Predictive value of thyroid hormones on the first day in adult respiratory distress syndrome patients admitted to ICU: comparison with SOFA and APACHE II scores

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BACKGROUND: Thyroid hormone dysfunction could affect outcome and increase mortality in critical illness. Therefore, in a prospective, observational study we analyzed and compared the prognostic accuracy of free tri-iodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), along with the APACHE II and SOFA scoring systems in predicting intensive care unit (ICU) mortality in critically ill patients.

PATIENTS AND METHODS: Physiology scores were calculated for the first 24 hours after ICU admission in 206 patients with acute respiratory distress syndrome. APACHE II and SOFA scores were employed to determine the initial severity of illness. Thyroid hormones were measured within the first 24 hours. Logistic regression models were created for APACHE II scores, SOFA scores, and thyroid hormone levels. The models predicted high- and low-risk subgroups. Models that showed a good fit were stratified by Kaplan-Meier survival curves.

RESULTS: There were 98 (47.6%) survivors and 108 (52.4%) non-survivors. The survivors had a lower APACHE II score (11.50 vs 15.82, *P*<0.0005), a lower SOFA score (6.06 vs 9.42, *P*<0.0005), a younger age (57 vs 70 years, *P*=0.008), a shorter ICU stay (13 vs 16 days, *P*=0.012), and a higher fT3 level (2.18 vs 1.72 pg/mL, *P*=0.002) than non-survivors. ICU survival was most closely predicted by a model that included age and fT3 and a model that included APACHE II and APACHE II*sex.

CONCLUSION: In critically ill patients, serum fT3 concentrations markedly decreased after ICU admission among non-survivors. According to our findings, fT3 levels might have additive discriminatory power to age, SOFA and APACHE II scores in predicting short-term mortality in ARDS patients admitted to ICU.

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Global performance indicators may not precisely reflect variations in actual mortality probabilities for subgroups of critically ill patients.[1] Recent interest has focused on the performance of prognostic models for subgroups of intensive care unit (ICU) patients and the potential impact on their overall goodness-of-fit. When applied to subsets of ICU patients, large variations in performance have been reported.[2-4]

Altered thyroid function in critical illness is well known as the "sick euthyroid syndrome" or "non-thyroidal illness syndrome".[5,6] The most common finding in moderately ill patients is reduced circulating total tri-iodothyronine (TT3) concentration, while total thyroxine (TT4) and free thyroxine (fT4) concentrations may also be reduced in more severe disease. These changes are thought to result from reduced pe-

ripheral deiodination of T4 and reduced binding by plasma thyroid hormone binding proteins. Plasma thyrotropin concentration may be suppressed in the acute phase of critical illness and may rise into the hypothyroid range on recovery. Reduced plasma concentrations of T3 and T4 may cause ileus, insulin resistance, impaired triglyceride levels, reduced inotropy, and reduced protein synthesis and metabolism in muscles.[7] These effects may perpetuate the catabolism of sepsis. TT3 and TT4 concentrations are lower in non-survivors than in survivors,[8-14] and therefore thyroid hormone dysfunction could affect outcome and increase mortality in critical illness.

The Acute Physiologic and Chronic Health Evaluation II (APACHE II) is widely used for grading the derangement in the physiological homeostasis of individual patients as well as for prognostic calculations. This score is used for categorizing patients in clinical trials and for comparisons between intensive care units by calculation of the probability of hospital death and standardised mortality ratio.[15,16] In multicenter prospective studies, the Sepsis-related Organ Failure Assessment (SOFA) score has been used to determine individual severity. It allows for repeated measurements of multiple organ dysfunction/failure and thereby functions as an index for determining either sequential deterioration or improvement of the pathological condition of the patient during treatment.[17]

In this study, we analyzed and compared the prognostic accuracy of these two scoring systems and concentrations of thyroid-stimulating hormone (TSH), free tri-iodothyronine (fT3), and fT4 in predicting the ICU mortality of critically ill patients with acute respiratory distress syndrome (ARDS) when scores were measured 24 hours after admission to the ICU in survivors and non-survivors of critical illness.

Patients and Methods

This study was a prospective, observational study. Between January 1998 and July 2002, 206 patients with ARDS were included in the study. Inclusion criteria were a) the presence of bilateral pulmonary infiltrates, b) an absence of left heart failure, that is, a cardiac index of >3 L/min/m^2 and a pulmonary artery occlusion pressure of <18 mm Hg, and c) a $Pa0_2/Fi0_2$ ratio of <150 torr (20kPa).[18] Demographic, clinical and physiological data were prospectively collected and entered into a computerized database. Demographic information such as age, gender, duration of ICU stay and outcome were recorded.

Physiology scores were calculated for the first 24 hours after ICU admission. Patients under 18 years of age whose stay in the ICU was less than 24 hours and patients with known thyroid abnormalities were excluded. Patients with known underlying diseases or treatments that affect thyroid, adrenal or hypothalamic-pituitary function were not excluded. Patients transferred from another ICU were not included. A local ethics committee approval was obtained for this study. Written informed consent was obtained from patients or their next of kin whenever possible.

APACHE II and SOFA scores were used to determine the initial severity of illness. The APACHE II and SOFA scores were calculated for each patient using data from the first 24 hours of admission. Patients were followed until discharge from ICU or death. All patients were ventilated in a volume-controlled mode (Puritan Bennett 7200, Carlsbad, CA) and received continuous analgesic sedation with midazolam and fentanyl.

Within the first 24 hours, fT3, fT4, and TSH concentrations were measured. Blood samples were obtained only in the morning. Further samples were taken for repeated measurements at 8:00AM on the day following ICU admission. Venous blood was collected into a 10 mL sterile plain tube (without anticoagulant) before administration of any medications and stored at -200ºC before assay when all samples were thawed to room temperature and mixed by gentle swirling or inversion. All sera were assayed on the same day to avoid interassay variation. fT3, fT4, and TSH levels were measured with a solid-phase, two-site chemiluminescent enzyme immunometric assay method (IMMULITE 2000, EURO/DPC, Llanberis, UK). For fT3, the total assay and intra-assay coefficient variation of this procedure was 5.4% to 10.0% and 4.3% to 9.1%, respectively. For fT4, the total assay and intra-assay coefficient variation of this procedure was 4.8% to 9.0% and 4.4% to 7.5%, respectively. For TSH, the total assay and intra-assay coefficient variation of this procedure was 4.5% to 12.5% and 3.8% to 12.5%, respectively. The lowest detectable limits of fT3, fT4, and TSH were 1.0 pg/mL, 0.18 ng/dL and 0.002 (IU/mL, respectively.

Results are expressed as mean±SD and median and interquartile range in the case of parametric or nonparametric variables, respectively. The main outcome measurement was ICU mortality. The Shapiro-Wilk test was used to assess the normality of continuous data. Comparison between any two groups was by the unpaired t test for normally distributed data or

Table 1. Patient demographic data, thyroid hormone levels, APACHE II and SOFA scores, and causes of adult respiratory distress syndrome in survivors and non-survivors.

Characteristic	Survivors (n=98, 47.6%)	Non-survivors (n=108, 52.4%)	P value
Median (IQR) age (years)	57 (32-70)	70 (59-72)	0.008
Gender (M:F)	2.13:1	3.23:1	0.460
Mean (SD) fT3 (pg/mL)	2.18 (0.78)	1.72 (0.73)	0.002
Median (IQR) fT4 (ng/dL)	1.04 (0.85-1.22)	0.80 (0.50-1.39)	0.139
Median (IQR) TSH (mIU/mL)	0.76 (0.50-2.4)	1.04 (0.30-1.57)	0.434
Median (IQR) APACHE II scores	11 (10-13)	16 (14-17)	<0.0005
Median (IQR) SOFA scores	6 (4-8)	9 (8-11)	<0.0005
Median (IQR) ICU stay (days)	13 (9-21)	16 (12-23)	0.012
Cause of ARDS			
Aspiration	14	17	
Septic shock	36	39	
Pneumonia	30	37	
Lung contusion	10	8	
Pulmonary emboli	8	7	

IQR: Interquartile range, SD: Standard deviation, TSH: thyroid-stimulating hormone, fT3: free tri-iodothyronine, fT4: free thyroxine, APACHE II: Acute Physiologic and Chronic Health Evaluation II scoring system, SOFA: Sepsis-related Organ Failure Assessment scoring system, ARDS: acute respiratory distress syndrome.

the non-parametric Mann-Whitney U test for non-normally distributed data. Using the independent predictors, we used logistic regression analysis with a forward stepwise variable selection to predict the probability of death. Logistic regression models were created for each APACHE II scores, SOFA scores, and thyroid hormone levels. Fit was assessed by chi-square statistics proposed by Hosmer-Lemeshow (H-L) Goodness of Fit Test.[19] The subjects were divided into approximately 9 groups of roughly the same size based on the percentiles of estimated probabilities. This goodness of fit statistic had a chi-square distribution and the discrepancies between the observed and expected number of observations in these groups were summarized by the Pearson chi-square statistic. Area under the curve (AUC) of the receiver operating characteristic (ROC) curves were used to assess the predictive power. AUCs were calculated according to Hanley and McNeil.[20] The sensitivity, specificity, predictive rate, and Youden Index of our predictive models were estimated by means of logistic regression. For the best logistic models, the overall survival was calculated using the Kaplan-Meier procedure.[21] Models were used to divide patients into low- and high-risk subgroups and the overall survival was compared using the one sample log-

rank test.[22] Statistical analysis was carried out using a software package (SPSS for Windows 12.0) and a two-tailed test was used with the significance level (α) set at 0.05.

Results

A total of 206 patients with ARDS were enrolled in the study. Fifty-six percent of the patients were admitted from the ward, 34% from the emergency room, and 10% from other hospitals. Baseline characteristics of the study-patients are shown in Table 1. All patients needed mechanical ventilation.

There were 98 (47.6%) survivors and 108 (52.4%) non-survivors. The survivors had a lower age (57 vs 70 years, P=0.008), APACHE II scores (11 vs 16, P<0.0005), SOFA scores (6 vs 9, P<0.0005), ICU stay (13 vs 16 days, P=0.012), and higher fT3 (2.18 vs 1.72 pg/mL, P=0.002) than non-survivors. Differences in other parameters were not statistically significant (P>0.05) (Table 1). To evaluate to what extent the applied scoring systems were valid for ICU mortality, the sensitivity, specificity, overall correctness of prediction, and positive and negative predictive values were all determined. The highest overall correctness of prediction was found for the SOFA and APACHE II score (Table 2).

We found 6 logit models by logistic regression analysis (R=risk of ICU death):

Model I=ln(R/(1-R))=1.674-0.810*fT3

Model II=ln(R/(1-R))= -6.640+0.495*APACHE II

Model III=ln(R/(1-R))= -5.183+0.686*SOFA

Model IV=ln(R/(1-R))= -0.865+0.042*age-0.787*fT3

Model V=ln(R/(1-R))= -7.159+0.561*APACHE II-1.762*sex-0.084*APACHE II*sex

Model VI=ln(R/(1-R))= -5.365+0.413*SOFA+0.032*age+0.005*SOFA*age

Based on the chi-square of H-L goodness of fit statistics, Model I, Model IV and Model V showed a good fit while the Model II, Model III and Model VI did not show a good fit (Table 3). Within Models I, IV and V, The best Youden Index and highest predictive rate were found for Model V (54.2% and 77.1%, respectively). Model V model was followed by Model IV (34.4% and 67.6%, respectively). ROC curves were used to evaluate the discriminative power of the models (Figure 1). Model II, III, V, and VI and the highest AUCs and were the most reliable models for discriminating between survivors and non-survivors (Table 3). Model IV and Model V had the highest AUCs among the models with good fit.

Table 2. Cut-off points, area under the curves, and predictive values of APACHE II, SOFA, T3, and age.

	Cut-off point	AUC (SE)	Sensitivity (%)	Specificity (%)	PR (%)	PPV (%)	NPV (%)
APACHE II	12	0.850 (0.038)	85.5	74.0	80.0	78.3	82.2
SOFA	6	0.859 (0.037)	92.7	72.0	82.9	78.5	90.0
T3 (pg/mL)	2.1	0.675 (0.053)	74.5	62.0	68.6	68.3	68.9
Age (years)	56	0.651 (0.053)	87.3	50.0	69.5	65.8	78.1

APACHE II: Acute Physiologic and Chronic Health Evaluation II scoring system, SOFA: Sepsis-related Organ Failure Assessment scoring system, T3: tri-iodothyronine, PR: predictive rate, PPV: positive predictive value, NPV: negative predictive value.

For Model IV, the 30-day mortality was 31.7% in the low-risk (R<0.5) group vs. 67.7% in the high-risk (R≥0.5) group, and mean survival time was 16.8 days (SE=2.3 days) for the low-risk group, and 8.6 days (SE =1.0 day) for the high-risk group (Figure 1). For Model V, the 30-day mortality was 24.5% in the low-risk (R<0.5) group vs. 79.6% in the high-risk (R≥0.5) group, and mean survival time was 16.2 days (SE=2.3 days) for the low-risk group, and 8.6 days (SE=1.1 days) for the high-risk group. For Model IV, the percentage survival in the low-risk group (R<0.5) was significantly higher (P=0.002) than that of the high-risk group (R≥0.5) (Figure 2). For Model V, the percentage survival in the low-risk group (R<0.5) was significantly higher (P<0.001) than in the high-risk group (R≥0.5) (Figure 3). ICU survival was most closely predicted by models that included age and fT3 (Model IV) and APACHE II and APACHE II*female (Model V).

Discussion

The main result of our study is the novel finding that fT3 is important in the predicting outcome of ARDS patients in the ICU. This is the first study that has investigated the predictive value of thyroid hormones in ARDS patients.

Many investigators have assessed the outcome and identified early prognostic indicators in a global population of patients admitted to the ICU for a life-threatening complication. The most common finding in moderately ill patients is reduced circulating TT3 concentration, while TT4 and fT4 concentrations may also be reduced in more severe disease. These changes are thought to result from reduced peripheral deiodination of T4 and reduced binding by plasma thyroid hormone binding proteins. Plasma thyrotropin concentration may be suppressed in the acute phase of critical illness and may rise into the hypothyroid range on recovery. Reduced plasma concentrations of T3 and T4 may cause ileus, insulin resistance, impaired triglyceride levels, reduced inotropy, and reduced protein synthesis and metabolism in muscle.[8] These effects may perpetuate the catabolism of sepsis. TT3 and TT4 concentrations are less in non-survivors than in survivors,[5,9,10] and therefore thyroid hormone dysfunction could reduce outcome in critical illness. Serum concentrations of TSH, TT3 and TT4 are correlated with outcome in acute severe illness. Some studies have found that low TSH,[5] low TT3,[9,10] high TSH and low TT3,[11] and low TT4[12,13] are correlated with mortality; however, other studies have found no correlation of TT3, TSH, fT4 or fT3 with outcome.[23,24] In the various studies, patients differ, with only medical patients in some studies[9-11] and patients with multiple trauma in others,[13] or both medical and surgical patients in others.[5,14,23] The severity of illness also varies between studies. For this reason, we evaluated patients with ARDS admitted to the adult ICU and compared measurements of thyroid hormones between survivors and non-survivors and assessed their value in the prediction of outcome from critical illness.

ICU studies have demonstrated that there was an association between hormones and mortality. Wade et al.[25] found that plasma cortisol, aldosterone, and androstenedione concentrations were increased in the ICU patients compared to normal subjects, being greater in the seriously ill patients, while plasma dehydroepiandrosterone sulfate (DHEAS) concentrations were low in ICU patients. Nierman et al.[26] measured total testosterone and bioavailable testosterone (bioT) concentrations within 48 hours of ICU admission. They found that bioT concentrations well below the lower limit of normal for their age range. Christeff et al.[27] investigated the effect of septic shock on the production of estrogens, other steroid hormones, and gonadotropins in men. They found that the changes in serum estrogen might be used as an accurate marker of individual outcome.

Ray et al[28] found that TT3 and TT4 concentra-

Table 3. Comparision of H-L goodness of fit tests, AUCs, and predictive values of predictive models

Models	Independent variables	OR (CI 95%)	P	χ2 H-L	DF	P	Sen (%)	Spe (%)	PR (%)	YI (%)	AUC (SE)	P
Model I	fT3	0.45 (0.26-0.77)	0.004	10.31	8	0.244	70.9	62.0	66.7	32.9	0.675 (0.053)	0.002
Model II	APACHE II	1.64 (1.36-1.98)	<0.0005	45.32	8	<0.0005	78.2	78.0	78.1	56.2	0.850 (0.041)	<0.0005
Model III	SOFA	1.99 (1.55-2.55)	<0.0005	35.63	7	<0.0005	80.0	74.0	77.1	54.0	0.859 (0.037)	<0.0005
Model IV	Age	1.04 (1.02-1.07)	0.002	9.86	7	0.197	76.4	58.0	67.6	34.4	0.723 (0.052)	<0.0005
	fT3	0.46 (0.26-0.80)	0.006									
Model V	APACHE II	1.75 (1.42-2.17)	<0.0005	14.03	7	0.051	78.2	76.0	77.1	54.2	0.861 (0.036)	<0.0005
	Sex	0.72 (0.56-1.78)	>0.05									
	APACHE II* sex	0.92 (0.85-0.99)	0.036									
Model VI	SOFA	1.51 (1.10-2.09)	0.012	20.91	7	0.004	76.4	84.0	80.0	60.4	0.891 (0.033)	<0.0005
	Age	1.033 (0.91-1.18)	>0.05									
	SOFA*age	1.01 (1.00-1.01)	0.012									

CI: confidence interval, DF: degree of freedom, Sen: sensitivity, Spe: specificity, PR: predictive rate, YI: Youden index, SE: standard error of AUC
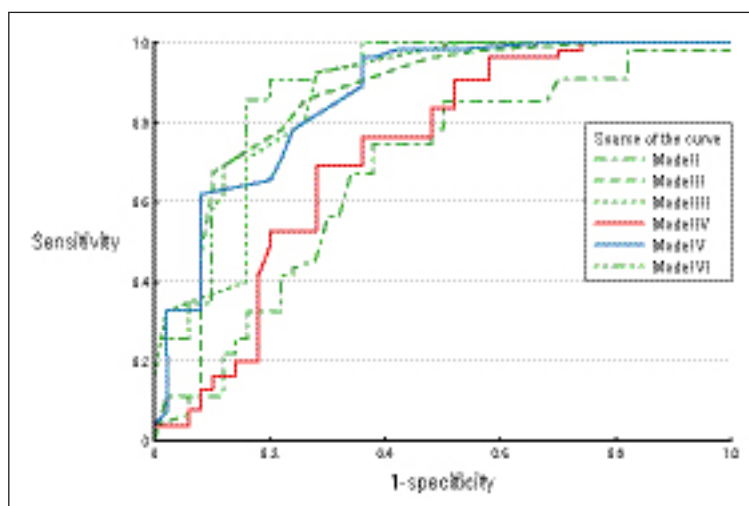

Figure 1. Receiver operating characteristic curves for Model I (AUC=0.675), Model II (AUC=0.850), Model III (AUC=0.859), Model IV (AUC=0.723), Model V (AUC=0.861), and Model VI (AUC=0.891).
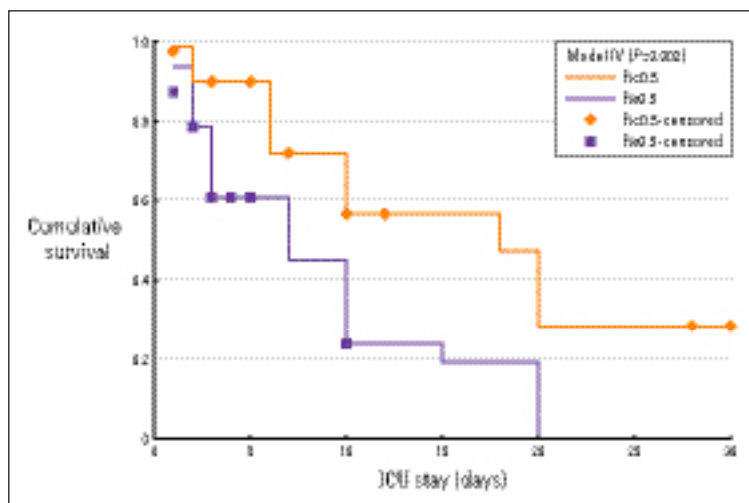

Figure 2. Cumulative survival in 206 patients with ARDS according to Model IV (dashed curve, R<0.5, n=78; solid curve, R≥0.5, n=128) after the first day of admission to a medical ICU. Day 0 is the day of ICU admission. Differences in the survival percentages were determined using Log Rank test (P=0.002).

tions were significantly less in non-survivors than in survivors on admission and on day 1 but not on day 2 in critically ill patients. TSH, fT3 and fT4 concentrations did not differ significantly between survivors and non-survivors at any time. They thought that these differences did not allow accurate prediction of outcome in critical illness. Rothwel et al.,[5] investigated concentrations of T3, T4, TSH, and cortisol that were measured on admission to an ICU in 200 consecutive patients who did not receive dopamine and found that thyrotropin concentration at admission is of prognostic value in critically ill patients. Slag et al.[29] found that there was a high correlation between low T4 levels and mortality. Jareg et al.[30] found that the basal cortisol and T3 concentrations obtained from blood samples collected within 48 hrs of ICU admission appear to be better discriminators of patient outcome than the APACHE II scores. In our study, we found that incremental increases in the risk of ICU death are associated with lower fT3.

Patients with a low risk of death, for example, those admitted for monitoring or routine postoperative care, tend to spend a short time in the ICU. Conversely, patients with an extremely high probability of death are likely to demonstrate either rapid improvement with therapy or death early in the ICU stay. In critically ill patients serum fT3 concentrations markedly decrease after ICU admission among non-survivors.

Our study had several limitations that deserve comment. First, repetitive measurements of thyroid hormones for certain intervals would increase the validity of our results. Adding DHEAS, testosterone measurements and lung injury scores would be beneficial. Second, increasing sample size would enable us to make firmer conclusions.
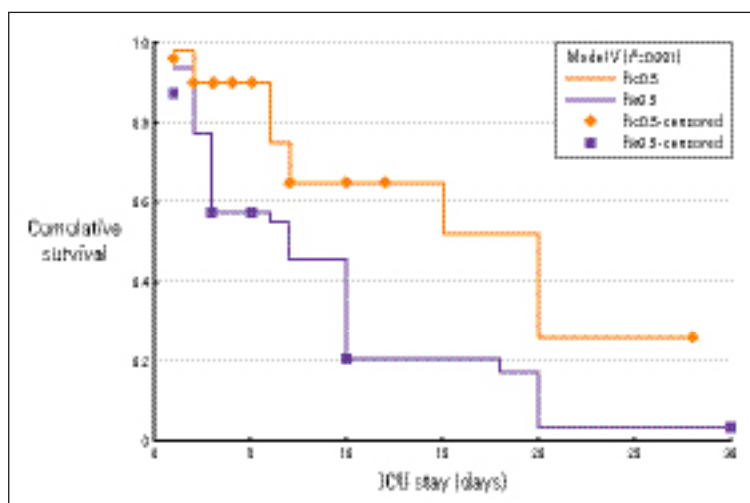

Figure 3. Cumulative survival in 206 patients with ARDS to Model V (dashed curve, R<0.5, n=78; solid curve, R≥0.5, n=128) after the first day of admission to a medical ICU. Day 0 is the day of ICU admission. Differences in the survival percentages were determined using Log Rank test ($P<0.001$).

In this study, the best Youden Index and highest predictive rate were found for the Model V within models (Model I, IV, and V) which showed good fit and this model was followed by Model IV showing the second best performance which showed the best fit. For Model IV, the 30-day mortality was 31.7% in low-risk group vs. 67.7% in high-risk group, and mean survival time was 16.8 days for low-risk group and 8.6 days for the high-risk group.

According to our findings, we suggest that fT3 levels might have additive discriminatory power to age, SOFA and APACHE II scores in predicting the short-term mortality in ARDS patients admitted to ICU. This study provides strong evidence to support the use of Model IV as a statistically valid method to predict survival in patients with ARDS.

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