Prognostic significance of nonthyroidal illness syndrome in critically ill adult patients with sepsis

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ABSTRACT

Aim: This study was performed to investigate the association of non-thyroidal illness syndrome (NTIS) with 28-day mortality in adults with sepsis.

Methods: We performed a prospective observational analysis of adult patients with sepsis. Patients' demographic data, comorbidities, the blood test results including thyroid hormone analysis at admission, Acute Physiologic and Chronic Health Evaluation II score and Sequential Organ Failure Assessment score were compared between 28-day survivors and non-survivors. Further patients were divided into 3 groups; non-NTIS, NTIS group A (low total tri-iodothyronine (T3) and NTIS group B (low T3 with low thyroxine (T4). Multivariate Cox proportional hazards regression analysis was performed to determine the risk factors for mortality.

Results: A total of 360 patients were included, and overall mortality was 30%. The mortality of non-NTIS patients was 13.4%; group A, 50.1%, and group B 69.1% ($P < .001$). The median T3 (IQR) in non-survivors and survivors was 0.74 (0.56–1.17) and1.58 (0.91–2.13) and median free T3 (IQR) 2.40 (1.13-3.01) and 4.03 (3.03-7.13) respectively ($P < .001$). In Cox proportional hazards analysis, NTIS group A (hazard ratio, 1.66; 95% confidence interval [CI], 1.00-2.76) and group B (hazard ratio, 2.57; 95% CI, 1.53-4.34). The area under the receiver-operating curve of NTIS groups was 0.68 (95% CI, 0.63-0.72).

Conclusion: The T3 and free T3 were significantly lower in non-survivors compared with that in survivors and that a combination of low T3 with low T4 was associated with greater mortality than low T3 alone. A lower free T3 is independently associated with 28-day mortality.

Key Words: Critically ill, mortality, nonthyroidal illness syndrome, sepsis

INTRODUCTION

Sepsis continues to be a major burden on Intensive Care Units (ICUs), with a mortality rate of 50% for severe sepsis in developed countries. In India, mortality rate of cases with severe sepsis is much higher (65.2%). Predicting outcomes in sepsis is important to formulate more aggressive management approach. Many prognostic factors associated with outcome in sepsis such as age, sex, severity of illness, and biomarkers of sepsis have been reported.

Critical illness is associated with changes in the metabolism and transport of thyroid hormones and changes in hypothalamic–pituitary–thyroid axis collectively known as the nonthyroidal illness syndrome (NTIS), resulting in decreased concentrations of total triiodothyronine (T3) and free triiodothyronine (fT3), low thyroxine (T4),
and normal range or slightly decreased concentration of thyroid-stimulating hormone (TSH).\textsuperscript{[8]} NTIS is the most common endocrine disorder seen in critically ill patients.\textsuperscript{[6]} Initially, there is a decreased serum concentration of T3 and FT3, and increased levels of reverse triiodothyronine (rT3). Serum T3 decreases further as the severity of illness increases; fT3 also decreases but to a less extent. Serum total T4 and TSH concentration are usually normal in mild-to-moderate NTIS. In severe NTIS low-total T4, and sometimes, low TSH can be observed.\textsuperscript{[7]}

The prognostic significance of NTIS in critical illness is well known,\textsuperscript{[8,11]–[3] however, its significance in sepsis is still controversial. Some investigators have found a poor prognosis in sepsis with low thyroid hormone levels,\textsuperscript{[11–13]} but others have not.\textsuperscript{[14]} Furthermore, the prognostic significance of NTIS in adult patients with sepsis, in Eastern India is not known.

The aim of the present study was to investigate the association of NTIS with 28-day mortality in adult patients with sepsis in the ICU.

**MATERIALS AND METHODS**

We analyzed the prospectively collected adult patients’ data with sepsis at an urban, tertiary care, medical ICU of a Teaching Medical College Hospital in Eastern India, between September 1, 2015, and March 30, 2017. Informed consent was obtained from the patients or their relatives.

The Institutional Ethics Committee approved this study.

Adult patients older than 18 years who were admitted to the medical ICU and were diagnosed as having sepsis were included in the study. Patients were classified into systemic inflammatory response syndrome without underlying infection and sepsis including severe sepsis and septic shock based on the international consensus criteria.\textsuperscript{[15,16]} Patients were managed following the international guidelines for the management of severe sepsis and septic shock: 2012.\textsuperscript{[17]} The management protocol included fluid resuscitation with crystalloids with a target central venous pressure of 8–12 mm Hg, vasoactive agents with a mean arterial pressure of 65–90 mm Hg, with norepinephrine as the first choice vasopressor. None of the patients received dopamine.

The exclusion criteria included patients with known thyroid diseases and abnormal thyroid gland on palpation (enlarged thyroid and thyroid nodules), psychiatric illness, those on hormonal therapy except insulin, and those taking amiodarone, on corticosteroids, on dopamine, pregnant cases, or history of childbirth in the past 6 months.

NTIS was identified among the study patients by thyroid hormone analysis. In addition, based on the serum T3 and T4 levels NTIS patients were grouped into two groups – Group A and B. Group A included patients with low T3 and normal or high T4. Group B included patients with a combination of low T3 and low T4.

**Laboratory measurements**

Blood samples for thyroid hormone analysis total triiodothyronine (T3) and free T3 (fT3); total thyroxine (TT4), free thyroxine (fT4); TSH; and rT3, were obtained within 24 h of admission to the medical ICU. Third generation TSH assay and thyroid hormone analysis except rT3 was measured using IMMULITE 2000 (Siemens Healthineers, India), rT3 level was measured by nonenzymef involved flash chemiluminescence immunoassay method using the Maglumi 1000 (Snibe Co., Ltd); and the reference values of our institution were: T4, 65–130 nmol/L; fT4, 12–24 pmol/L; T3, 1.1–2.6 nmol/L; fT3, 3.70–7.30 pmol/L; rT3, 0.15–0.43 nmol/L; and TSH, 0.27–4.6 µIU/mL. Other blood tests such as arterial blood gas analyses, serum chemistry, complete blood count, C-reactive protein, and procalcitonin were also performed simultaneously. Blood cultures were performed before initiation of antibiotics and were defined as positive if aerobic, anaerobic, or fungal organisms grew.

**Data collection and processing**

We extracted data from standardized data collection forms that included information on demographics; comorbidities including diabetes, hypertension, liver disease, and chronic obstructive pulmonary disease; and initial hemodynamics including blood pressure, heart rate, temperature, primary site of infection, laboratory results, and microbiological reports. They also included Acute Physiologic and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score,\textsuperscript{[18]} and outcome variables such as 28-day mortality, duration of ICU and hospital stay (days), need for renal replacement therapy, and invasive mechanical ventilation.

The primary outcome was 28-day mortality after admission to the medical ICU, and a follow-up was performed for patients who were discharged before 28 days. The other outcomes were the rate of positive blood culture, duration of hospital stay, need for renal replacement therapy, and invasive mechanical ventilation.

**Statistical analyses**

Patients were divided into 28-day survivors and nonsurvivors. The Student’s t-test or Mann–Whitney U-test was performed depending on the normality distribution of variables. Continuous variables were analyzed using the Kolmogorov–Smirnov test for
normality distribution, and values expressed as the median with the interquartile range (IQR). Categorical variables were described as a frequency with percentage and compared using Chi-square test or Fisher’s exact test, as appropriate.

The APACHE II and SOFA scores between non-NTIS, NTIS Group A, and NTIS group B were compared using one-way analysis of variance whereas the 28-day mortality, rate of renal replacement therapy, mechanical ventilation, and positive blood culture were compared using the Chi-square test. The duration of hospital stay (days) was analyzed by the Wilcoxon rank-sum test.

The cumulative survival rates across non-NTIS and the NTIS groups were analyzed using Kaplan–Meier curves and the log-rank test.

We performed multivariate Cox proportional hazards regression methods to determine the independent factors of mortality during a 28-day follow-up period, and the results are expressed as hazard ratio and 95% confidence interval (CI). The area under the receiver operating characteristic (ROC) curve was used as a measure of discrimination of NTIS groups for 28-day mortality.

A two-tailed P < 0.05 was considered statistically significant. All analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

### RESULTS

During the study, a total of 390 patients were initially included in the study. Of them, 30 patients were excluded as per exclusion criteria. Therefore, 360 patients were included in the final analysis, and there was no loss to follow-up at 28 days. Overall 130 patients died (36.1%). NTIS was found in 67% (n = 241) of sepsis patients. Among sepsis patients, without NTIS (non-NTIS group, n = 119), 16 patients (13.4%) died during the 28-day follow-up period.

The mean age of the NTIS patients was 70.0 ± 13.4 years, 210 (58.3%) patients were male, and 114 patients (47.3%) died during the 28-day follow-up period. Nonsurvivors were older and had more male patients [Table 1]. The three most frequent primary sites of infection were respiratory, urinary, and hepatobiliary tracts. The frequency of respiratory tract infection was higher in nonsurvivors than in survivors, whereas that of urinary tract infection was lower in nonsurvivors than in survivors. The comorbidities were not different between survivors and nonsurvivors; the initial mean arterial pressure was lower in nonsurvivors compared with survivors. Baseline characteristics of the patients are shown in Table 1. No statistically significant difference was detected between survivors and nonsurvivors concerning age, sex, and common clinical parameters.

| Table 1: Baseline characteristics of the patients* |
|-----------------------------------------------|
| Variables                     | Survivors (n = 127) | Nonsurvivors (n = 114) | P    |
| Age (year), median (IQR)      | 70.5 (62.0-77.0)    | 75.0 (68.3-83.0)       | <0.001 |
| Male, n (%)                   | 66 (51.9)           | 70 (61.4)              | 0.040  |
| Source of admission to MICU, n (%) | 58 (45.6)           | 46 (40)                | 0.245  |
| Emergency department          |                    |                       |       |
| Hospital floor                | 45 (35.4)           | 49 (42.9)              | 0.178  |
| Another ICU                   | 14 (11)             | 12 (10.5)              | 0.767  |
| Another hospital              | 10 (7.8)            | 7 (6.2)                | 0.430  |
| Primary site of infection, n (%) |                |                       |       |
| Respiratory                   | 46 (36.2)           | 70 (61.8)              | <0.001 |
| Urinary                       | 30 (23.6)           | 7 (6.1)                | <0.001 |
| Hepatobiliary                 | 20 (15.7)           | 13 (11.4)              | 0.240  |
| Gastrointestinal              | 9 (7.1)             | 7 (6.1)                | 0.776  |
| Soft tissue                   | 6 (4.7)             | 4 (3.5)                | 0.331  |
| Miscellaneous                 | 16 (12.6)           | 12 (10.5)              | 0.276  |
| Comorbidity, n (%)            |                    |                       |       |
| Diabetes                      | 40 (31.5)           | 35 (30.7)              | 0.546  |
| Hypertension                  | 60 (47.2)           | 49 (42.9)              | 0.415  |
| COPD                          | 10 (7.8)            | 11 (9.6)               | 0.464  |
| Liver disease                 | 3 (2.4)             | 6 (5.2)                | 0.075  |
| Mean arterial pressure (mmHg), mean ± SD | 82.3±14.06         | 72.90±11.5             | 0.010  |
| APACHE II score, median (IQR) | 21 (17-28)          | 27 (19-31.8)           | 0.007  |

*IQR: Interquartile range, COPD: Chronic obstructive pulmonary disease, MICU: Medical Intensive Care Unit, APACHE II: Acute Physiologic and Chronic Health Evaluation, SD: Standard deviation, ICU: Intensive Care Unit

The laboratory parameters of survivors and nonsurvivors among NTIS patients are shown in Table 2. The pH
of arterial blood, serum cholesterol, and albumin concentration was significantly lower in nonsurvivors than those in survivors. Serum potassium, blood urea nitrogen, and creatinine concentration were higher in nonsurvivors than in survivors. White blood cell count, hematocrit, and platelet count were not different between survivors and nonsurvivors. In nonsurvivors the median T3 (IQR) was 0.74 (0.56–1.17) vs 1.58 (0.91–2.13) in the survivors. The median fT3 (IQR) in nonsurvivors vs survivors was 2.40 (1.13–3.01) and 4.03 (3.03–7.13) respectively [Table 2; P < 0.001]. The T3 and fT3 were significantly lower in nonsurvivors compared with that in survivors (P < .001) [Figures 1 and 2].

When the patients were divided into three groups according as non-NTIS (n = 119), NTIS Group A (low T3) (n = 168), and NTIS Group B (combination of low T3 and T4) (n = 73), the mortality rates were as follows: The mortality of non-NTIS patients was 13.4%; Group A, 39.9%; and Group B 64.4% (P < 0.001) [Table 3; P < 0.001]. Kaplan–Meier curve with log-rank test showed that NTIS was associated with increased mortality and that Group B NTIS was associated with greater mortality than Group A during the 28-day follow-up period [Figure 3]. The APACHE II and SOFA score also increased across non-NTIS, Group A, and Group B [Table 3]. Hence, mortality was highest in patients with a combination low T3 and low T4. However, the rates of renal replacement therapy, mechanical ventilation, and days of ICU stay were not different.

The most common Gram-positive microorganisms from blood culture were coagulase-negative Staphylococcus, Staphylococcus aureus, and Streptococcus pneumoniae, and Gram-negative microorganisms were Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

In multivariate Cox proportional hazards regression analyses, age, urinary tract infection, history of chronic liver disease, pH, blood urea nitrogen, creatinine, albumin, and APACHE II score were independent prognostic factors. fT3 had the largest area under the ROC of 0.790 (95% CI, 0.765–0.836) among the thyroid hormones analyzed and was the only thyroid hormone indicator with independent prognostic value.

In Cox proportional hazards analysis, groups with lower fT3 were independently associated with 28-day mortality compared with groups with a normal fT3; fT3 < 3.70 pmol/l (hazard ratio, 1.66; 95% CI, 1.00–2.76) and

| Table 3: The outcomes of patients* |
|-----------------------------------|
| Outcome measure                     | Non-NTIS (n = 119) | NTIS Group A (low T3) (n = 168) | NTIS Group B (low T3 + low T4) (n = 73) | P         |
|-----------------------------------|--------------------|---------------------------------|----------------------------------------|-----------|
| Mortality, n (%)                  | 16 (13.4)          | 60 (35.7)                       | 54 (73.9)                              | <0.001    |
| APACHE II score, median (IQR)     | 15 (11-21)         | 20 (14-26)                      | 21 (16-27)                             | <0.001    |
| SOFA score, median (IQR)          | 6 (5-9)            | 7 (5-10)                        | 9 (6-11)                               | <0.001    |
| Renal replacement therapy, n (%)  | 6 (5.0)            | 14 (8.3)                        | 5 (6.8)                                | 0.236     |
| Mechanical ventilation, n (%)     | 28 (23.5)          | 56 (33.3)                       | 22 (3.01)                              | 0.167     |
| Days in hospital, median (IQR)    | 7.5 (6-11)         | 8.5 (5-12)                      | 9 (7-12)                               | 0.562     |

*IQR: Interquartile range, APACHE II: Acute Physiologic and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic and Chronic Health Evaluation, NTIS: Nonthyroidal illness syndrome, T3: Total triiodothyronine, fT3: Free triiodothyronine.
and T4, but not TSH, were significantly lower in patients with sepsis, and lower in nonsurvivors compared to survivors. None of our patients with septic shock received dopamine; instead norepinephrine was the first choice vasopressor. The study by Kunt et al. and also the present study establish the prognostic significance of NTIS in sepsis.

In a cohort of 26 children with meningococcal sepsis, Joosten et al. found lower T3 in the 18 survivors rather than the nonsurvivors.[24] This is a contrast to the above studies where T3 was either lower or not statistically decreased in nonsurvivors of sepsis. Dopamine suppresses the pituitary release of TSH, hence lower T3 production.[25] Ten of the survivors in the study by Joosten et al. had received dopamine, and this could be the reason of the lower T3 in survivors.

Lodha et al. studied the thyroid function in 24 children with sepsis and septic shock.[13] They found that children with septic shock had lower T3, T4, fT3, fT4, and TSH compared with children with sepsis alone. However, only TSH was found to be significantly lower in survivors TSH in survivors versus nonsurvivors was 0.26 (0.22–0.88) versus 1.21 (0.27–2.96) μIU/mL (P = 0.04). Similar to this study, in our study, fT3 decrease with increased severity of illness as discernible by the increased APACHEII and SOFA scores.

In a small cohort study of 27 adults with septic shock by Leon-Sanz et al. low thyroid hormone concentrations at presentation was found in all patients however only survivors had a significant increase in T3 and T4.[26] Furthermore, survivors had a greater TSH response to TRH, indicating a less deranged hypothalamic–pituitary–thyroid axis. As the sample size was small, the initial difference in T3 and T4 may not have been statistically significant. This study showed improvement in thyroid function only in survivors, which is an indirect evidence of worse thyroid hormone derangement in nonsurvivors. In our present study, nonsurvivors had greater suppression of thyroid hormones (T3 and T4) at presentation reflecting greater derangement of thyroid hormones similar to what is evident by the Leon-Sanz et al.

Mangas-Rojas et al., in a prospective cohort study of 37 adult patients with sepsis observed a decrease in serum T3 levels in nonsurvivors and survivors (P < 0.001).[27] Nonsurvivors had lower T3 and T4 compared with survivors. The T3 (ng/dl) in nonsurvivors versus survivors was 30.40 ± 13.4 vs. 52.5 ± 19.6, P < 0.001. The T4 (μg/dl), in nonsurvivors was 5.50 ± 1.70, whereas in survivors it was 7.20 ± 2.80, P = 0.04. The SOFA score of illness as discernible by the increased APACHEII and SOFA scores.
The greatest discriminative efficacy of thyroid hormones study with an unfavorable sepsis evolution corresponded to a T3 value below 35 ng/dl. Similar to this study, in our study, nonsurvivors had lower T3 and greater decrease in T3 was associated with unfavorable outcome.

Meyer et al. in a prospective study on 103 critically ill adults with sepsis found that the median T3 levels on admission were lower in patients with sepsis and the lowest T3 levels were found in patients with severe sepsis and septic shock.[29] In their study, there was no difference in T3 and fT4 on admission in nonsurvivors compared with survivors; however, the fT4 decreased significantly during the follow-up among nonsurvivors and on the day of death nonsurvivors had lower T3 and fT4 as compared with survivors. The median T3 and fT3 were lower in nonsurvivors as compared to survivors in our study, and a combination of low T3 and T4 was associated with worse prognosis. Unlike in the developed countries, our patients present late to the ICU and many patients are referred to our ICU after primary treatment elsewhere [Table 1]. This delay of could be the reason for decreased T3 and fT4 among nonsurvivors and survivors at the time of admission itself. If we compare these two studies, both suggest decreased T3 is significantly correlated with severity of sepsis and that a combined low T3 and T4 are associated with worse prognosis.

The mechanism behind low serum T3 and fT3 and its correlation with severity of clinical illness are multifactorial. Cytokines play a major role in the pathogenesis of sepsis. Cytokine such as tumor necrosis factor, interferon-alpha (INF alpha), and interleukin-6 (IL-6) levels are elevated in patients with sepsis.[30] Crossmit et al. assessed the acute effects of INF alpha, administration on thyroid hormone metabolism in healthy men. They found no decrease in serum T4 and fT4 levels; however, there was a significant decrease in serum TSH, T3, and fT3. The INF alpha-induced a moderate increase in IL-6 but not that of IL-1 and tumor necrosis factor. The acute effects of INF-alpha mimics the NTIS possibly mediated in part by IL-6.[30] Stouthard et al. assessed the effects of IL-6 on thyroid hormone metabolism in humans. In the acute phase, they found no effects of IL-6 on T4 and fT4 but a decrease in TSH, T3, and T3.[31] Inhibition of the enzyme 5′-deiodinase that catalyzes the conversion of T4 to T3 is known to occur in NTIS.[32] Cytokines also contribute to the inhibition of 5′-deiodinase leading to low serum T3 and fT3 in NTIS in sepsis.[33] These studies not only show that cytokine are pathogenic factors in NTIS but also that the pattern of alteration in thyroid hormones is quiet similar to our present study on patients with sepsis. Alteration in cytokines levels may be the predominant mechanism behind NTIS in sepsis.

Tanyctyes are specialized ependymal cells lining the floor and inferolateral borders of the third ventricle in the mediobasal hypothalamus (MBH). Recent animal studies have shown that bacterial lipopolysaccharide (LPS) induces type 2 iodothyronine deiodinase (D2) activation in tanycytes independently of circulating thyroid hormone and leads to the central hypothyroidism associated with infection.[34] Further Sánchez et al., in their studies on Sprague Dawley rats have shown that the LPS-induced increase in D2 gene expression in the tanycytes of MBH is generally not mediated by the associated increase in glucocorticoids, and other mechanisms, such as an increase in proinflammatory cytokines, may be of primary importance in the D2 response to LPS.[35]

As plasma selenium levels are often low in sick patients, especially those with severe illness and sepsis, it has been suggested that the expression of the selenoenzymes D1, D2, and D3 may be limited by the low selenium supply in these patients, and that this represents a mechanism for the pathogenesis of the low T3 and seems in the NTIS.[36]

The current evidence thus suggests that down-regulation of thyroid hormone transporters does not occur in the NTIS, and other mechanisms must be responsible for the impaired uptake of thyroid hormone that is manifest in illness. Such mechanisms may include depletion of hepatic ATP or the presence in plasma of substances that impair hepatic uptake of thyroid hormone. NEFA and numerous substances that accumulate in the plasma of patients with renal or liver dysfunction inhibit cellular transport of T4 into cultured hepatocytes.[37]

There can be many confounding factors when analyzing thyroid function, one being any acute or chronic illness, which we are studying, and others being patients with known thyroid diseases, psychiatric illness, those on hormonal therapy and those taking amiodarone, on corticosteroids, on dopamine, pregnancy, chronic kidney disease (CKD), and nephrotic Syndrome and most such cases were excluded from the present study.[38,39]

Our study did not include cases of CKD and Nephrotic Syndrome [Table 1]; also, there is no difference in acute renal failure among the survivors and nonsurvivors. However, serum albumin concentration was significantly lower in nonsurvivors than those in survivors [Table 2]. Desai et al. studied the clinical utility of measuring thyrotropin (TSH) in serum by immunoradiometry and of measuring TT4, total T3 (TT3), FT4, and FT3 in ill hypoalbuminemic patients by taking a group of 110 healthy volunteers, 45 ill hypoalbuminemic patients, and 42 ill normoalbuminemic patients. The hypoalbuminemic group had significantly lower FT4, FT3, TT4, TT3, and FTI concentrations, but only FT3 and TT3 were significantly lower in the ill normoalbuminemic group as compared with controls.[40] In our study, 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 with those low T3 alone; nonsurvivors had greater suppression of thyroid hormones (T3 and T4). This has important implications, signifying lower fT3 and T3 in sepsis as a marker of poor prognosis, independent of serum albumin. However, in patients with NTIS, a combination of low T3 and T4 is a better predictor of survival than low T3 alone.

The treatment of NTIS with thyroid hormone supplementation was beyond the scope of our present study. Although studies of such treatment in sepsis is lacking, considering the higher mortality rate of sepsis patients with NTIS, these are potential candidates for thyroid hormone replacement. There appears to be no obvious contraindications of thyroid hormone replacement therapy in sepsis with NTIS except in patients with heart failure and arrhythmias but current studies show that even in these groups intravenous T3 is well tolerated with favorable outcomes.[41,42] A study by Acker et al. raises some concern in acute kidney injury cases but on careful analysis of the study, the small dose of thyroxine administered over 2 days actually might not be related to increased mortality. The same authors studied thyroid hormone replacement in the treatment of posttransplant acute tubular necrosis and found no increased mortality in the treatment group.[43,44] Well-designed randomized case–control studies of thyroid hormone replacement in sepsis with NTIS are needed in the near future to harness the possible benefits of such therapy.

CONCLUSION

Our study showed that NTIS in sepsis was associated with an increased mortality, and that a combination of low T3 and T4 was associated with greater mortality than low T3 alone during the 28-day follow-up period. Thyroid hormone abnormalities are commonly found in septic patients. Hence, more studies should aim to establish the association of NTIS and poor prognosis in sepsis. Along with the known prognostic scoring systems, NTIS could be incorporated as predictor of outcome in sepsis. Treatment with thyroid hormone replacement in sepsis is an important aspect to consider pending well-designed future studies.

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Conflicts of interest
There are no conflicts of interest.

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