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EVALUATION OF THYROID ACTIVITY IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Background: Liver cirrhosis is increasingly becoming a public health problem. The aim of study is to evaluate the relationship levels thyroid stimulating hormone (TSH), triiodothyronine (T3), free thyroxine (fT4) and and liver cirrhosis(LC) severity, measured by Child-Pugh (CP) and MELD scores. Methods: 419 patients diagnosed with liver cirrhosis were included in the study. Biological tests for TSH, T3, fT4 on admission and discharge were used. All analysis was performed using, One-Sample Wilcoxon test and Kruskal-Wallis test. Results: The mean values for TSH were statistically significant higher compared to normal values only at admission (p<.05), and the mean values for T3 were statistically significant lower both on admission (p<.001) and on discharge (p<.001). No effect was observed for fT4. TSH on the admission and discharge moments were statistically significant differences (p<.001), T3 (p<.001) and fT4 (p<.004). The CP also influenced the hormone's values for TSH at admission (p<.01 and discharge (p<.001), and T3 at admission (p<.001) and discharge (p<.001) but not for fT4. For MELD score, a low power positive associations were observed only with TSH, on admission and discharge and negative associations with F3, in both situations. Conclusions: Elevated TSH levels at admission, coupled with their negative correlation with the CP score and differences between TSH-CP group C and groups A and B, highlighting the necessity for vigilant endocrine monitoring in hepatic patients. Also, admission T3 levels are lower than normal and negatively correlate with cirrhosis severity and MELD scores underscore potential clinical utility of monitoring thyroid function in assessing disease progression and improving patient survival outcomes.

Keywords: Low T3, severity of cirrhosis; metabolic changes, prognosis of cirrhosis

Introduction

Chronic liver disease is a public health problem with an estimated 1.5 billion cases worldwide (1, 2). Etiologically, non-alcoholic liver disease (NAFLD) accounts for 59%, hepatitis B virus hepatitis (HBV) accounts for 29% of cases, hepatitis C virus hepatitis (HCV) 2%, and alcoholic liver disease (ALD) 2% (3).

Huang estimates that underdiagnosis and inadequate treatment of chronic liver disease will lead to an increase in decompensated cirrhosis and related deaths over the next 10 years [4]. The estimated number of deaths associated with cirrhosis worldwide in 2019 was 1,472,000, representing 2.4% of global deaths (4, 5), and in Romania in 2019, cirrhosis of the liver was the 6th leading cause of death with a mortality rate of 46 deaths/100000 (6).

Hepatic cirrhosis develops because of inflammation, leading to the formation of fibrous tissue and regenerative nodules in the liver parenchyma. There is an asymptomatic phase (compensated cirrhosis) and a symptomatic phase (decompensated cirrhosis). Progressive portal hypertension, systemic inflammation, and liver failure determine the course of the disease (7).

There is a bidirectional relationship between the liver and the thyroid. The liver plays a major

physiological role in the activation, transportation, metabolism, and clearance of thyroid hormones. On the other hand, thyroid hormones affect hepatocyte activity and liver metabolism (8). Piantanida showed significant changes in thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) levels in these patients, suggesting the presence of subclinical or clinical thyroid dysfunction (8). Insufficient data, small study groups, lack of standardization of assessment methods raise questions as to how thyroid hormones are involved in the course and prognosis of liver cirrhosis.

The main objective of the research is to investigate the relationship between the variability of thyroid hormones and the severity of liver cirrhosis. In this regard, as a specific objective we aim to evaluate the relationship between thyroid hormone levels (T3, fT4 and TSH) and liver cirrhosis severity, measured by Child-Pugh and MELD scores. Hypotheses are i): Thyroid hormones are statistically significantly altered in patients with liver cirrhosis compared to normal values; ii): Severity of cirrhosis (assessed by Child Pugh and MELD scores) exerts a statistically significant effect on TSH, T3 and FT4 levels.

Methods

Liver cirrhosis severity was assessed using two measures: the Child-Pugh score and the MELD score.

The Child-Pugh score was designed to predict mortality in patients with cirrhosis based on five criteria: serum bilirubin, serum albumin, ascites, neurologic disorder and prothrombin time. The severity of cirrhosis established by this indicator shows 3 steps: A - 5 to 6 points, B - 7 to 9 points and C - 10 to 15 points (9).

MELD (Model for End-Stage Liver Disease) is a reliable indicator of short-term survival in patients with end-stage liver disease, designed based on serum bilirubin, serum creatinine, international normalized ratio (INR) and etiology of liver disease. The lowest MELD score is 6 and the highest is 40 (10, 11).

Sample collection

Thyroid Stimulating Hormone (TSH, thyrotropin) - collection was performed under a jeune conditions, but not after a recent thyroid biopsy or thyroid surgery. Venous blood was sampled, the collection container being vacutainer without anticoagulant, with or without separating gel. The serum is separated by centrifugation and the fresh serum is processed; if this is not possible, the serum should be stored at 2-8°C or -20°C. At least 0.5 mL of serum is and the method of determination is electrochemiluminescence detection immunochemistry (ELISA). Considering the age of the patients in the study group, we considered as normal values the range between 0.27 and 4.2 μIU/mL and excluded any analytical or drug interference (12).

Thyroxine (T4). The collection was carried out , from venous blood, the collection container being a vacutainer without anticoagulant, with and/or without separating gel. The serum is separated by centrifugation and the fresh serum is processed; if this is not possible, it should be stored at 2-8°C or -20°C. The volume of the collected sample is at least 0.5 mL serum, and the method of determination is immunochemical, with electrochemiluminescence detection by electrochemiluminescence assay (ELISA). The reference values are between 12.0-22.0 pmol/L and we excluded any possible interference with some elements of the kit, but also with the drugs the patient was taking that could have influenced the resulting value (13).

Triiodothyronine (T3) is mainly responsible for the actions of thyroid hormones in different target organs. Most of the T3 hormone is produced outside the thyroid gland, mainly in the liver, by enzymatic deiodination at the 5' position of T4. For this reason, the serum T3 concentration reflects the functional status of peripheral tissues rather than the secretory performance of the thyroid gland. Reduced conversion of T4 to T3 results in a decrease in serum T3 concentration (14). Like T4, more than 99% of T3 is bound to transporter proteins, but with a 10-fold lower affinity. The method of collection and determination is like the determination of fT4, and the range considered as reference is between 1.3-3.1 nmol/L (14).

Inclusion criteria

All patients aged at least 18 years, able to read and write, who gave informed consent, diagnosed with liver cirrhosis after clinical,

paraclinical-biologic examination and imaging investigations, classified into severity categories and treated appropriately, present in the records of an internist or gastroenterologist, or newly diagnosed during hospitalization were included in the study.

The diagnosis of cirrhosis of the liver was confirmed clinically by the presence of signs and symptoms of liver failure and portal hypertension, and paraclinical based on biological tests and imaging methods. The Child Pugh and MELD scores were calculated so that each case was categorized in terms of course and severity.

Exclusion criteria

Patients who refused to sign informed consent were not included in the study. Also, patients under medication treatment that might have influenced thyroid hormone metabolism (e.g. iodine contrast agent and Amiodarone, which enhances the conversion of T4 to Triiodothyronine T3), but also other classes of drugs, such as glucocorticoids and Dopamine, which decrease TSH secretion with subsequent decrease in T3 were excluded

Participants

The study included 419 patients diagnosed with liver cirrhosis, hospitalized between March 2022 and March 2023 in Constanța County Hospital, Romania.

Data analysis methods

All analysis was performed using R (15) and packages: caret (16), colorspace (17-19), dplyr (20), ggplot2 (21), ggpubr (22), haven (23), Hmisc (24), kableExtra (25), lattice (26), mvtnorm (27), papaja (28), readxl (29), rstatix (30), sasLM (31), tinylabels (32), VIM (33) and writexl (34).

We initially proceeded with the identification of outliers, missing values and performing an univariate descriptive analyses, including the analysis of compliance with the univariate normality assumption for continuous data, based on Shapiro-Wilk statistical test (35, 36), and the skewness and kurtosis indicators.

Extreme univariate values (located beyond or above 3 standard deviations to the left respectively to the right of the mean) were replaced by missing values, and imputation was performed by the K-nearest neighbor method (33).

To test the hypotheses we will use, depending on the fulfillment of the assumptions, either the One-Sample t-test, comparing the mean of a population with a theoretical value (One-Sample t-test) and the Paired Samples t-test, comparing the means of two related populations from which the samples where extracted (Paired Samples t-test), or their non-parametric equivalents (One-Sample Wilcoxon signed rank test, respectively Wilcoxon signed rank test on paired sample). Similarly, we will use One-Way ANOVA if the assumptions are met, or the Kruskal-Wallis test comparing the means of the ranks of several populations from which the samples are drawn if not. To study the effect of the MELD score on thyroid hormones, we will use simple linear regression, in which the values of thyroid hormones will function as predictors.

Results

Socio-demographic data

The age of the participants ranged from 32 to 91 years (M=63.26, SD=9.57), 68.97% male. After diagnosis, patients were hospitalized between 0 and 96 months (M=20.35, SD=20.22), and the duration of hospitalization ranged from 0 to 41 days (M=7.21, SD=6.73).

In terms of etiology, most have a TE etiology (50.60%), followed by those with HVC (18.62%) and HVB (17.90%) etiology, as well as mixed etiology (12.41%). The Child Pugh score groups patients into 3 groups, the most common being group „B” (49.16%), followed by group „C” (32.22%) and group „A” (18.62%).

Univariate descriptive analysis

Following outlier analyses, we found that scores above 10.4 on discharge TSH, above 5.4 on inpatient T3, and above 4.3 on discharge T3 were assessed as outliers and replaced with missing and then were imputed. For the inpatient data, MELD score, TSH, and fT4 were positively skewed, postulating the existence of high values, but not extreme. Also, the MELD score and TSH have a leptokurtic distribution, with low variability around the mean (Table 1), so the assumption of univariate normal distribution were not fulfilled.

Table1. Univariate descriptive analysis - data collected at admission

Variabile	MELD	TSH (mUI/L)	T3 (pmol/L)	fT4 (pmol/L)
N	419	419	419	419
Mean	14.08	4.28	0.74	14.14
Ab.Std	4.32	1.82	0.6	2.62
Median	14	4.1	0.7	13.5
Min	5	1.3	-0.75	8.8
Max	31	12.45	2.5	23
Skew (ES)	0.72 (0.12)	0.77 (0.12)	0.13 (0.12)	0.82 (0.12)
Kurt (ES)	0.92 (0.24)	1.16 (0.24)	-0.44 (0.24)	0.42 (0.24)
Normal		0.4 - 4.0	1.2 - 3.0	12.0 - 22.0

The discharge data shown the same trends: positively skewed distributions for TSH, T3 and fT4, and a platikurtic distribution for T3. The other variables were normally skewed (mesokurtic), but due to the skewness, the distribution cannot be considered normal (Table 2).

Table 2. Univariate descriptive analysis - data collected at admission

Variables	TSH (mUI/L)	T3 (pmol/L)	fT4 (pmol/L)
N	419	419	419
Mean	3.9	0.76	12.77
Ab.Std	1.26	0.53	3.04
Mediana	3.55	0.65	12.4
Min	1.35	-0.28	8.8
Max	8.15	2.25	23.4
Skew (ES)	0.67 (0.12)	0.6 (0.12)	0.86 (0.12)
Kurt (ES)	-0.01 (0.24)	-0.66 (0.24)	0.26 (0.24)
Normal	0.4 - 4.0	1.2 - 3.0	12.0 - 22.0

Bivariate correlation analysis

Since the assumption of univariate normality was not met, the variables were correlated using the Spearman correlation coefficient ρ Spearman (Table 3) after converting the ordinal variable „Child Pugh score" into the corresponding numerical values.

Hypothesis analysis

H_1: Thyroid hormones are statistically significantly altered in patients with liver cirrhosis compared to normal values.

Since the assumption of univariate normality was not met, the analysis was conducted using the non-parametric Wilcoxon signed rank test to compare the mean of the ranks of the values with the theoretical value (extracted from one of the limits of normal clinical interval). In the case of thyroid hormones, we found that the mean values for TSH was 4.28 (SD=1.82, median=4.1) on admission, and 3.9 (SD=1.26, median=3.55) on discharge, normal values ranging from 0.4 to 4.0 mIU/L. It is easy to observe that patients have statistically significantly higher TSH values on admission (W=46853.5, p=.016, es=0.1), and the effect size was small. At discharge, the values decreased (M=3.9, SD=1.26, median=3.55), but the differences were not statistically significant.

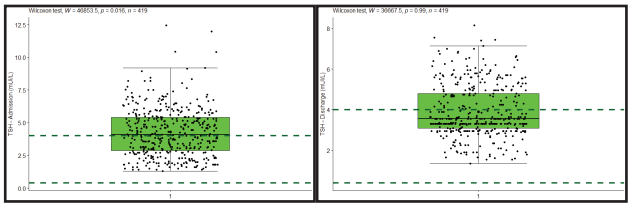

Figure 1 Comparisons of the mean ranks of the values with the theoretical value 4.0 for TSH - on admission (left) and discharge (right)

Mean values for T3 was 0.74 (SD=0.6, median=0.7) on admission and 0.76 (SD=0.53,

Table 3. Spearman ρ correlation matrix

	1	2	3	4	5	6	7	8
(1) Child.Pugh	-							
(2) MELD	.57***	-						
(3) TSH – Admission	.17***	.18***	-					
(4) TSH – Discharge	.22***	.22***	.76***	-				
(5) T3 – Admission	-.28***	-.20***	-.37***	-.31***	-			
(6) T3 – Discharge	-.34***	-.19***	-.20***	-.15**	.55***	-		
(7) fT4 – Admission	.01	-.02	-.19***	-.07	.28***	.13**	-	
(8) fT4 – Discharge	.05	.09	.06	.21***	.11*	.50***	.41***	-
Means		14.08	4.28	3.9	0.74	0.76	14.14	12.77
Standard deviations		4.32	1.82	1.26	0.6	0.53	2.62	3.04

**** p<.001; ** p<.01; * p<.05*

median=0.65) on discharge, normal values ranging from 1.2 to 3.0 pmol/L. Indeed, patients shown statistically significantly lower T3 values on admission (W=12307, p<.001, es=0.62), with a strong effect size. At discharge, the values increased (M=0.76 (SD=0.53, median=0.65) and the same statistically significant differences were found. The effect size was moderate in this case (W=11295, p<.001, es=0.32).

For fT4, the mean values were 14.14 (SD=2.62, median=13.5) on admission and 12.77 (SD=3.04, median=12.4) on discharge, with normal values ranging from 12 to 22 pmol/L. No statistically significant differences were observed, so our data shown that this hormone was not altered in patients with liver cirrhosis.

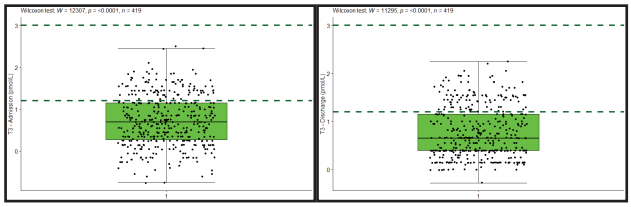

Figure 2 Comparisons of the mean ranks of the values with the theoretical value 1.2 for T3 - on admission (left) and discharge (right)

In association with this hypothesis, we aimed to investigate a secondary null hypothesis, H0A: the treatment administered does not have a statistically significant effect on thyroid hormones, using the Wilcoxon signed rank test on paired samples. and comparing the hormone levels at admission with the hormone levels at discharge.

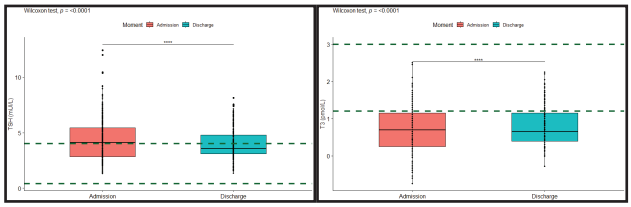

Figure 3 Comparisons of the mean rank mean values between admission and discharge for a) TSH and b)T3

In the case of TSH, the mean of ranks at admission was 4.28 (SD=1.82, median=4.1), and at discharge it decreased to 3.9 (SD=1.26, median=3.55), between the two values statistically significant differences (V=652416, p<.001, es=0.3) were observed. Our data showed that it is possible that the treatment can reduce the TSH level, and the effect size was strong.

Strong statistically significant effects were also found for the hormone T3 (V=500304, p<.001, es=0.25); the mean of ranks at admission (M=0.74, SD=0.6, median=0.7) were statistically significantly lower compared to the mean ranks at discharge (M=0.76, SD=0.53, median=0.65).

Although we have shown that fT4 does not statistically significantly exceed normal values in patients with liver cirrhosis, a statistically significant difference between the mean ranks of the two time points (V=380698, p<.001, es=0.32) was observed, and the effect size was moderate.

Indeed, our data show that the mean of the ranks at admission (M=14.14, SD=2.62, median=13.5) was statistically significantly higher compared to the mean of the ranks at discharge (M=12.77, SD=3.04, median=12.4).

H2: Severity of cirrhosis (assessed by Child Pugh and MELD scores) exerts a statistically significant effect on TSH, T3 and FT4 levels.

We used the nonparametric Kruskal-Wallis test with Child-Pugh score as an independent variable, because the assumptions of the analysis were not met, and pairwise comparisons were performed by Dunn test, with Bonferroni corrections for significance threshold.

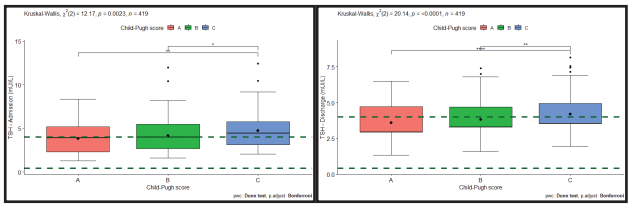

Figure 4 Comparisons of mean rank mean values between groups as determined by Child-Pugh TSH score at admission (left) and discharge (right)

A small but statistically significant effect of the severity of cirrhosis ($\chi2(2)=12.17$, p=.002, $\eta2=0.02$) was found for TSH at hospitalization.

Multiple comparisons shown that the highest TSH values at hospitalization were found in group „C” (N=135, M=4.72, SD=1.82, Median=4.45), statistically significantly higher (Dunn=3. 14, p=.005) than the values in group „A” (N=78, M=3.84, SD=1.57, Median=3.9) and group „B” (N=135, M=4.72, SD=1.82, Median=4.45, Dunn=3.14, p=.005).

No statistically significant differences were observed between the values obtained in group „A” (N=78, M=3.84, SD=1.57, Median=3.9) and those obtained in group „B” (N=206, M=4.15, SD=1.86, Median=4, Dunn=1, p=.949). The same observations were also observed for TSH at discharge, and the effect size was also small ($\chi2(2)=20.14$, p<.001, $\eta2=0.04$).

Multiple comparisons at discharge shown that the highest TSH values were also found in group „C” (N=135, M=4.19, SD=1.25, Median=3.55), statistically significantly higher (Dunn=2.82, p=.014) than the values in group „A” (N=206, M=3.82, SD=1.24, Median=3. There were no statistically significant differences between the values obtained in group „A” (N=78, M=3.6, SD=1.26, Median=2.95) and those obtained in group „B” (N=206, M=3.82, SD=1.24, Median=3.3, Dunn=3.31, p=.003).

In terms of hospitalization, regarding T3 values, the effect was statistically significant and moderate ($\chi2(2)=34.44$, p<.001, $\eta2=0.08$).

Multiple comparisons shown that the highest hospitalization T3 values were found in group „A” (N=78, M=0.97, SD=0.55, Median=0.8), but not statistically significantly different from the values in group „B” (N=206, M=0.81, SD=0.6, Median=0.85). However, statistically significant differences (Dunn=-5.41, p<.001)) was observed between the values in group „A” (N=78, M=0.97, SD=0.55, Median=0.8) and those in group „C” (N=135, M=0.5, SD=0.54, Median=0.5), as well as between the values in group „B” and those in group „C” (Dunn=-4.54, p<.001).

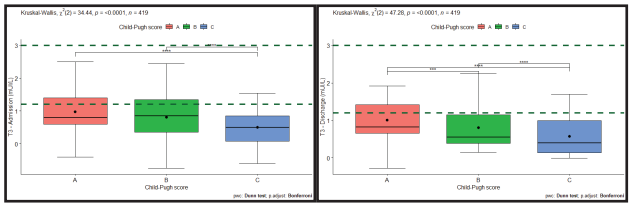

Figure 5 Comparisons of mean rank mean values between groups determined by Child-Pugh score at T3 at admission (left), discharge (right).

Multiple comparisons shown that the highest values of T3 at discharge were found in group „B” (N=206, M=0.8, SD=0.53, Median=0.55), statistically significantly different (Dunn=-3.6, p<.001) from those of group „A” (N=78, M=1, SD=0.48, Median=0.82), and from those of group „C” (N=135, M=0. 57, SD=0.51, Median=0.4, Dunn=-4.35, p<.001). Statistically significant differences (Dunn=-6.75, p<.001) also appeared between the participants in group „A” (N=78, M=1, SD=0.48, Median=0.82), and those in group „C” (N=135, M=0.57, SD=0.51, Median=0.4).

In the case of fT4 values, no statistically significant differences determined by the Child-Pouhg score were observed neither in the inpatient ($\chi^2_{(2)}=0.03$, p=.986, $\eta^2=0$) nor in the discharge ($\chi^2_{(2)}=1.08$, p=.584, $\eta^2=0$).

For the MELD score, we observed a statistically significantly association with TSH on admission ($F_{(1,\ 417)}=16.36$, p<.001) and on discharge ($F_{(1,\ 417)}=15.65$, p<.001), however with a low predictive power ($R^2=.04$, $R^2_{adj.}=.04$, respectively $R^2=.04$, $R^2_{adj.}=.04$).

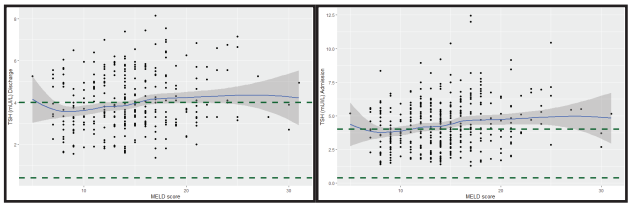

Figure 6 Prediction of estimated TSH value at admission (left) and discharge (right) based on MELD score

When the MELD score is increasing by one unit, the estimated inpatient TSH score will increase by 0.08 units, and this association was statistically significant (B=0.08, t=4.04, p<.001). The relationship was also observed for the outpatient when the MELD score is increasing by one unit, the estimated outpatient TSH score increase by 0.06 units, and, again a statistically significant association (B=0.06, t=3.96, p<.001) was observed.

The MELD score was associated with T3 both at admission ($F_{(1,\ 417)}=11.65$, p<.001) and at discharge ($F_{(1,\ 417)}=15.65$, p<.001), also with low predictive power ($R^2=.04$, $R^2_{adj.}=.04$, respectively $R^2=.04$, $R^2_{adj.}=.04$). When the MELD score is increasing by one unit, the estimated T3 score at admission will decrease by 0.02 units, and this association is statistically significant (B=-0.02, t=-3.41, p<.001). At discharge the same values were observed, increasing the MELD score by one unit will decrease the estimated

score at T3 by 0.02 units, and the association is again statistically significant (B=-0.02, t=-3.15, p<.001).

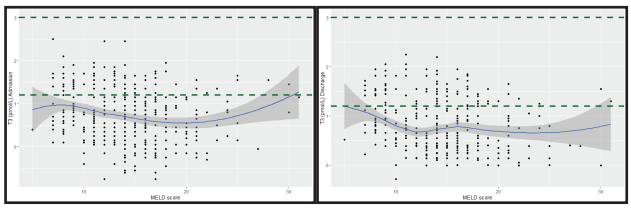

Figure 7 Prediction of estimated T3 on admission (left) and discharge (right) based on MELD score

The MELD score is not associated with fT4, having no predictive power for this hormone.

In the present study, 68.97% of the participants were male, yielding results similar to those of Huang, who found 66% males in the study group (4).

The mean TSH values on admission were 4.28 pmol/L and 3.90 pmol/L on discharge, observing that the mean TSH values on admission were higher than the upper limit of normal values, while the mean TSH values on discharge were within normal range but decreasing from the mean TSH values on admission. Similar data have been obtained by Langer, showing an analogous evolution of TSH values in patients with acute and chronic liver failure: 4.2 pmol/L at admission and 3.4 pmol/L at discharge (37).

Discussions

In the present study, T3 values averaged 0.74 pmol/L, a value below the normal limit. Bethiun obtained similar results, with mean values of 0.64 pmol/L (38), in agreement with Feng, reporting a value of 0.71 pmol/L (39).

For fT4 the mean of the values was 14.14 pmol/L, the value corresponding to the data published by Feng, with a mean of 16.32 pmol/L (39). On the other hand, Vincken reports a much lower mean for fT4 of 0.5 pmol/L (40).

We also observed that the severity of cirrhosis (as assessed by Child Pugh and MELD scores) exerts a statistically significant effect on TSH, T3 and fT4 levels, with statistically significant differences in the mean ranks of TSH values between Child Pugh score group C and groups A and B being found, which is in agreement with the results published by Raj, who showed that in patients with Child C cirrhosis TSH values can be up to 7.5-fold higher than normal values (41).

Also, similar results are obtained by Punekar, who shown the correlation between increasing TSH values in parallel with the severity of liver disease (42). On the other hand, Wu disproves this hypothesis, suggesting the limited possibility of using TSH as a prognostic factor in relation to the severity of liver cirrhosis (43).

Regarding T3, in the present study results showed a correlation between T3 value and severity of liver cirrhosis, in line with Punekar's findings that showed a decrease in T3 in relation to worsening disease and classification into a more advanced severity class (42). On the other hand, in Sartika's studies, no correlation between T3 values and severity of cirrhosis could be proved (44).

The Child Pugh score and the MELD score were statistically significantly correlated, with similar data obtained by Peng (45), and the Child score is negatively correlated with TSH values, both at admission and discharge, which is confirmed in studies by Wu (43). Huang, however, provides contrary evidence (4), and the present study showed the negative association between the MELD score and T3 value. However, the issue is controversial in the literature, being confirmed by Punekar's research (42) and refuted by Sartika's published results (44).

Conclusions

Elevated TSH levels at admission, coupled with their negative correlation with the CP score and differences between TSH-CP group C and groups A and B, highlighting the intricate interplay between thyroid function and liver disease severity, the necessity for vigilant endocrine monitoring in hepatic patients. Also, admission T3 levels are lower than normal and negatively correlate with cirrhosis severity and MELD scores underscore potential clinical utility of monitoring thyroid function in assessing disease progression and improving patient survival outcomes.

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For this article authors contribution is: Conceptualization, A.B. and E.C.; methodology, A.B.; software, D.B.; validation, A.N., E.C.; formal analysis, D.B.; investigation, A.B.; resources, A.B.; data curation, D.B.; writing—original draft preparation, A.B.; writing—review and editing, A.N.; visualization, D.B.; supervision, E.C. No funding or sponsorship was received for this study or publication of this article.

Conflict of interest

There is no conflict of interest declared by the authors.

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