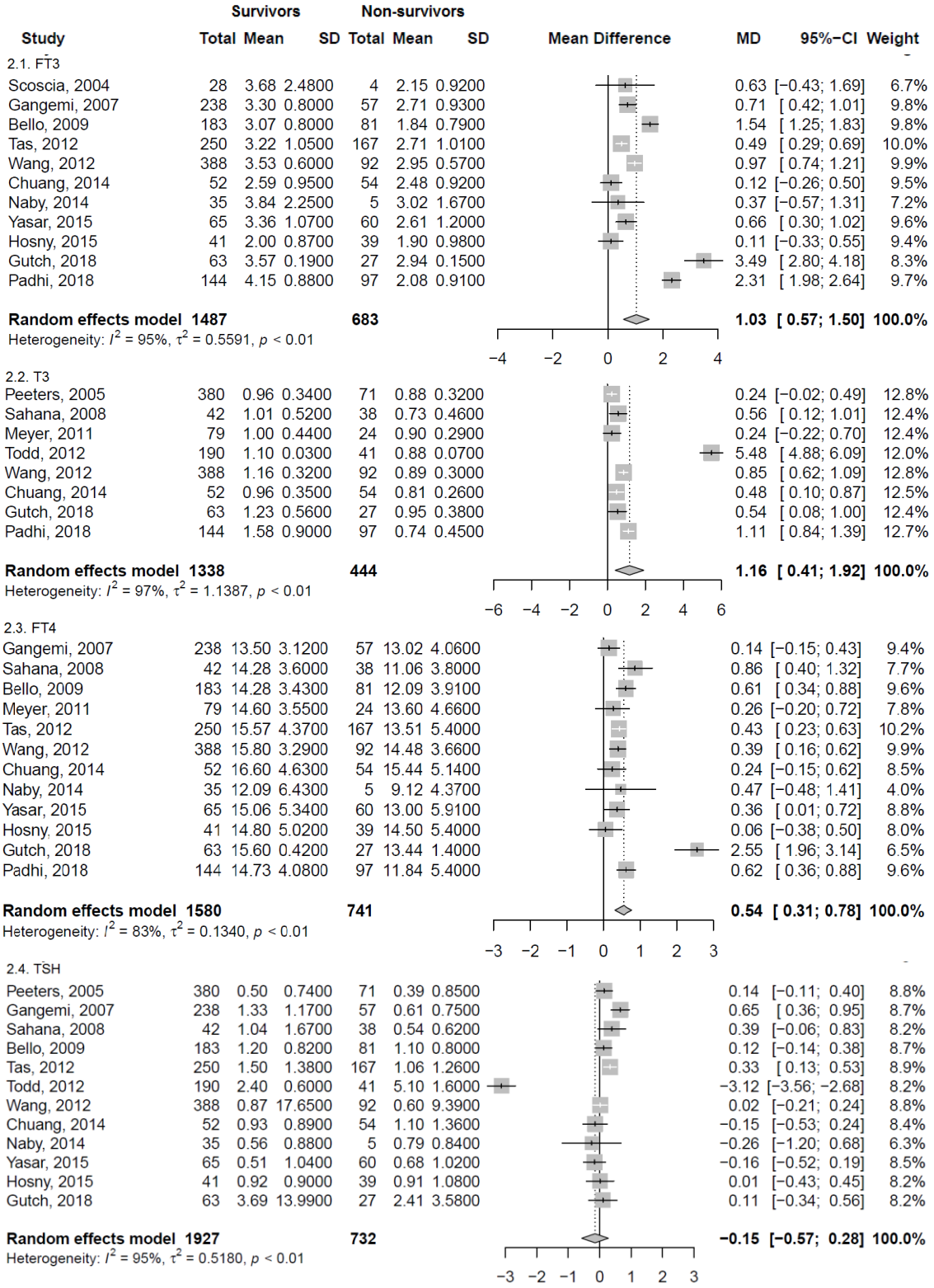


Figure 2: Forest plot of the effect of low thyroid hormone level and mortality.

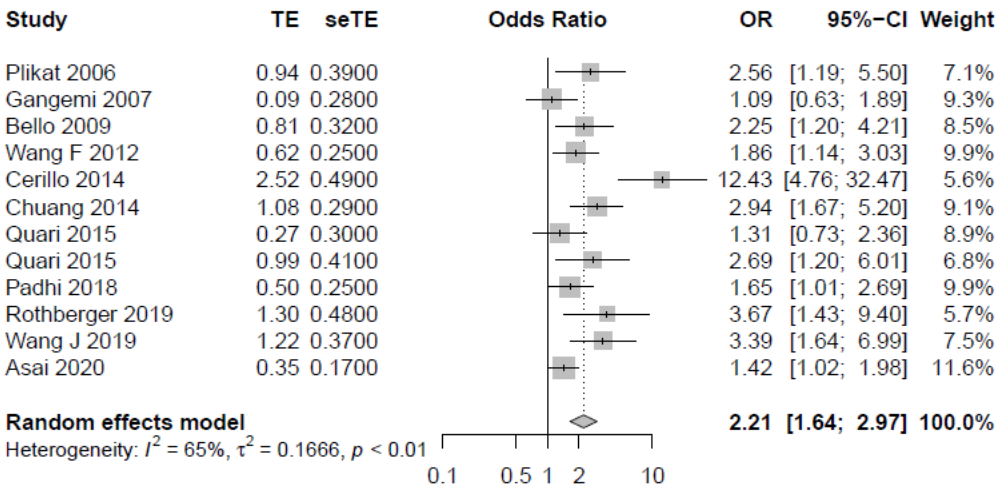


Figure 3: Forest plot of the OR for mortality associated with NTIS

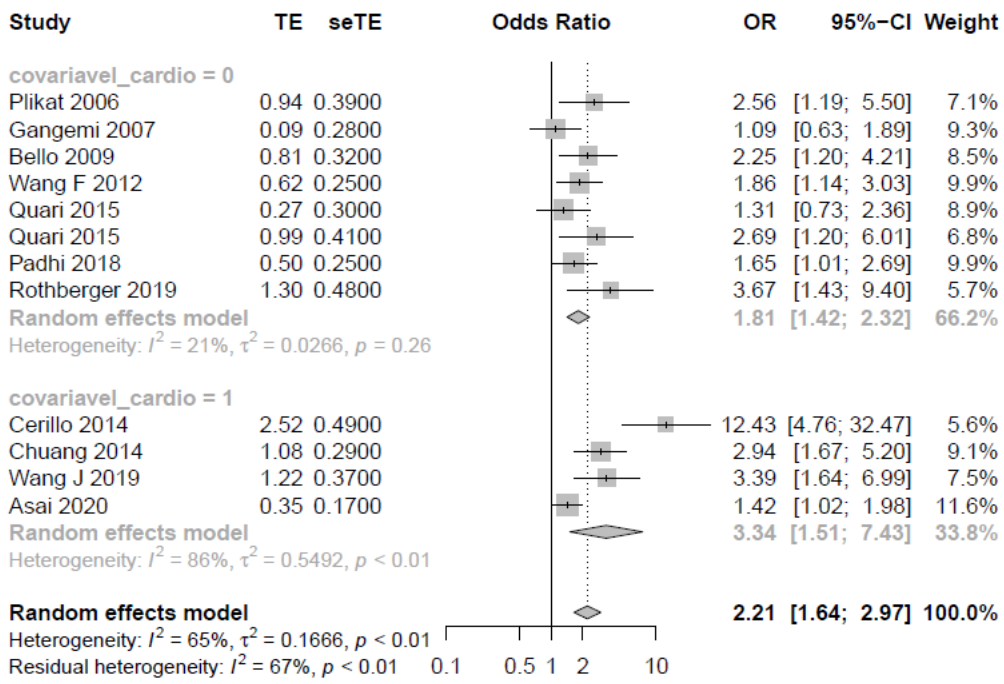


Figure 4: Forest plot of the OR for mortality in a stratified analysis for cause of admission

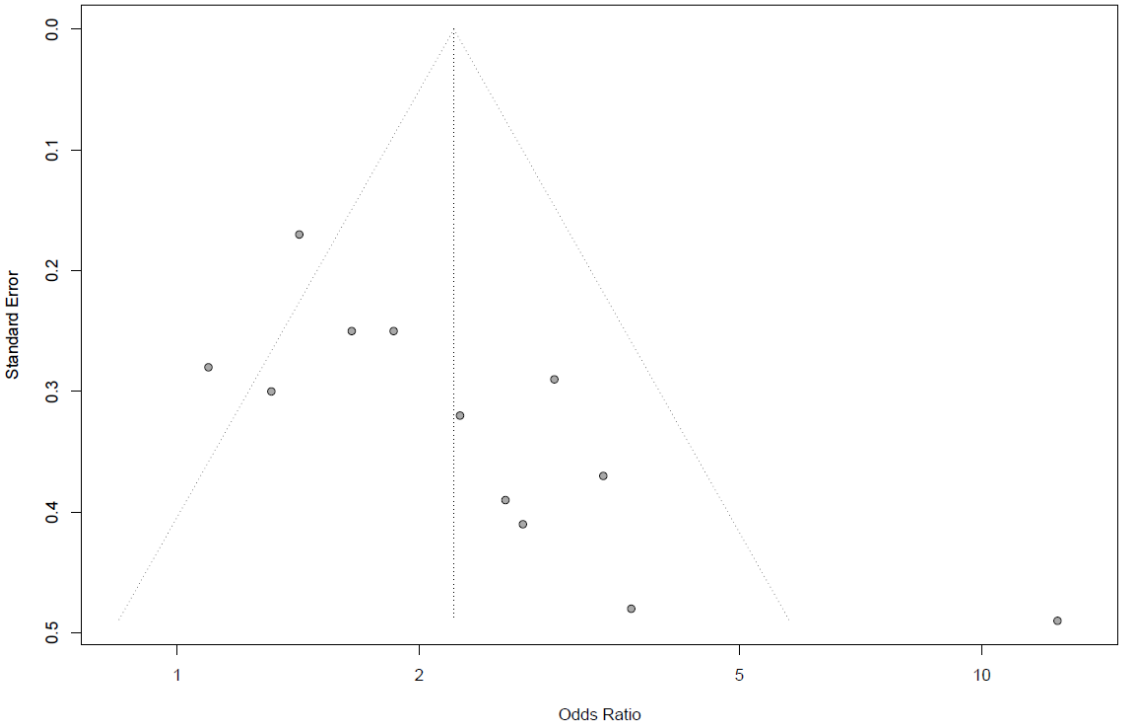


Figure 5: Funnel plot of publication bias

CAPÍTULO 2

LOW T3 LEVELS INDEPENDENTLY PREDICT OUTCOME IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK ADMITTED TO AN INTENSIVE CARE UNIT: A PROSPECTIVE COHORT STUDY

Low T3 levels independently predict outcome in patients with sepsis and septic shock admitted to an intensive care unit: a prospective cohort study

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Short title: T3 levels and outcome prediction in sepsis or septic shock

Keywords: thyroid hormone, Low T3 syndrome, sepsis, septic shock, oxidative stress.

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ABSTRACT

Context: Non thyroidal illesss syndrome occurs frequently in patients with sepsis. The clinical relevance of this association is still under debate.

Objective: To determine the prognostic impact of thyroid hormones levels measured on ICU admission on mortality and on evolution to chronic critical illness.

Design: This was a prospective cohort study performed between October 2017 and April 2019. Patients were followed for 28 days or until death or discharge.

Setting: Intensive care unit of tertiary hospitals in southern Brazil.

Patients: 260 patients with sepsis or septic shock within the first 24 hours of evolution were included. Baseline characteristics and blood samples for thyroid hormones were collected.

Main Outcome Measure(s): association of altered TH levels with 28-day mortality. A secondary measure was evolution to chronic critical illness, defined as length of stay in ICU of >7 day

Results: Low T3 levels were present at admission in 86.5% of patients. Lower levels of T3 yielded an AUC of 0.76 (95% CI, 0.70–0.82) for mortality and of 0.75 (95% CI, 0.68–0.82) for evolution to chronic critical illness, with a better performance than commonly used prognostic scores. The cut-off value of 60 pg/mL for T3 levels had a sensitivity of 81% and specificity of 64% for predicting death, with an odds ratio of 4.89 (95% CI, 2.48–9.66).

Conclusions: Low T3 levels at admission independently predict progression to chronic critical illness and mortality within 28 days in patients with sepsis and septic shock, indicating a potential prognostic role in this setting.

1. INTRODUCTION

Nonthyroidal illness syndrome (NTIS) refers to characteristic changes in thyroid hormone levels that occur in response to systemic illness. The typical changes include low plasma concentrations of triiodothyronine (T3), low or normal thyroxine (T4), and elevated reverse T3 (rT3) in the presence of inadequate normal levels of thyrotropin (TSH) (1), pointing out to a loss of the neuroendocrine feedback mechanism (2). Although these alterations have long been regarded as an adaptative response to minimize catabolism and accelerate recovery during critical illness (3,4), current evidence show mixed results. While some studies indicate that low serum T3 levels are associated with increased mortality (5-10), prolonged weaning from mechanical ventilation (11,12), and reduced cardiac output (13), others failed to show any prognostic implication (14-16).

Proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) appear to play a pivotal role in NTIS (17). The mechanism behind these changes was partially elucidated using a human cell culture system (18), in which the addition of IL-6 lead to the production of reactive oxygen species (ROS) in the cell, compromising deiodinase function and altering the peripheral T3/T4 activation/inactivation process. The use of n-acetylcysteine (NAC), an antioxidant that replenishes glutathione (GSH)/thiols, prevented the inhibitory effect of IL-6 on deiodinase mediated T4 to T3 conversion, indicating that IL-6 inhibits the function of deiodinases by increasing cellular ROS, thereby reducing GSH, or a GSH-like, endogenous cofactor (19). Additionally, derangements of iodothyronine deiodinases function, and proinflammatory cytokines have also been implicated in other steps of the pathogenesis such as impairment of hormonal synthesis, reduction of TH binding proteins and altered hypothalamic-pituitary feedback regulation (17). Among the critically ill, patients with sepsis present with a pronounced increase in the production of pro-inflammatory cytokines

when compared to critically ill patients with other diagnosis of similar severity (20). In this respect, baseline levels of thyroid hormones, including T4, T3, and TSH might be substantially lower in septic patients than in non-septic patients (21), suggesting that cytokines are indeed the predominant mediators of NTIS and are related to severity of disease.

Sepsis is one of the most common indications for ICU admission and, despite improvements in early detection and management, continues to be a major cause of morbidity and mortality worldwide (22,23). Although mortality rate has substantially decreased over the past two decades (24), a significant number of patients with sepsis endure prolonged, complicated ICU stays, becoming chronically critically ill. The term 'Chronic Critical Illness' (CCI) describes patients with a protracted ICU course lasting for more than seven days, who require complex medical care and that become dependent of one or more life support techniques (25, 26). Patients who survive the initial sepsis insult progress to a persistent inflammation, immunosuppression, and catabolism syndrome (PICS). PICS describes ongoing inflammation, manageable organ failure, protein catabolism and poor nutrition leading to cachexia, poor wound healing, and immunosuppression with increased susceptibility to secondary infections. Collectively, these alterations cause functional dependence and poor long-term survival (27, 28).

Multiple scores were developed to assess disease severity and estimate mortality in ICU. Some of the well-established scores are the Charlson comorbidity index (29), which quantifies the burden of chronic diseases; the *Simplified Acute Physiology Score* (*SAPS* III) (30), that evaluates mortality risk; and the *Sequential Organ Failure Assessment score* (SOFA) which measures the extent and severity of organ dysfunction (31). 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 (32-35). Reduced serum

and tissue concentrations of T3 may also be involved in the pathogenesis of persistent organic dysfunction (36, 37), immunosuppression (38), muscular loss (39), and cognitive decline (40).

Since there are similarities in the clinical features of PICS and the metabolic derangements caused by low T3 levels, we aimed to investigate the prevalence of low T3 in a cohort of patients admitted to ICU for sepsis and septic shock and to determine the impact of low T3 on mortality and on evolution to CCI.

2. MATERIALS AND METHODS

2.1. Patients

This is a prospective cohort study performed between October 2017 and April 2019 that recruited 576 consecutive adults admitted to the intensive care unit (ICU) of a tertiary hospital in Southern Brazil. Patients with a diagnosis of sepsis or septic shock within 24 hours of evolution were eligible. Sepsis was defined as organ dysfunction (increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more) caused by a dysregulated host response to infection. Septic shock was defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities occur, being clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate level greater than 2 mmol/L (>18mg/dL) in the absence of hypovolemia (41). Time of presentation was determined through chart review for patients admitted to the ICU from the medical and surgical wards. For patients admitted from the emergency department, the time of presentation was defined as the time of triage. Low T3 was defined as low serum T3 levels with normal/low-normal TSH serum levels (42). Exclusion criteria were the following: 1) age younger than 18 years or older than 80 years; 2) history of primary thyroid disease; 3) pregnancy or immediate postpartum period; 4) imminent death or directive of exclusive palliative care.

The study was designed to enroll 260 patients. On the basis of previous data (43,44) on prevalence of NTIS and local mortality rates for patients with septic shock, the sample size was calculated to provide a statistical power of 90% to detect an absolute difference between the two groups of 20% in mortality (assuming a two sided level .05) using Epitools Epidemiological Calculators (45). Patient selection is shown on Figure 1.

The Institutional Ethics Committees approved the study protocol (CAAE: 64743617.0.0000.5327) and a written informed consent was obtained from all patients or their legally responsible next of kin.

2.2. Measurements

Clinical and demographic characteristics and time of presentation with sepsis or septic shock criteria were collected at ICU admission. Venous blood samples were obtained within the first 24hs. Data related to severity score systems – Charlson comorbidity index, SAPS III and SOFA - were also collected on the first day after ICU admission. Serum total T3, T4, free T4 (FT4), and TSH were measured by electrochemiluminescent immunoassay (ADVIA Centaur XP; Siemens). The interassay coefficients of variation were as follows: T3, 7.1%; T4, 10%; FT4, 7%; and TSH below 6%. The intraassay coefficients of variation were as follows: T3, 6.2%–7%; T4, 3%–8%; FT4, 3%–6%; and TSH, 2.4%–3.9%. Normal ranges were as follows: FT4, 0.93–1.7 ng/dL; T4, 4.6–12 ng/dL; T3, 75–200 ng/dL; and TSH 0.27 – 4.2 mU/L. Sulfhydryl content was measured with the method of Aksenov and Markesbery, where the reduction of 5,5′-dithio-bis (2-nitrobenzoic acid) (DTNB) by thiols generates TNB and is measured at 412 nm. In brief, 30 μL of 0.1 mM DTNB was added to 120 μL of serum. A 30-min incubation followed at room temperature in a dark room. Results were calculated as nmol of TNB/mg of protein.

2.3. Outcome measures

The primary outcome was to evaluate the association of altered TH levels with 28-day mortality. The predefined time endpoint is a consensual measurement in intensive care trials that enables outcome comparison. A secondary measure was evolution to chronic critical illness, defined as length of stay in ICU of >7 days.

2.4. Statistical analysis

Categorical data are presented as frequencies and their differences were analyzed using the χ^2 or Fisher's exact test. Quantitative data with normal distribution are presented as mean ± SD, and their differences were analyzed using the Student's *t* test. Nonparametric variables are presented as median ± interquartile range and analyzed by Mann-Whitney's *U* test. The correlations between variables were determined by Pearson's correlation test. Independent mortality predictors assessment was done by multivariate binary logistic regression. Associated factors ($p < 0.05$ was retention criterion for each factor) from the univariate analysis were included in the multivariable logistic regression analysis. Power of the association between risk factors and outcomes was expressed as odds ratio (OR). In order to set the critical point to predict mortality for T3 levels, receiver operating characteristic (ROC) curve was applied and results are presented as area under the curve (AUC) with sensitivity and specificity. All data were analyzed using Statistical Package for Social Sciences (SPSS) version 23 software (SPSS Inc., Chicago, IL, United States), with significance of $p < 0.05$.

3. RESULTS

3.1. Study population and TH levels at ICU admission

From the 260 patients included, 66.1% presented with septic shock. Pneumonia was the most common cause of sepsis (47%). The mean age was 58.3 ± 14 years, and 56% of the patients

were male. The Charlson comorbidity index was elevated (4.5±2.2) in the entire cohort studied, with a predicted 10-years survival of about 50%. As expected, there were significant differences in the severity scores between survivors and non survivors. NTIS was present on admission in 225 (86.5%) patients. Of these, 100 patients (38.4%) had both T3 and T4 levels below the reference range. T3 mean values were below the normal range in all patients, with statistical difference between those with sepsis and septic shock (65.32 ± 17.5 vs 52.22 ± 15.0, p > 0.001). TSH, T4 and FT4 mean values were within the normal range in all groups. Interestingly, there were no differences in TH levels related to site of infection or origin, with exception of TSH levels, which were significantly higher, but still in the normal range, in patients with healthcare infections when compared to those with community acquired infections (2.77 mcU/L vs 1.82 mcU/L, p < 0.001). Mortality was 14.8% among patients with sepsis and 47.1% on those with septic shock. Baseline characteristics of all patients and survivors and non survivors are displayed on Table 1.

Figure 2 presents mean and median values for TH according to clinical evolution. T3 and T4 levels were associated with worse outcome, while there was no difference in serum TSH levels (p=0.64) between the groups. Figure 3 shows the correlation between T3 and sulphydryl levels in both sepsis (r2=0.6, P<0.0001) and septic shock (r2=0.72, P<0.0001).

3.2. T3 levels at ICU admission were an independent predictor of 28-day mortality and evolution to chronic critical illness

Patients who presented with NTIS at ICU admission had higher mortality rate compared to those with normal TH levels (41.3% vs 2.9%, p< 0.001). Among patients with NTIS, those with low T3 and low T4 levels had the worse outcome when compared to those with only low T3 levels (mortality rate: 55% vs 30%, p< 0.001). There were significant differences between survivors and non-survivors in the univariate analysis in the following variables: age, serum

lactate levels, c reactive protein levels, T3, T4 and FT4 levels, SAPS III, SOFA score and Charlson comorbidity index. Through multivariate analysis, only three variables independently predicted 28-day mortality (Table 2): SAPS III, Charlson comorbidity index and T3 levels at ICU admission. Interestingly, there is no covariance between T3 levels and the severity scores, as evidenced by Pearson correlation score. Lower levels of T3 yielded an AUC of 0.76 (95% CI, 0.70–0.82) (Figure 4). AUC for SAPS III was 0.68 (95% CI, 0.60–0.76) and for Charlson comorbidity index was 0.67 (95% CI, 0.59–0.74). The cut-off value of 60 pg/mL for T3 levels had a sensitivity of 81% and specificity of 64% for predicting death, with an odds ratio of 4.89 (95% CI, 2.48–9.66).

Evolution to CCI was more frequent in patients with NTIS compared to those with normal TH levels (62% vs 23.5%, $p< 0.001$). Among patients with NTIS, there was no significant difference on those with low T3 and low T4 levels compared to those with only low T3 levels (68.4% vs 57.4%, $p= 0.11$) regarding CCI. Only SAPS III and T3 levels independently predicted evolution to chronic critical illness (Table 3). Lower levels of T3 yielded an AUC of 0.75 (95% CI, 0.68–0.82). AUC for SAPS III was 0.62 (95% CI, 0.54–0.70) (Figure 5). The cut-off value of 60 pg/mL had a sensitivity of 72.5% and specificity of 72% for predicting evolution to CCI, with an odds ratio of 2.20 (95% CI, 1.61–3.01).

3.3. Influence of length of stay before ICU admission on prevalence of NTIS and outcome

Almost one-third (31.9%) of the included patients faced a prolonged hospitalization prior to ICU admission. Patients with a hospital length of stay (LOS) greater than 7 days prior to ICU were compared to those with fewer days of evolution regarding TH levels at ICU admission and outcome. No differences was observed in TH levels when patients with hospital LOS > 7 days were compared with those with LOS < 7 days (T3: 55.7 ± 18.4 vs 58.6 ± 17.4 pg/dL, $p = 0.20$; FT4: 1.06 ± 0.36 vs 1.06 ± 0.37 pg/dL, $p = 0.94$; T4: 5.26 ± 2.09 vs 5.61 ±

2.26 pg/dL, p = 0.23; TSH: 2.06 ± 2.17 vs 2.57 ± 2.50 mU/L, p = 0.09). Mortality rate was also comparable between the groups (44.3% vs 43.4%, p = 0.89).

4. DISCUSSION

This study prospectively explores the independent association between low T3 levels and adverse outcomes in patients with sepsis and septic shock admitted to ICU. Our key findings are as follows: 1. low T3 levels were extremely prevalent in this cohort of patients; 2. Patients with low T3 levels at ICU admission were at a higher risk of progression to chronic critical illness and mortality within 28 days. Moreover, the results demonstrated that the levels of T3 alone were independently associated with worse outcomes, with no covariance with other commonly used severity scores; 3. T3 < 60 ng/dL had the best sensitivity and specificity performance to predict mortality and evolution to CCI. 4. TH levels were similarly affected in patients with a long in-hospital stay before ICU admission and in those with acute illness. Nevertheless, T3 levels were associated with severity of disease and were reduced as organ dysfunction ensues.

The prevalence of NTIS in ICU settings varies greatly, been described in the range of 16% to 80% (5, 11, 46-49). In our population, the prevalence of 86.5% of patients with low T3 levels is partly explained by the cohort being composed exclusively by patients with sepsis diagnosis. Sepsis is characterized by the activation of immune pathways in response to infection. This interaction triggers the release of proinflammatory and anti-inflammatory mediators simultaneously, with the intensity of responses depending on multiple factors of both the host and the pathogen. Proinflammatory cytokines cause activation and proliferation of leukocytes, activation of the complement system, upregulation of endothelial adhesion molecules and chemokine expression, tissue factor production, and induction of hepatic acute

phase reactants. The exaggeration of the above immune response results in collateral damage and death of host cells and tissues. Parallel to these findings, sepsis induces multiple defects in immunity, causing protracted inflammation, immune suppression, and susceptibility to infections, leading to chronic deterioration, persistent organ disfunction and increased long-term mortality (50-54).

Patients with sepsis have higher risk to develop alterations in the hypothalamic-pituitary-thyroid (HPT) axis, since increased concentration of circulating pro-inflammatory cytokines are associated with NTIS (55-57). The interaction between the complex network of cytokines and the TH axis probably plays a physiopathological role, even though it is not possible to build a simplistic model. One of the possible paths involves derangements of deiodinase expression and function caused by augmented inflammatory cytokines and oxidative stress. Changes in the intracellular redox state can disrupt deiodinase function by depleting cofactor(s) and impairing reactions which require a reductive intracellular environment. Here we showed that sulfhydryl levels paralleled those of T3 in both groups, suggesting that the consumption of thiol products and oxidation of protein-bound sulfhydryl groups might alter thyroid hormone metabolism in these patients. We can also understand from these results that, as expected, the antioxidant defenses are diminished in these patients. High levels of oxidative stress alter the enzymatic activities of deiodinases type 1 and 2 (D1 and D2), inducing a decrease in D1, which will both reduce plasma T3 production and rT3 clearance; the decrease in D2 will cause impairment of intracellular T4 to T3 conversion. In opposition, D3 activity is oppositely affected, maybe due to its plasma membrane location and access to substrate or cofactor, which causes further decrease in plasma T3 and increase in the inactivation of T4 to rT3 (58). We have recently shown a correlation between sulfhydryl and GSH levels with D3 activity in several tissues under NTIS (59). Moreover, in humans, the administration of the antioxidant NAC that is able to sustain the reduced thiol state of the cysteine protein residues, restored the redox

equilibrium and prevented the derangement in TH concentrations that typically occur, indicating that oxidative stress is involved in the NTIS pathophysiology (60).

Apart from the peripheral changes on TH metabolism in response to infection, regulatory neuroendocrine mechanisms are also involved (61). It has been shown that HPT axis feedback disfunction occurs in prolonged critical illness, with reduced pulsatility of TSH secretion (62). In our study, patients with prolonged in-hospital stay prior to ICU admission did not perform different from those with acute onset disease regarding all TH levels, and most importantly, TSH levels. Data from cellular and animal models suggests that IL1, IL6 and TNF alfa inhibit TSH basal release and decrease hypothalamic TRH mRNA and gene expression (63, 64). Furthermore, cytokines could stimulate the activity of 5'-deiodinase in the anterior pituitary cells in a para-/autocrine manner, locally regulating T3/T4 levels and reducing TSH release (65). The inability to increase TSH secretion in response to low T3 levels that occur early in the course of NTIS may be mediated by cytokines and could be viewed as a marker of neuroendocrine feedback dysfunction.

Some limitations in our study should be considered: a) Patients were from a single center; b) the outcome data were limited to in-hospital events; c) Although patients with prolonged LOS had serial measurements of TH, our study was not statistically powered to evaluate this data; d) rT3 levels were not measured, so NTIS could not be fully characterized.

Nevertheless, our study revealed that low T3 levels alone measured at ICU admission independently predicted evolution to chronic critical illness and death. Contrary to the common belief that TH alterations in the early phase of disease are adaptative and present survival advantage (66), patients with lower T3 levels showed a significantly higher risk of persistent organ disfunction and mortality. Low T3 levels might represent an integrative measure of multiple harmful pathological processes occurring in patients with critical illness, such as inflammation and energetic imbalance, which are associated with adverse outcomes.

5. CONCLUSION

The present study provides evidence for low T3 levels as an independent prognostic factor in patients with sepsis and septic shock, with reduced T3 levels at ICU admission presenting higher risk of evolution to chronic critical illness and death. These results further support the need for clinical trials assessing the effect of therapeutic interventions to counteract the deleterious effects of the lack of T3 on this population.

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Table 1: Baseline characteristics and blood concentration of biomarkers in all patients and comparison by diagnosis at admission to ICU.

	All patients (n=260)	**Sepsis (n=88)**		**p**	**Septic Shock (n=172)**		**p**
		Survivors (n=75)	**Non - Survivors (n=13)**		**Survivors (n=91)**	**Non - Survivors (n=81)**	
Demographic characteristics							
Age, years	58.3±14.7	56.8 ±14.2	56.9 ± 21.3	0.99	56.0 ±15.1	63.4 ± 11.8	0.001
Male sex, %	55.4	69.2	57.3	0.31	51.6	55.6	0.36
Site of infection, %							
Pulmonary	41.1	43.2	38.6	0.01	37.8	43.2	0.5
Abdominal	26.7	17.6	46.2		28.9	29.6	
Urinary tract	10.9	13.5	0		12.2	8.6	
Others	21.3	25.7	15.4		21.1	18.5	
Healthcare-associated infection (%)	42.7	40.0	76.9	0.01	42.9	39.5	0.38
Predictive scoring systems on admission							
SAPS	71.8±17.7	62.7 ±14.2	68.1 ±14.2	0.22	72.9 ±16.8	81.8±18.8	0.003
SOFA	7.8±3.4	5.0 ±2.6	6.0±3.2	0.24	9.0±2.6	10.0±3.1	0.015
CHARLSON	4.5±2.2	3.9±2.3	5.1±1.9	0.11	4.3±2.2	5.6 ±1.9	<0.001
Routine laboratory findings							
Lactate (<2.2 mmol/L)	2.9±2.4	1.8±1.3	2.1±1.6	0.50	2,9±2.1	4,8±3.4	<0.001
C Reactive Protein (mg/L)	201.8±121	183.1±133	216.9±120	0.41	195±109	224±126	0.12
White blood count (x10) ¶	13.6 (8-18.6)	16.3 (11.5-19.7)	13.1 (7.9-16.7)	0.07	15.2 (8.9-23.1)	11.4 (4.7-17.7)	0.8
Thyroid hormones							
NTIS (%)	86.5	70.7	100	0.01	89.8	98.9	0.02
TSH (0,27-4,2 UI/mL)	2.26±2.34	2.1±2.1	2.3±1.8	0.74	2.4±2.4	2.1±2.4	0.44
T4 (4,6-12 ng/dL)	5.4±2.1	6.5±2.1	4.6±0.8	0.001	5.3±1.9	4.6±2.1	0.018
fT4 (0,93-1,7 ng/dL)	1.05±0.35	1.17±0.33	1.01±0.36	0.10	1.05±0.3	0.95±0.4	0.06
T3 (75-200 ng/dL)	56.2±16.9	68.1±17.3	49.7±8.8	<0.001	57.2±16.4	46.6±12.5	<0.001
Outcomes							
LOS, days ¶	4 (3-10)	4 (2-6)	5 (3-12)	0,98	6 (3-14)	4 (2-9)	0.002

Normal range values are shown in the left column. Values are mean and standard deviation, unless otherwise indicated. ¶ values are median and 25-75 interquartile range. *. LOS = length of stay; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment score

Table 2: Predictors of death within 28 days as identified by univariate analysis and multivariate logistic regression.

Univariate			
	Survivors (n = 166)	Non -Survivors (n=94)	p
Age, years	56.3 ±14.6	62.5 ± 13.5	0.001
SAPS	68.3 ±16.5	79.3 ±18.7	<0.001
SOFA	7.2±3.3	9.4±3.3	<0.001
CHARLSON	4.1±2.2	5.4 ±1.9	<0.001
Lactate (<2.2)	2.4±1.9	4.4±3.3	<0.001
C Reactive Protein	190±120	223±125	0.04
T4 (4,6-12 ng/dL)	5.86±2.1	4.55±2.01	<0.001
FT4 (0,93-1,7 ng/dL)	1.12±0.34	0.96±0.37	0.001
T3 (75-200 ng/dL)	62.09±17.64	47.05±12.1	<0.001

Multivariate					
	Estimate	SE	Odds ratio	95% CI	p
Intercept	-.849	.4903	.428	.164 – 1.118	.083
T3	-.038	.0051	.962	.953 - .972	.0001
T3<60	1.58	.34	4.89	2.48-9.66	.0001
SAPS III	.012	.0052	1.012	1.002-1.023	.017
Charlson	.149	.0411	1.161	1.071-1.256	.0001

Table 3: Predictors of evolution to chronic critical illness as identified by univariate analysis and multivariate logistic regression

Univariate					
	Short ICU stay (n = 168)		Chronic critical illness (n=91)		p
SAPS	65.6 ±16.1		72.9 ±17.1		0.003
SOFA	6.6±3.2		8.1±3.3		0.002
Lactate (<2.2)	2.2±1.6		3.0±2.4		0.015
T4 (4,6-12 ng/dL)	6.18±1.8		5.42±2.2		0.011
T3 (75-200 ng/dL)	68.3±16.3		53.5±15.3		<0.001
Multivariate					
	Estimate	SE	Odds ratio	95% CI	p
Intercept	-.008	.3345	.992	.515 – 1.911	.981
T3	-.022	.0042	.978	.970 - .986	.000
T3<60	.79	.16	2.2	1.61-3.01	.000
SAPS III	.008	.0034	1.008	1.002-1.015	.015

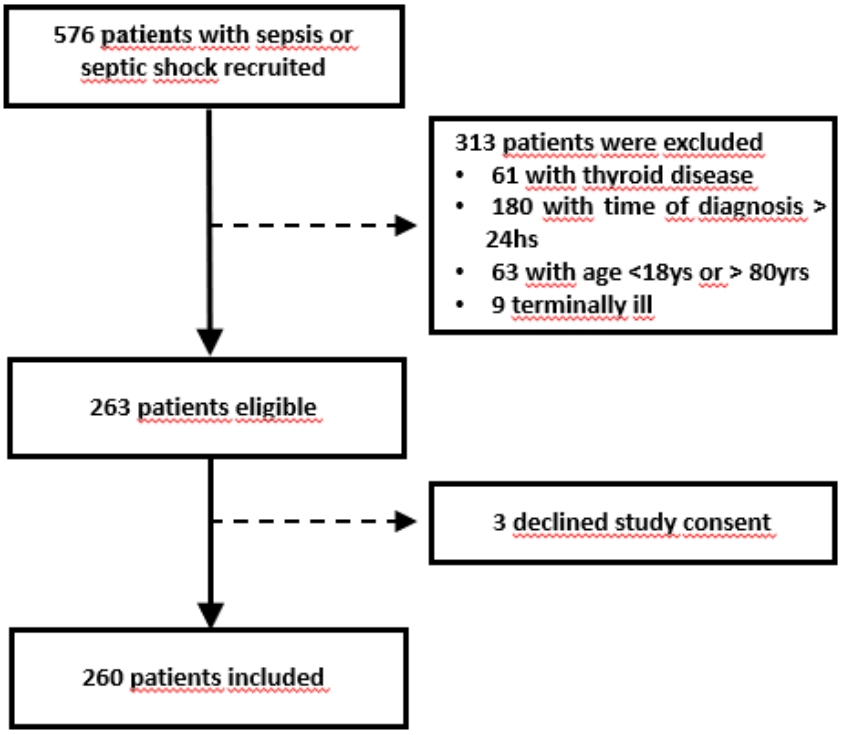


Figure 1.: Patient selection

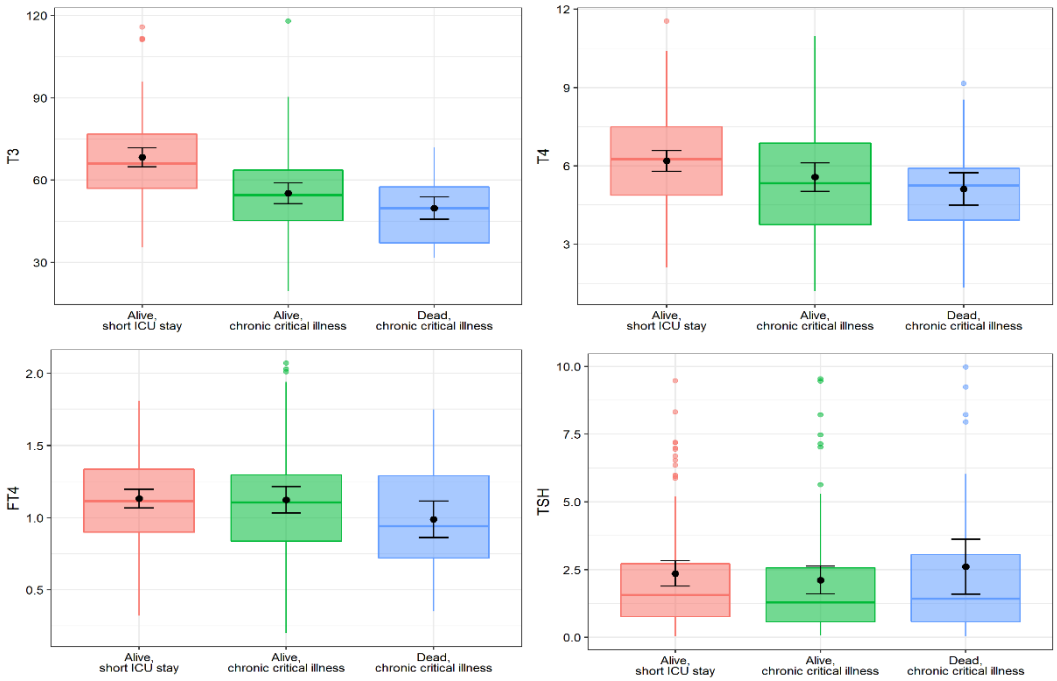


Figure 2: Mean (SD) and median (IQR) values for TH hormones according to clinical evolution

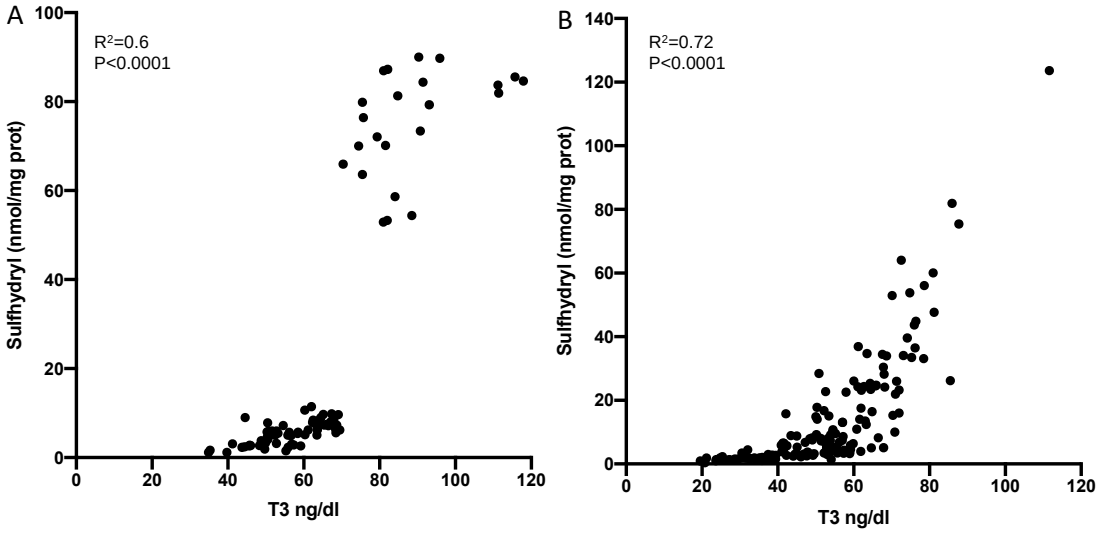


Figure 3: Sulfhydryl levels are correlated with serum T3 in sepsis (A) and septic shock (B) patients.

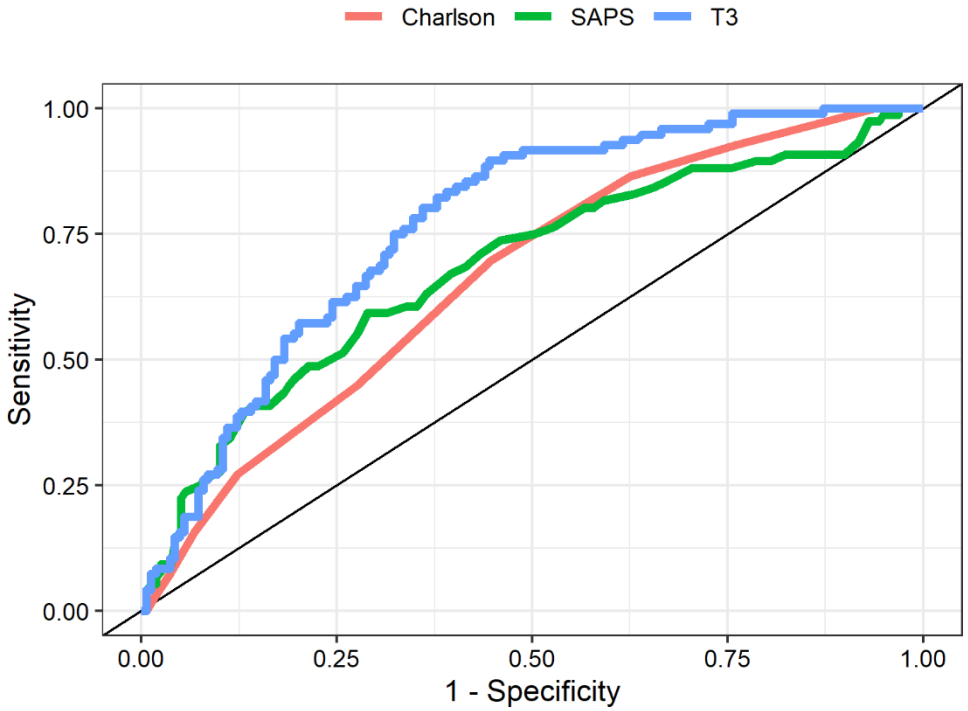


Figure 4: Receiver-operator characteristic curves of T3, to predict 28-day mortality. AUC for lower levels of T3 was 0.76 (95% CI, 0.70–0.82).

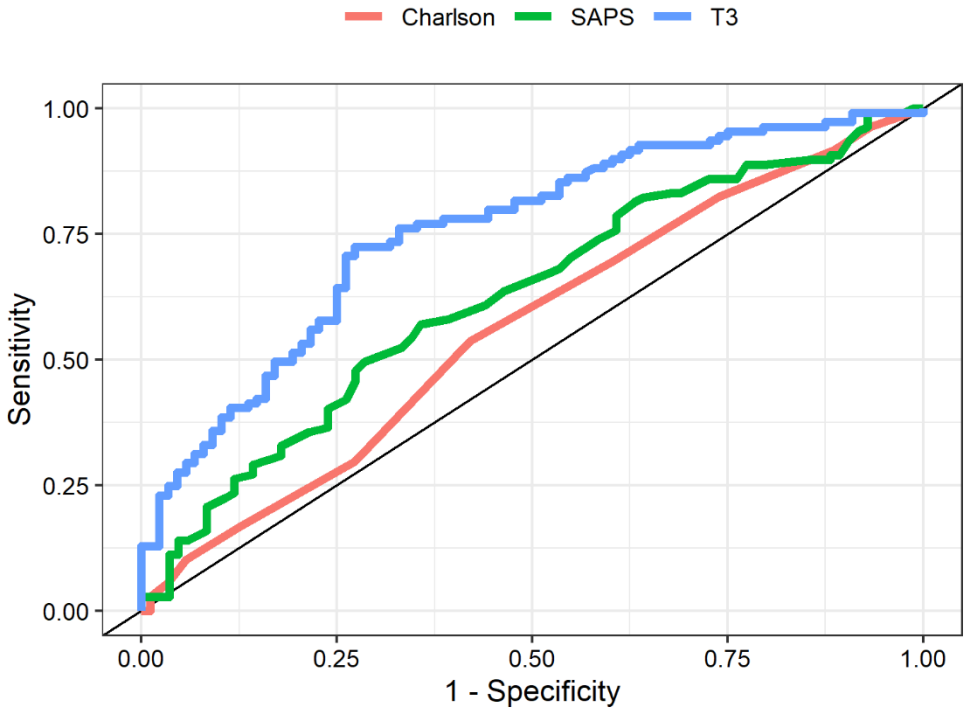


Figure 5: Receiver-operator characteristic curves of T3 to predict Evolution to chronic critical illness. AUC for lower levels of T3 was 0.75 (95% CI, 0.68–0.82).

PERSPECTIVAS

O primeiro artigo dessa tese consiste em uma revisão sistemática sobre a influência prognóstica dos hormônios tireoidianos em pacientes criticamente enfermos. Os resultados sugerem que alterações de T3 e T4 em pacientes críticos estão associados a pior desfecho. No entanto, esse estudo tem limitações relacionadas a qualidade metodológica dos artigos incluídos e, por essa razão, novos estudos com maior controle para possíveis fatores de confusão são necessários.

Já o segundo artigo avaliou o impacto da presença da síndrome do T3 baixo em pacientes com sepse e choque séptico na admissão na UTI. Nesse estudo de coorte, níveis séricos baixos de T3 foram capazes de predizer evolução para doença crítica persistente e mortalidade intra-hospitalar de forma independente de outros escores de risco. Este resultado traz maior segurança para realização de futuros estudos que avaliem a possibilidade de tratamento da síndrome do T3 baixo em pacientes críticos. Até o presente momento, a crença de que a síndrome poderia representar uma resposta adaptativa desestimulou tentativas de tratamento.

Com o objetivo de esclarecer os mecanismos fisiopatogênicos da síndrome em suas diferentes fases, temos ainda dois projetos em andamento. O primeiro consiste em análise de marcadores inflamatórios e de estresse oxidativo na coorte de pacientes com sepse e sua correlação com a função tireoidiana. O segundo projeto avaliará a atividade das desiodases em pacientes com tempo de internação prolongada e como os hormônios da tireoide afetam o status funcional e o desfecho desse grupo.

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