Association between thyroid function tests at baseline and the outcome of patients with sepsis or septic shock: a systematic review

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Short title: Thyroid function and sepsis outcome
Conflict of interest: None
Funding: None
Word counts: abstract 248, text 2648
Number of tables: 2
Number of figures: 1
Number of references: 47
ABSTRACT

Introduction. The severity of critical illness is associated with various patterns of thyroid hormone abnormalities. We sought to evaluate whether the outcome of patients with, specifically, sepsis or septic shock is associated with the thyroid function tests obtained at diagnosis or admission in the intensive care unit (ICU).

Methods. We performed a systematic review of relevant studies by searching PubMed.

Results. We included 9 studies, that all had a prospective cohort design. Seven involved children or neonates and 2 involved adults. Mortality was the outcome evaluated in 8 studies, while the length of ICU stay was evaluated in the remaining study. In univariate analysis, 6 of the 9 included studies showed that, either the free or total, triiodothyronine or thyroxine were lower in the group of patients with sepsis or septic shock who had unfavorable outcome compared with those who had favorable outcome. Two other studies showed higher thyroid-stimulating hormone values in the group of patients with unfavorable outcome. No significant relevant findings were noted in the remaining study. Regarding the correlation of sepsis prognostic scoring systems with thyroid function tests, the 3 studies that provided specific relevant data showed variable findings.

Discussion. Most of the relevant studies identified favor the concept that decreased thyroid function at baseline might be associated with a worse outcome in patients with sepsis or septic shock. Although these findings are not consistent, the role of thyroid function in affecting or merely predicting the outcome of sepsis or septic shock merits further investigation.

Keywords: euthyroid sick syndrome, hypothyroidism, infection, mortality, thyroid function tests, systemic inflammatory response syndrome
INTRODUCTION

Thyroid hormones play an important role in the adaptation of metabolic function to stress and critical illness. In hospitalized patients, thyroid hormone alterations are very common, particularly in those of increased age, or critical illness. Low triiodothyronine (T3) is commonly observed in the latter group of patients, which can be attributed to increased deiodination of thyroxine (T4) to reverse triiodothyronine T3 (rT3), rather than triiodothyronine (T3), and increased catabolism of T3 to 3,3-diiodothyronine (T2). With increasing severity of illness, low total and free thyroxine (T4), and sometimes low thyroid-stimulating hormone (TSH) can be observed. Decrease in plasma thyroxine-binding globulin (TBG) or transthyretin as well as accumulation of substances that lower the plasma thyroid-hormone binding capacity appear also to be important for the above-mentioned alterations in thyroid hormone levels during critical illness.

For the vast majority of patients, thyroid function abnormalities observed during critical illness are transient and do not represent an underlying thyroid disease. Still, certain data suggest that the magnitude of thyroid hormone alterations in patients admitted in the intensive care unit due to various causes is associated adversely with the patient outcome. In this review, we sought to evaluate systematically the association between baseline thyroid function and the outcome of patients with, specifically, sepsis or septic shock.

METHODS

Data sources
To identify studies eligible for inclusion in this review we searched in PubMed, at February 1, 2009, applying the following combined search term: (thyroid disease OR thyroid OR hypothyroidism OR hyperthyroidism OR TSH OR thyroxine OR triiodothyronine OR thyroid hormones) AND (infection OR sepsis OR bacteremia OR pneumonia OR nosocomial infection OR septic shock). The bibliographies of relevant articles were also hand-searched. We performed an updated PubMed search in October 1, 2010.

Study selection criteria
We selected for inclusion in our review case-control or cohort studies (either prospective or retrospective), or clinical trials that provided data on the association between thyroid hormones at baseline and the outcome of patients of any age with sepsis or septic shock. We considered as baseline thyroid function tests those referring to the time of diagnosis of sepsis or the time of
admission in the intensive care unit (ICU). We specifically evaluated English, French, German, Italian, and Spanish language articles.

**Data extraction**

Data extracted from each of the included studies were those referring to the study design, the characteristics of the study population and the subgroups of patients compared, the baseline values of thyroid hormones and their statistical association with the patient outcome through univariate or multivariate analysis, where reported. We also extracted data on the correlation of the thyroid hormones at baseline with sepsis prognostic scores.

**RESULTS**

**Characteristics of the included studies**

From the literature searches we performed in PubMed we retrieved a total of 3633 articles. After first screening based on the title and the abstract, we selected 202 articles for further detailed evaluation, after which, we identified 9 studies as eligible for inclusion in this review.\(^{12-19}\) The process of selecting articles for inclusion in this review is depicted graphically in Figure 1. All of the 9 included studies had a prospective cohort design. Five of the studies involved children,\(^ {1,13-15,17}\) two additional studies involved exclusively neonates,\(^ {12,16}\) and the remaining 2 studies involved adults.\(^ {18,19}\) Mortality was the outcome evaluated in 8 of the studies,\(^ {1,12-19}\) while in the remaining study the outcome evaluated was the length of stay in the pediatric intensive care (PICU).\(^ {13}\) In 6 of the included studies, it was specifically reported that the blood samples for thyroid hormone measurements were taken before administration of dopamine.\(^ {1,12-16,19}\)

**Association of thyroid hormones at baseline with outcome**

In Table 1, we present data on the association between serum thyroid hormone levels at baseline and the outcome of patients with sepsis or septic shock. Specifically, 6 of the 9 studies included in this review showed, by univariate analysis, that among patients with sepsis or septic shock those with an unfavorable outcome had lower baseline serum levels of, either total or free, T\(_3\) or T\(_4\), compared with those with a favorable outcome.\(^ {12-16,19}\) In two other studies that involved children and adults, respectively, who in both studies were admitted in the ICU with septic shock, there was no difference in baseline T\(_3\) or T\(_4\) between non-survivors and survivors.\(^ {1,18}\) In the remaining study, which evaluated children with meningococcal sepsis admitted in the PICU, those who did not survive had
higher baseline serum levels of T₃ compared with those who survived, while no difference was detected in the total and free T₄ levels.¹⁷ In this study, non-survivors had also higher baseline levels of TSH.

Higher baseline TSH values in non-survivors were also observed in another one of the included studies, which evaluated children with septic shock admitted in the PICU. This study did not demonstrate differences in the levels of T₃ or T₄ between non-survivors and survivors.¹ On the contrary, lower baseline TSH was associated with higher mortality in a study that evaluated septic neonates admitted in the ICU;¹² this was also accompanied with lower T₃ and T₄. Regarding the baseline TSH levels in the remaining 6 studies, they did not differ between patients with an unfavorable outcome compared with those with a favorable outcome. In addition, a lower rT₃ value and a higher T₃/rT₃ ratio was associated with an adverse outcome in 2 studies,¹⁴,¹⁷ whereas non-significant findings were observed in the other two studies that assessed the same parameters.¹³,¹⁹

Three of the included studies evaluated further the above-described associations in multivariate analysis. One of these studies showed that in pediatric patients who survived meningococcal septic shock, lower baseline serum T₄ was an independent predictor of an unfavorable outcome, specifically prolonged ICU stay.¹³ The baseline IL-6 level was also independently associated with this outcome. The length of ICU stay was estimated to increase by 15% for every doubling of the IL-6 concentration and 16% for every 10 nmol/l decrease in the T₄ level.¹³ The second study that included pediatric ICU patients with meningococcal sepsis or septic shock showed that the effect of the thyroid function tests on mortality lost significance in the multivariate analysis and that IL-6 was the only independent predictor of this outcome.¹⁴ In the remaining study, which was performed on newborns admitted in the ICU with bacterial sepsis, the presence of euthyroid sick syndrome was independently associated with mortality.¹²

In table 2, we present data on the correlation of thyroid function tests at baseline with various sepsis prognostic scores. Such associations were reported in 3 of the 9 included studies, which all evaluated children with meningococcal sepsis or septic shock admitted in the PICU.¹³,¹⁴,¹⁷ In one of these studies, both the pediatric risk of mortality (PRISM) score and the sequential organ failure assessment (SOFA) score had a moderate negative correlation with the baseline T₄ value.¹⁴ In another study, the PRISM score had a rather weak positive correlation with baseline TSH.¹⁷ In the remaining study, no significant relevant associations were noted.¹³
DISCUSSION

The majority (6 out of 9) of the evaluated relevant studies showed that lower baseline thyroid hormone values, either T₃ or T₄, are associated with worse outcome in patients with sepsis or septic shock. The above observations apply mainly to children rather than adults, as the latter group was evaluated in only two of the included studies. Still, definitive conclusions on the above issue cannot be drawn on the basis of the herein available data, as the associations observed were not always consistent between the included studies, or within each study with regard to different thyroid function tests evaluated. Moreover, the association of thyroid hormones at baseline and the outcome in sepsis or septic shock was not commonly evaluated in appropriate multivariate models to adjust for the effect of potential confounders.

It is interesting that one of the included studies showed that, among the 26 children with meningococcal sepsis studied, the 18 who survived had lower T₃ levels at PICU admission compared with the 8 who did not survive. This finding stands in contrary with the rest of the included studies, that either showed the opposite or none relevant association. One potential explanation for the discordant findings of the study in regard is that 10 of the survivors received treatment with dopamine, whereas the non-survivors received norepinephrine or dobutamine. Dopamine can suppress the pituitary release of TSH and thus potentially the production of T₃ while norepinephrine is believed to stimulate the secretion of TSH. Notably, the non-survivors in this study also had higher TSH levels. Yet, it was not specifically stated whether dopamine administration preceded the collection of blood samples for the thyroid hormone measurements. However, in the great majority of the remaining studies thyroid hormone measurements were performed prior to dopamine use.

In addition, in the study in regard in which higher T₃ levels were observed in non-survivors of meningococcal septic shock, the age of the non-survivors was significantly lower than that of the survivors (10 vs. 29 months, respectively). The changes that occur in thyroid hormone levels during the first months of life could, at least in part, account for the differences in the T₃ levels observed in this study. Specifically, in neonates the plasma thyroid hormone levels are typically elevated compared with older children. This is related to the TSH surge that occurs in the immediate postnatal period and to the elevated TBG levels secondary to maternal estrogen. In normal term neonates, the total and free T₄ levels fall gradually over the next 4 to 6 weeks, but
remain higher than in older children and adults for a few months. The T₃ levels gradually reach those of infancy, between 2 and 12 weeks of life. In early neonatal life there has also been observed increased activity of type III deiodinase (D3) enzyme with secondary increase in rT₃ levels and increase in the degradation of T₃ to T₂, which reaches the adult range during the fourth postnatal month.

It is questionable whether the findings of our review can be applicable to adult patients with sepsis or septic shock, who were evaluated in only 2 of the included studies. Relevant data suggest that children have different hemodynamic responses to critical illness and septic shock. Children more commonly suffer from progressive cardiac failure compared with adults and can respond to inotropic therapy. Mortality in pediatric septic shock is usually lower than in adults.

It is generally accepted that the alterations in thyroid hormones observed during critical illness constitute part of an adaptive metabolic response. This is based on the finding that the great majority of patients recover normal thyroid function after the critical illness subsides. It has also been suggested that the decrease in metabolic function observed during the systemic inflammatory response syndrome and the accompanying multi-organ dysfunction may help protect cell-survival. Still, thyroid disorders are relatively common in the general population, with an estimated prevalence of 1–10%. The presence of even subclinical abnormalities might be important, as subclinical hypothyroidism has been linked to excess mortality in certain patient groups. Some studies have also found that a subset of patients with critical illness can have true hypothyroidism. High TSH or reduced rT₃ can be suggestive of such a diagnosis. Thus, the findings of some of the studies included in our review that higher TSH, lower rT₃, or lower T₃ and T₄ are associated with an unfavorable outcome of patients with sepsis or septic shock could imply that, at least for a minority of these patients, thyroid hypofunction during sepsis or septic shock might influence per se the outcome of this condition. This hypothesis merits further evaluation in appropriately designed studies.

Some studies performed in animal models of sepsis or septic shock support the hypothesis that relative thyroid insufficiency is associated with a worse outcome. For example, lower baseline serum thyroxine and free thyroxine have been associated with decreased likelihood for survival in severely-ill dogs (puppies) with paroviral diarrhea. In an experimental sepsis model in rats, those previously thyroidectomized showed abolishment of the hyperdynamic response that physiologically
accompanies early stage sepsis. The administration of thyroxine reversed the decrease in survival observed in the thyroidectomized animals.\textsuperscript{32}

Another experimental study in rats showed that thyroid hormone supplementation during sepsis can increase survival.\textsuperscript{33} A particular beneficial effect of thyroid hormone administration in rats with experimentally induced sepsis has been documented on lung mechanics and histology, which was mainly attributed to enhanced synthesis of surfactant.\textsuperscript{34,35} Still, other studies on experimentally induced sepsis have failed to show a benefit of thyroid hormone replacement.\textsuperscript{7,32,36} In humans, there is little evidence regarding thyroid hormone substitution during critical illness. Of note, some relevant clinical studies have suggested that T\textsubscript{4} supplementation can lead to reduction of the needs for vasoactive drug administration in circulatory shock.\textsuperscript{37}

Thyroid hormone supplementation during sepsis or septic shock can lead to a reciprocal decrease in TSH. This issue needs particular attention as there appears to be a rather complex pathophysiological interplay between TSH and the immune system. Specifically, TSH has been shown to affect the function of various types of hematopoietic and immune system cells that express the TSH-receptor.\textsuperscript{38,39} Such cells mainly include subsets of hematopoietic cells in the bone marrow, as well as peripheral monocytes, dendritic cells, and T-lymphocytes. Furthermore, some of the above cell types can produce biologically-active TSH that can have autocrine and paracrine actions which can influence the early stages of the immune response to an antigen.\textsuperscript{38,39} These actions can include the regulation of the synthesis and release of mediators of inflammation, such as IL-6 and TNF-\textalpha. Various immune system cells have also been found to express T\textsubscript{3}, a process that is under the influence of TSH.\textsuperscript{40} It has thus been hypothesized that the immune system cells can affect the systemic thyroid hormone activity.

It is debatable whether the data included in our review regarding the association between thyroid function and sepsis or septic shock can be extrapolated to other types of critical illness. Several inflammatory cytokines, such as interleukin 1-beta, interleukin-6, and tumor necrosis factor-alpha (TNF-a) can suppress, via direct or indirect pathways, the thyroid function at different levels.\textsuperscript{41,42} In sepsis the increase in the production of pro-inflammatory cytokines is more pronounced compared with other types of critical illness.\textsuperscript{43,44} In this respect, baseline levels of thyroid hormones, including T\textsubscript{4}, T\textsubscript{3}, and TSH, can be substantially lower in septic patients compared to non-septic patients with critical illness of similar severity.\textsuperscript{45} The degree of endothelial activation and dysfunction can also be
greater in sepsis compared with other types of critical illness, as reflected by higher levels of E-selectin, intercellular adhesion molecule-1 (ICAM-1) and von Willebrand factor activity that have been observed in some studies.\(^{(43, 44, 46)}\)

The findings of our review regarding the association between thyroid hormone abnormalities and the outcome of patients with sepsis or septic shock indicate that these abnormalities could be of prognostic value. In the studies included in our review, the association between established sepsis prognostic systems and baseline thyroid hormones was at the most moderate. Thus, the prognostic value of thyroid hormones may be independent of other prognostic markers. Likewise, other studies performed in critically ill patients have shown that taking into consideration the baseline thyroid function tests can add to the predictive capacity of the APACHE score.\(^{11, 47}\)

In conclusion, the majority of the identified studies that evaluated the baseline thyroid function tests in patients with sepsis or septic shock provide data that favor the existence of an association between lower T\(_3\) or T\(_4\) and worse outcome. Since thyroid hormone abnormalities are very common in septic patients, future studies should aim to more clearly establish the strength of above association or even examine whether a causal relationship between thyroid hypofunction and adverse outcome exists. The role of the thyroid hormone abnormalities as predictors of outcome in septic patients on top of the known risk prognostic scoring systems warrants also further evaluation.

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

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements: None
REFERENCES


9. 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. *J Clin Endocrinol Metab* 2005 90 4559-4565.


21. Fukuda S. Correlations between function of pituitary-thyroid axis and metabolism of catecholamines by the fetus at delivery. Clin Endocrinol 1987 27 331-338


36. Little JS. Effect of thyroid hormone supplementation on survival after bacterial infection. *Endocrinology* 1985 **117** 1431-1435.


39. Klein JR. Physiological relevance of thyroid stimulating hormone and thyroid stimulating hormone receptor in tissues other than the thyroid. *Autoimmunity* 2003 **36** 417-421.


<table>
<thead>
<tr>
<th>Ist Author, publication year</th>
<th>Study design</th>
<th>Characteristics of whole study population</th>
<th>Compared groups of patients (unfavorable vs. favorable outcome), Number</th>
<th>Age in yrs, median (range) or mean±SD</th>
<th>Sex (males/total)</th>
<th>Thyroid hormone levels, units (format)</th>
<th>Values of thyroid hormones in the compared groups</th>
<th>Comparison in univariate analysis</th>
<th>Significance</th>
<th>Variables entered in the model</th>
<th>Independent predictor variables</th>
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<tr>
<td>Kurt A. et al, 2010 [12]</td>
<td>Prospective case-control study</td>
<td>Cases: 143 newborns admitted in PICU with sepsis due to <em>Staphylococcus aureus</em>, <em>Streptococcus pneumoniae</em>, <em>Escherichia coli</em>, <em>Klebsiella pneumoniae</em>, <em>Pseudomonas aeruginosa</em>, <em>Klebsiella oxytoca</em></td>
<td>Sepsis non survivors vs. sepsis survivors, 20 vs.123</td>
<td>All were term– or preterm– neonates</td>
<td>72/143</td>
<td>T₃, ng/dl [mean±SD]</td>
<td>112.8±51.0</td>
<td>172.2±61.5</td>
<td>p&lt;0.001</td>
<td>Euthyroid sick syndrome</td>
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<td>T₄, ng/dl [mean±SD]</td>
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<td>7.1±2.3</td>
<td>P&lt;0.01</td>
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<td>2.2±1.4</td>
<td>4.1±2.1</td>
<td>P&lt;0.01</td>
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<td>Lodha R. et al, 2006 [1]</td>
<td>Prospective cohort study</td>
<td>24 children admitted in PICU with septic shock due to pulmonary, CNS, or GI infections due to bacteremia by <em>Escherichia coli</em>, or <em>Streptococcus pneumoniae</em>, or <em>Staphylococcus aureus</em></td>
<td>Non-survivors vs. survivors, 12 vs. 12</td>
<td>3</td>
<td>13/24</td>
<td>T₃, ng/dl [median (95% CI)]</td>
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<td>fT₃, pg/ml [median (95% CI)]</td>
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<td>fT₄, ng/dl [median (95% CI)]</td>
<td>0.77 (0.57-0.95)</td>
<td>NS</td>
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<td>den Brinker M. et al, 2005 [13]</td>
<td>Prospective cohort study</td>
<td>44 children in PICU who survived from Patients with long vs. short PICU stay,²</td>
<td>2.5 (0.1-15.7) vs. 5 (0.3-15.7)</td>
<td>6/11 vs.21/33</td>
<td>T₃, nmol/l [geometric mean±SE]</td>
<td>0.24 (0.20-0.28)</td>
<td>0.38 (0.36-0.40)</td>
<td>p=0.022 (r = -0.35)</td>
<td>NS</td>
<td>Dopamine administration, T4 on</td>
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<td>T₄, µmol/l [median (95% CI)]</td>
<td>1.21 (0.27-2.96)</td>
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<td>den Brinker M. et al, 2005 [14]</td>
<td>Prospective cohort study</td>
<td>45 children admitted to PICU with meningococcal sepsis or septic shock</td>
<td>Non-survivors vs. survivors and sepsis survivors, 8 vs. 30 and 7</td>
<td>T₄, nmol/l [median (IQR)] 0.49 (0.34-0.61) 0.40 (0.30-0.52) and 0.45 (0.42-0.61) 56 (49-73) and 86 (68-92) 18 (15-20) and 19 (14-20) 0.71 (0.33-0.80) 0.88 (0.52-1.14) 9 (6-10) T₃, nmol/l [median (IQR)] 0.58±0.16 1.00±0.16 p&lt;0.001</td>
<td>T4, T3, T3/rT3, TSH, TBG, age, gender, time to first petechia, IL-6</td>
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<p>| Yildizdas D. et al, 2005 [14] | Prospective cohort study | 72 children admitted to the non-survivors vs. sepsis cases: 35/72 | T₃, nmol/l [mean±SD] 0.58±0.16 1.00±0.16 p&lt;0.001 | NA |</p>
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<th>Year</th>
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<td>2004 [15]</td>
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<td>PICU with sepsis or septic shock due to bacteremia by <em>Pseudomonas aeruginosa</em>, <em>Klebsiella pneumoniae</em>, <em>Staphylococcus aureus</em>, or <em>Escherichia coli</em></td>
<td>T&lt;sub&gt;4&lt;/sub&gt;, nmol/l</td>
<td>64.5±15.8 105.78±19.35 p&lt;0.001 NA</td>
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<td>12.77±3.22 20.64±3.48 p&lt;0.001 NA</td>
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<td>49 neonates with sepsis (documented bacteremia in 11 and meningitis in 8)</td>
<td>Non-Survivors vs. Survivors</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;, ng/dl</td>
<td>0.73±0.03 ND</td>
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<td>T&lt;sub&gt;4&lt;/sub&gt;, µg/dl [mean±SD]</td>
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<td>9.0±13.4 9.6±10.5 NS NA</td>
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<td>Joosten K.F. et al, 2000 [17]</td>
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<td>26 children admitted to PICU with sepsis due to bacteremia by <em>Neisseria meningitidis</em></td>
<td>Non-survivors vs. survivors</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;, ng/dl</td>
<td>16/26 0.83 vs. 2.4 (p&lt;0.05)</td>
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<td>14 (13-21) 16 (15-19) NS NA</td>
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<td>rT&lt;sub&gt;3&lt;/sub&gt;, nmol/l [median (IQR)]</td>
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<td>rT&lt;sub&gt;4&lt;/sub&gt;, pmol/l [median (IQR)]</td>
<td>0.75 (0.55-0.97) 1.44 (0.99-1.85) p&lt;0.01 NA</td>
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<td>T&lt;sub&gt;3&lt;/sub&gt;/rT&lt;sub&gt;3&lt;/sub&gt; [median (IQR)]</td>
<td>0.76 (0.64-0.85) 0.43 (0.17-0.35) p&lt;0.01 NA</td>
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<td>TSH, mE/l [median (IQR)]</td>
<td>0.97 (0.52-1.56) 0.29 (0.15-0.54) p&lt;0.01 NA</td>
</tr>
<tr>
<td>Leon-Sanz M. et al, 1997 [18]</td>
<td>Prospective cohort study</td>
<td>27 adults admitted in the ICU with septic shock due to pneumonia, peritonitis, urinary tract infection, or bacteremia</td>
<td>Non-survivors vs. survivors</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;, ng/ml [mean±SD]</td>
<td>50±19 18/27 0.038±0.19 0.038±0.16 NS NA</td>
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<td>T&lt;sub&gt;4&lt;/sub&gt;, ng/ml [mean±SD]</td>
<td>46.1±19.7 44.6±9.7 NS NA</td>
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<td>TSH, µIU/ml [mean±SD]</td>
<td>0.44±0.61 0.79±0.68 p=0.18 (NS) NA</td>
</tr>
<tr>
<td>Mangas-Rojas A. et al, 1997 [19]</td>
<td>Prospective cohort study</td>
<td>37 adults with sepsis</td>
<td>Non-survivors vs. survivors</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;, ng/dl [mean±SD]</td>
<td>57.6±17.8 37/37 30.40±13.40 52.5±19.60 p&lt;0.001 NA</td>
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<td>T&lt;sub&gt;4&lt;/sub&gt;, µg/dl [mean±SD]</td>
<td>4.6±3.1 7.3±4.0 p&lt;0.01 NA</td>
</tr>
</tbody>
</table>
al, 1990 study survivors, 15 vs. 22

<table>
<thead>
<tr>
<th></th>
<th>T₄, µg/dl [mean±SD]</th>
<th>TSH, µIU/ml [mean±SD]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>5.50±1.70</td>
<td>1.85±0.81</td>
</tr>
<tr>
<td>fT₄I</td>
<td>3.47±0.89</td>
<td>41.20±18.20</td>
</tr>
<tr>
<td>rT₃</td>
<td>4.53±1.79</td>
<td>40.80±12.90</td>
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<tr>
<td></td>
<td>p&lt;0.05</td>
<td>NS</td>
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<td></td>
<td>NA</td>
<td>NA</td>
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<tr>
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<td>7.20±2.80</td>
<td>1.86±0.68</td>
</tr>
</tbody>
</table>

(P)ICU: (pediatric) intensive care unit, CNS: central nervous system, GI: gastrointestinal tract, yrs: years, (f/r)T₃: (free/reverse) triiodothyronine, (f)T₄(I): (free) thyroxine (index), TSH: thyroid stimulating hormone, TBG: thyroxine-binding globulin, IQR: interquartile range, CI: confidence interval, SD: standard deviation, SE: standard error, NS: non-significant, NA: non-available, NEFA: non-esterified fatty acid level in the albumin fraction of blood serum

1. Values for the whole study population
2. Short PICU stay cases was defined as less than 7 days and long stay as more than 7 days.
3. CI extracted from graphs
4. r: Spearman's correlation coefficient
5. “By multivariate analysis euthyroid sick syndrome was related by augmented mortality” (p<0.001)
Table 2. Correlation between baseline thyroid hormones and sepsis prognostic scores in patients with sepsis or septic shock included in different studies.

<table>
<thead>
<tr>
<th>1st Author, publication year</th>
<th>Baseline sepsis prognostic score, median(range) or mean±SD (patients with unfavorable vs favorable outcome)</th>
<th>T&lt;sub&gt;3&lt;/sub&gt;</th>
<th>T&lt;sub&gt;4&lt;/sub&gt;</th>
<th>fT&lt;sub&gt;3&lt;/sub&gt;</th>
<th>fT&lt;sub&gt;4&lt;/sub&gt;</th>
<th>TSH</th>
<th>TBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>den Brinker M. et al, 2005 [14]</td>
<td>PRISM: 32 (23-43) vs. [21 (8-35) and 9 (5-13)]</td>
<td>NS</td>
<td>r = -0.62 (p&lt;0.05)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>r = -0.54 (p&lt;0.05)</td>
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<td>SOFA: 15 (13-19) vs. [9 (3-17) and 2 (0-6)]</td>
<td>r = -0.69 (p&lt;0.05)</td>
<td>r = -0.57 (p&lt;0.05)</td>
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<tr>
<td>Joosten K.F. et al, 2000 [17]</td>
<td>PRISM: 31 (29-34) vs. 17 (14-17)</td>
<td>r = 0.29 (NS)</td>
<td>r = -0.34 (NS)</td>
<td>ND</td>
<td>r = -0.41 (NS)</td>
<td>r = 0.42 (p&lt;0.05)</td>
<td>ND</td>
</tr>
</tbody>
</table>

(f)T<sub>3</sub>: (free) triiodothyronine, (f)T<sub>4</sub>: (free) thyroxine, TSH: thyroid stimulating hormone, TBG: thyroxine-binding globulin, PRISM: pediatric risk of mortality score, SOFA: sequential organ failure assessment score, APACHE: acute physiologic and chronic health evaluation score, NS: non-significant, ND: no data were reported, r: Spearman’s correlation-coefficient
Figure 1. Flow diagram of the detailed process of the selection of articles for inclusion in our review.

Potentially relevant articles retrieved from PubMed (N=3633)

Articles selected for further evaluation after first screening of title and abstract (N=202)

Articles excluded after detailed screening according to specific criteria (N=193)
- Articles focusing on the association of thyroid function with other than sepsis/septic shock types of critical illness or with infections without sepsis/septic shock (N=42)
- Animal studies (N=51)
- Articles that did not give data for the outcome of patients with altered thyroid function (N=3)
- Review articles (N=64)
- Studies that provided data for thyroid function tests that did not refer to baseline (N=2)
- Case reports: (N=6)
- Articles studying other than thyroid hormones (e.g., adrenal hormones) (N=25)

9 individual articles qualifying for inclusion in our review