Thyroid Hormone Levels Predict Mortality in Intensive Care Patients With Cirrhosis

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Abstract: *Introduction:* Mortality rates of intensive care patients are quite high. The aim of this study was to determine the availability of thyroid function tests and predictive scoring systems on the outcome of cirrhotic patients admitted to the intensive care unit. *Methods:* A total of 106 patients were included in the final analysis, of which 32 were men (30.2%) and 74 were women (69.8%). Predictors of mortality that were investigated include acute physiology and chronic health evaluation (APACHE II), model for end-stage liver disease (MELD), Child-Turcotte-Pugh (CTP) and sequential organ failure assessment (SOFA) scores and thyroid function tests including free triiodo-L-thryronin (fT3), free tetraiodothyronine/thyroxine (fT4) and thyroid-stimulating hormone/thyrotropin (TSH) levels. *Results:* High APACHE II, MELD, CTP and SOFA score and suppression of fT3 were all found to be associated with higher mortality in our intensive care patients who have cirrhosis (*P* < 0.001). Suppression of fT3 was also found to be reciprocally correlated with high APACHE II, MELD, CTP and SOFA scores (*P* < 0.001). fT4 had also reciprocal correlation with APACHE II, MELD, CTP and mortality. There is no correlation between TSH levels and predictive scores or mortality. *Conclusions:* Calculation of APACHE II, MELD, CTP and SOFA scores and measurement of fT3 and fT4 levels may all be useful as predictors of mortality in intensive care patients who have cirrhosis.

Key Indexing Terms: Intensive care unit; Cirrhosis; Thyroid hormones; APACHE II; MELD; Child-Turcotte-Pugh; SOFA; Mortality. [Am J Med Sci 2012;344(3):175–179.]

Patients admitted to the intensive care unit (ICU) generally have multiorgan failure, and it is only natural that failure of more than 1 organ would be associated with high morbidity and mortality. Several endocrine disorders may be encountered in intensive care patients, either due to severe stress posed by the underlying disorder or as a result of drugs used. The most commonly encountered condition is euthyroid sick syndrome (ESS), common contributors being the underlying disorder, drugs administered and nutritional status. ESS mainly manifests itself with low free T3 (fT3) levels, although decreases in fT3, free T4 (fT4) and thyroid-stimulating hormone (TSH) may occur in varying combinations. The number of hormones suppressed and the degree of suppression have shown to be associated with higher mortality rates.[1,2]

The main aim of this study was to determine whether thyroid hormones have any predictive value for mortality in intensive care patients who have cirrhosis. A possible correlation between thyroid hormone suppression and other predictors of mortality such as acute physiology and chronic health evaluation (APACHE II), model for end-stage liver disease (MELD), Child-Turcotte-Pugh (CTP) and sequential organ failure assessment (SOFA) scores was also investigated. To our knowledge, this study is the first one evaluating the relationship between thyroid function tests and those scoring systems to predict the outcomes in cirrhotic patients admitted to the ICU.

MATERIALS AND METHODS

This study was undertaken in the Medical ICU Department of the Faculty of Medicine at Çukurova University, Turkiye Yuksek Ihtisas Training and Research Hospital and Ankara Education and Research Hospital between lanuary 2008 and lanuary 2010 with the approval of the Local Ethics committee. During this period, patients who are cirrhosis were admitted to the ICU with varying indications [hepatic coma, bleeding varices, sepsis, spontaneous bacterial peritonitis or hepatorenal syndrome (HRS)]. Informed consent was obtained from lucid patients or from the next of kin of incapacitated patients. Patients were screened for an underlying thyroid disorder by obtaining a thorough medical history and a detailed physical examination and by checking for the presence of thyroid autoantibodies. Patients with a history or a new diagnosis of either hypothyroidism or hyperthyroidism were excluded from this study.

HRS as defined in the joined meeting of American Association Study of the Liver.[3] The criteria are (1) normal renal imaging; (2) urinary protein concentration <500 mg/day and urinary red blood cells count <50 cells per high power field; (3) no use of nephrotoxic drugs; (4) absence of shock; and (5) no improvement of serum creatinine (decrease to a level <1.5 mg/dL) after 2 days with diuretic withdrawal and volume expansion by means of human albumin infusion. HRS type-1 was defined as an increase of serum creatinine of at least twice the baseline level up to a final value >2.5 mg/dL within 14 days, whereas HRS type-2 was characterized by a slower increase of creatinine.

Blood samples were obtained 24 hours after admission into the ICU for the determination of fT3, fT4, TSH levels and thyroid autoantibodies, using the E-170 Elecsys electro chemiluminescence immunochemistry module. For patients started on drugs which are known to affect thyroid hormone levels, such as dopamine, dobutamine, steroids and amiadarone, blood samples were obtained before treatment was initiated. All samples were tested without delay, and the results were verified by external quality control assessment. In addition, the 24-hour APACHE II, MELD, CTP and SOFA score were calculated for each ICU patient.

APACHE II, MELD, CTP and SOFA score and thyroid hormone levels were compared between deceased and discharged patients. Similarly, the means, maximum and minimum levels and standard deviations for each of the thyroid hormones were

calculated, and once again, a comparison was made between age, men and women, and deceased and discharged patients. Mean values for age, APACHE II, MELD, CTP and SOFA scores were calculated for patients in which thyroid hormone was suppressed, and a comparison was made with patients with normal values. Finally, any differences between the sexes and between deceased and discharged patients with regard to thyroid hormone were evaluated.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 18 software (SPSS, Chicago, IL). Depending on the parameter involved, analysis of variance, Mann-Whitney *U* and χ^2 tests were used. Results were given as mean ± standard deviation. A backward logistic regression analysis, with the Hosmer-Leme-show goodness-of-fit test, was used to determine the most informative combination of predictors of mortality in intensive care patients with cirrhosis. A *P* value <0.05 was considered statistically significant.

RESULTS

A total of 106 consenting patients were enrolled in this study, of which 32 were men (30.2%) and 74 were women (69.8%). Of the 106 patients, 65 (61.3%) had some form of ESS, whereas in the remaining 41 patients (38.7%), thyroid function tests were normal. We detected etiological factors for cirrhosis as hepatitis B virus (33%), hepatitis C virus (20%), hepatitis B virus and hepatitis D virus (0.9%), alcohol (16%), autoimmune hepatitis *(6.6%)*, cryptogenic cirrhosis (6.6%), Wilson disease (0.9%) and primary biliary cirrhosis (0.9%). We determined complications for cirrhosis as hepatic coma 51 (48.1%), variceal bleeding 56 (52.8%), ascites 26 (24.5%), spontaneous bacterial peritonitis 24 (22.6%), hepatorenal syndrome 6 (5.7%) and hepatocellular carcinoma 2 (1.9%). Main and secondary diagnosis and the causes of death (hepatic or nonhepatic) in all patients were added to Table 1. There was no significant difference between the sexes and age with regard to prognostic markers.

Although patients' sex did not seem to influence thyroid function tests, more patients who died during follow-up in the ICU had lower level of fT3 and fT4, when compared with those who were discharged *(P* values were <0.001and 0.025, respectively). TSH level did not have a statistically significant effect on the outcome of the cirrhotic patients (Table 2).

Patients with low fT3 had higher APACHE II, MELD, CTP and SOFA scores when compared with those with normal fT3 levels *(P* < 0.001). Regardless of levels of fT3, patients' sex and age did not seem to have a statistically significant effect on the outcomes. Moreover, fT4 had reciprocal correlation with APACHE II, MELD and CTP scores *(P* levels were 0.019, 0.008 and <0.001, respectively). There was no correlation between predictive scores and TSH levels (Table 3). APACHE II, MELD, CTP and SOFA scores were significantly higher in patients who died than in those who were discharged from the ICU *(P* < 0.001; Table 2).

The cutoff value for fT3 for the detection of death in cirrhotic patients was calculated as ≤2.15 using receiver operating characteristic (ROC) analysis [sensitivity, 91.7%; specificity, 71.4%; AUC, 0.872 (0.808–0.936); *P* < 0.001] (Figure 1). Cutoff values were ≥10.5, ≥14.5, ≥19 and ≥9.5 for SOFA, APACHE II, MELD and CTP scores, respectively. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and accuracy of each scoring system in predicting mortality was shown in Table 4.

In logistic regression analysis, independent predictive factors for determining mortality in intensive care patients with

cirrhosis were calculated as fT3 [odds ratio = 0.105, 95% confidence interval (CI): 0.02–0.054] and SOFA (odds ratio = 1.461, 95% CI: 1.21–1.76) (Table 5).

DISCUSSION

In this study, APACHE II, MELD, CTP and SOFA scores and suppression of fT3 were all found to be associated with a higher mortality rate in intensive care patients. Suppression of fT3, in particular, was a significant indicator of mortality, and a correlation was established between fT3 level, APACHE II, MELD, CTP and SOFA scores. fT4 had also correlation with mortality and those predictive scores other than SOFA.

Both transient and permanent fluctuations in the hypothalamo-hypophyseal axis may affect many endocrine systems

TABLE 1. Primary causes of death in patients with hepatic coma and variceal bleeding

	Hepatic coma		Variceal bleeding	
	Deceased (n = 20)	Discharged (n = 31)	Deceased (n = 16)	Discharged (n = 40)
Ascites	13	2	6	5
Spontaneous bacterial peritonitis	16	2	0	6
Hepatorena syndrome	0	2	1	2
Hepatocellular carcinoma	2	0	0	0
Sepsis	2	0	0	0
Without comorbid medical conditions	0	27	15	32

TABLE 2. Outcomes of the patients according to clinical features, thyroid tests and scoring systems

	Deceased	Discharged	*P*
Number	36	70	
Age (yr)	55.5 (17–80)	56 (40–80)	0.955
Hepatic coma	20 (55.6%)	31 (44.3%)	0.271
Variceal bleeding	16 (44.4%)	40 (57.1%)	0.215
Ascites	19 (52.8%)	7 (10%)	<0.001
Spontaneous bacterial peritonitis	16 (44.4%)	8 (11.4%)	<0.001
Hepatorenal syndrome	1 (2.8%)	5 (7.1%)	0.357
Sepsis	2 (5.6%)	—	0.046
fT3	1.7 ± 0.4	2.5 ± 0.5	<0.001
fT4	1.0 ± 0.2	1.1 ± 0.2	0.025
TSH	0.94 (0.3–4.2)	0.99 (0.13–5.6)	0.78
CTP	10.5 (6–15)	7 (5–24)	<0.001
SOFA score	17 (5–24)	6 (1–16)	<0.001
MELD	24 (1–0)	10 (4–33)	<0.001
APACHE II	20.5 (10–46)	12 (2–32)	<0.001

fT3, free triiodo-L-thryronin; fT4, free tetraiodothyronine/thyroxine; TSH, thyroid stimulating hormone/thyrotropin; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh.