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# Comparison and relationship of thyroid hormones, IL-6, IL-10 and albumin as mortality predictors in case-mix critically ill patients

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ABSTRACT

*Objective:* To compare the ability of thyroid hormones, IL-6, IL-10, and albumin to predict mortality, and to assess their relationship in case-mix acute critically ill patients.
*Methods:* APACHE II scores and serum thyroid hormones (FT3, FT4, and TSH), IL-6, IL-10, and albumin were obtained at EICU admission for 79 cases of mix acute critically ill patients without previous history of thyroid disease. Patients were followed for 28 days with patient's death as the primary outcome. All mean values were compared, correlations assessed with Pearson' test, and mortality prediction assessed by multivariate logistic regression and ROC.
*Results:* Non survivors were older, with higher APACHE II score ($p = 0.000$), IL-6 ($p < 0.05$), IL-10 ($p = 0.000$) levels, and lower albumin ($p = 0.000$) levels compared to survivors at 28 days. IL-6 and IL-10 had significant negative correlation with albumin ($p = 0.001$) and FT3 ($p \leqslant 0.05$) respectively, while low albumin had a direct correlation with FT3 ($p < 0.05$). In the mortality prediction assessment, IL-10, albumin and APACHE II were independent morality predictors and showed to have a good (0.70–0.79) AUC-ROC ($p < 0.05$). Despite that the entire cohort showed low FT3 serum levels ($p = 0.000$), there was not statistical difference between survivors and non-survivors; neither showed any significance as mortality predictor.
*Conclusions:* IL-6 and IL-10 are correlated with Low FT3 and hypoalbuminemia. Thyroid hormones assessed at EICU admission did not have any predictive value in our study. And finally, high levels of IL-6 and IL-10 in conjunction with albumin could improve our ability to evaluate disease's severity and predict mortality in the critically ill patients. When use in combination with APACHE II scores, our model showed improved mortality prediction.


## 1. Introduction

Since the development of the "acute physiology and chronic health evaluation II" (APACHE II) [1], mortality prediction in critically ill patients remains a great concern for physicians and patient's family due to limited health resources and high economic costs [2]. Thereon during critical illness, part of the neuroendocrine alterations known as Non Thyroid Illness Syndrome (NTIS) or Low T3 syndrome (LT3) characterized by low T3, Low or normal T4, high rT3 and normal TSH [3–5] have been related with disease's severity and mortality in ICU setting [6–8]. However, the pathophysiology of LT3 is complex and not well understood due to the interaction of multiple factors during critical illness [9–14]. Thus release of high levels of pro-inflammatory cytokines during the acute response of critical illness have been reported to be related and possibly cause NTIS [15–17]. Furthermore, previous studies have demonstrated that pro-inflammatory cytokines and anti-inflammatory cytokines blood concentration are correlated with disease's severity and mortality as well, but mainly in septic patients [18–20]. Nevertheless, none study that analyze this biomarkers in the same patient have been done. Therefore in this prospective study, we attempt to evaluate the ability of thyroid hormones, cytokines (IL-6 and IL-10), and albumin as predictors of mortality in conjunction with APACHE II score in critically ill

*Abbreviations:* AUC, area under the curve; APACHE II, Acute Physiology and Chronic Health Evaluation II; EICU, emergency intensive care unit; ICU, intensive care unit; IFN, interferon; IL, interleukin; LT3, Low T3 syndrome; NTIS, nonthyroidal illness syndrome; FT3, Free Triiodothyronine; ROS, reactive oxygen species; ROC curve, receiver operating characteristic curve; rT3, reverse Triiodothyronine; T3, Triiodothyronine; T4, Thyroxine; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; TT3, total Triiodothyronine; TT4, total Thyroxine; TH, thyroid hormones; TBG, Thyroxine Binding Globulin.

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patients. In addition, we seek to identify potential relationship between these variables.

## 2. Materials and methods

### 2.1. Patients

This prospective and observational research was conducted at Emergency Intensive Care Unit (EICU), of Xiangya Hospital – Central South University, from August to December of 2014 with the approval of the local Ethics Committee and written informed consent from each patient.

During that period, 340 patients age 18 and older were admitted to EICU, and all were screened for underlying thyroid disorders by detailed medical record, physical examination (including palpation of the thyroid gland), blood test for thyroid hormones and thyroid antibodies at EICU admission (following the declaration of Helsinki). Their APACHE II score was also recorded within 24 h of admission. Patients with: previous or new diagnosis of hypothyroidism, hyperthyroidism or its subclinical types, pregnancy, breastfeeding condition, endocrine diseases (except Diabetes Mellitus), duration of stay <24 h, and those transferred from other hospitals with >36 h of hospitalization were all excluded, remaining 79 patients.

### 2.2. Measurements

For patients that met the inclusion criteria, blood samples were collected prior to interventions or therapy that could potentially interfere or alter serums level of thyroid hormones or cytokines, "ECLIA immune assay" detection kits via Electro-Chemiluminescent Roche E 170 System (Roche Diagnostics International Ltd., CH-6343 Rotkreuz, Switzerland) were used to measure serum levels of FT3, FT4, and TSH and thyroid Normal ranges of our laboratory were 2.8–7.1 pmol/L; 12–22 pmol/L, and 0.27–4.2 IU/L for $FT_3$, $FT_4$, and TSH respectively.

For cytokines' blood concentration measurement, blood samples were obtained after 24 h of EICU admission, centrifuged at 2000 rpm × 10 min; plasma was separated and frozen at −80° Celsius until the time of the assay according to standard recommendations for cytokines' assessment in blood samples [21–23]. "Sunny Elisa Human IL-6 and IL-10 test" Multisciences (Hangzhou Lianke biotechnology Ltd. China), were used to assess cytokines' concentration and measured by Colorimetric Reader GEN5-Biotek (Bioteck instruments Inc., Beijing, China), minimum detectable cytokine levels for IL-6 and IL-10 were <0.37 pg/ml. Interpolation to the standard curve of the measurements were obtained through linear regression by GraphPad Prism software version 6 (Inc. California, United States). Reference of cytokines levels in healthy individuals were taken from Maier et al. [24], whose values are 70 pg/ml and 30 pg/ml for IL-6 and IL-10 respectively.

### 2.3. Statistical analysis

Data is presented in means and 95% Confidence Interval (CI). Variable's mean were compared between survivors and non-survivors. Data that did not show a normal distribution due to extreme skewness was ranked and transformed to normal distribution (ND) before applied *t*-test analysis. The determination of correlations between variables were done by Pearson's correlation test; in order to set the critical point to predict mortality for APACHE II, TH, IL-6, IL-10 and albumin levels Receiver Operating Characteristic Curve was applied, results are presented as area under the curve (AUC) with sensitivity and specificity. Independent mortality predictors' assessment was done by multivariate binary logistic regression, after weight the cases and step wise input. All data were analyzed using Statistical Package for Social Sciences (SPSS) version 18 software (SPSS Inc., Chicago, IL, United States), with significance of any $p < 0.05$.

## 3. Results

### 3.1. General data

Of the 79 patients, 28 were females and 51 males. Average age was 53 ± 3 years old, with age range from 18 to 82. Table 1 shows the blood concentration of biomarkers by reason of admission to EICU. Non-survivors' age range was from 49 to 79 years old. The average of length of stay (LOS) in EICU for non-survivors was 2 days and for survivors 4 days. In-ward LOS for survivors was 12 days, and for none survivors 5 days. Mortality rate within 28 days was 19% with a survival rate of 81%.

### 3.2. Comparisons

Using the student *t*-test, the mean values obtained in the entire cohort were compared first with the normal range and later between survivors and non-survivors. Compared to survivors, non-survivor were older (p = 0.008), with higher APACHE II score (p = 0.003), higher IL-6 plasma levels (p = 0.03), higher IL-10 plasma levels (p = 0.004), and lower albumin serum levels (p = 0.007) (Table 2). Only FT3 was slightly low in the entire cohort studied (p = 0.000), however this value did not show any statistical difference between survivors and non-survivors. FT4 and TSH were both within normal range (Table 1).

**Table 1**
General data: blood concentration of biomarkers by reason of admission to EICU.

| Admission reasons | n | Age | FT3 2.8–7.1 pmol/L | FT4 12–22 pmol/L | TSH 0.27–4.2 IU/L | Albumin 40–55 g/L | [a]IL-6 70 pg/ml | [a]IL-10 30 pg/ml | APACHE II ⩾15 | S | N-S |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neurologic | 5 | 66 | 1.70 | 12.67 | 1.30 | 32.80 | 168.30 | 54.94 | 20.03 | 4 | 1 |
| Polytraumatism | 8 | 53 | 2.02 | 10.88 | 0.95 | 34.75 | 178.77 | 46.78 | 14.88 | 8 | |
| Cardiologic | 11 | 60 | 2.22 | 13.48 | 1.26 | 33.44 | 164.47 | 40.08 | 16.27 | 10 | 1 |
| Respiratory | 9 | 60 | 2.30 | 16.20 | 0.99 | 28.88 | 261.01 | 17.37 | 19.44 | 7 | 2 |
| Gastrointestinal | 7 | 54 | 1.99 | 10.97 | 0.68 | 26.75 | 209.27 | 56.63 | 10.84 | 6 | 1 |
| Metabolic | 3 | 34 | 1.87 | 11.93 | 0.90 | 29.85 | 324.93 | 109.02 | 22.00 | 3 | |
| Sepsis | 10 | 53 | 1.81 | 12.07 | 0.91 | 26.54 | 250.37 | 188.72 | 19.34 | 4 | 6 |
| Hematologic | 12 | 53 | 1.88 | 13.41 | 0.96 | 26.69 | 204.46 | 189.78 | 20.61 | 10 | 2 |
| Renal | 10 | 59 | 2.11 | 11.72 | 2.06 | 34.65 | 194.48 | 79.82 | 19.82 | 8 | 2 |
| Others | 4 | 47 | 2.46 | 10.88 | 1.79 | 34.29 | 108.39 | 16.70 | 13.25 | 4 | |

Mean concentration values, the superior row shows the normal range values.
[a] Reference of basal concentration for IL-6 and IL-10 in healthy individual. S: Survivors, NS: none survivors.