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ORIGINAL ARTICLE

CORRELATION OF THYROID FUNCTION TEST WITH SEVERITY OF LIVER DYSFUNCTION IN CIRRHOSIS OF LIVER

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Abstract

Background: *A normal function of both the thyroid gland and the liver is necessary to maintain normal thyroid hormone levels and action. This study aimed to find out the thyroid abnormalities in patients presenting with liver cirrhosis and also to look for any correlation between thyroid function test (TFT) abnormalities and severity of liver disease.* ***Methods:*** *This cross-sectional observational study was conducted at the department of Gastroenterology and department of Medicine in Sir Salimullah Medical College, Dhaka, for 12-months. A total of 328 patients with liver cirrhosis were included after written informed consent. A detailed history, thorough laboratory and physical examination were carried out in each patient. Severity of liver dysfunction was graded by using Child Pugh Scoring. Thyroid function test was done. Data were collected in separate case record form and analyzed by SPSS 24.0.* ***Results:*** *According to Child Pugh score 31.1% had disease severity score A, 24.1% had B and 44.8% had C. Mean FT3 level (fmol/l) significantly decreases (5.3±1.5 in class-A, 3.5±1.7 in class-B and 3±1.3 in class-C) and TSH level (µIU/ml) significantly increases (3.3±1.3 in class-A, 5.3±2.1 in class-B and 5.5±1.8 in class-C) with increases number of disease severity score ($p<0.05$).* ***Conclusion:*** *There is a negative and inverse correlation between decreasing FT3 with severity of liver cirrhosis as measured by child pugh score and a positive and direct correlation between increasing Serum TSH with severity of liver cirrhosis as measured by child pugh score. This suggests that thyroid function test can be used as a prognostic indicator in cirrhotic patient.*

Key words: *Thyroid function test, Thyroid function abnormalities, Liver dysfunction, Cirrhosis of liver, CTP score.*

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Introduction:

One of the main causes of illness and death worldwide is chronic liver disease (CLD). Alcohol intake, viral hepatitis, and nonalcoholic fatty liver disease are the avoidable causes.[1] The advanced stage of liver disease known as liver cirrhosis is marked by the formation of regenerating nodules, scarring, and histological changes to the hepatic tissue.[2] It accounted for 2.2% of deaths and 1.5% of disability-adjusted life years globally in 2016, ranking as the 11th and 15th main causes of death and morbidity, respectively.[3] Eight million people with chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections are estimated to reside in Bangladesh. "Compensated" and "decompensated" cirrhosis are the two forms that exist. Hepatic encephalopathy (HE), bleeding varices, ascites, jaundice, or cirrhosis worsened by one or more of these symptoms is known as decompensation. Hepatorenal syndrome, hyponatremia, and spontaneous bacterial peritonitis - all of which are indicative of decompensation. None of these characteristics apply to compensated cirrhosis patients.[4]

The thyroid gland produces two related hormones called triiodothyronine and thyroxine (T4) (T3). These hormones, which function through the thyroid hormone receptors α and β, are essential for cell differentiation during development and aid in preserving the adult's thermogenic and metabolic homeostasis.[5] Thyroid gland secretes T4 in excess of T3 by a factor of twenty. As the primary organ in the peripheral conversion of tetraiodothyronine (T4) to T3 by Type 1 deiodinase, the liver is involved in the metabolism of thyroid hormones. The primary enzyme, type I deiodinase, is derived from the liver and is responsible for 30–40% of the extrathyroidal synthesis of T3.[1] It can also convert T4 to T3 by both 5'-and 5-deiodination. In addition, the liver is involved in the manufacture of thyroid binding globulin, thyroid hormone conjugation, and thyroid hormone excretion. The THS are metabolized by the liver, which also controls their systemic endocrine effects. The liver is mainly responsible for the transportation, storage, activation, and metabolism of thyroid hormones. Impaired hepatic conversion of T4 to T3 is important in cirrhosis. Catalyzed by type-1 deiodinase, T4 is converted to T3. The liver is where this enzyme is mostly found. A decrease in serum T3 might, therefore, be explained by a presumed deficit of hepatic type 1-deiodinase activity. Impaired cellular absorption and hepatic deiodinization result in decreased T3 and T4 levels.[6]

Both the liver and the thyroid can be affected by thyroid disorders, liver illness affects the metabolism of thyroid hormones, and many systemic diseases impact both organs. Patients with subacute thyroiditis or hyperthyroidism may have abnormal liver function tests.[7] Thyroid hormones influence oxidative processes and the activity of enzymes that control lipogenesis, lipolysis, and other aspects of liver function. As a result, the thyroid and liver have a mutually beneficial interaction that influences other organ function.[8]

A study conducted in India in 2023, found a substantial inverse relationship between the severity of cirrhosis and the serum levels of FT3 and FT4.[6]

According to a different study in 2019, the severity of cirrhosis was significantly inversely correlated with the serum levels of FT3, and FT4.[9]

Another study in 2022, observed that TSH levels were directly correlated with the severity of liver disease.[1]

In a study conducted in Nepal in 2019, it was shown that there was a statistically significant correlation between the mean scores of FT3 and FT4 across the various CPS categories.[7]

A study in India in 2018 revealed that in patients with liver cirrhosis, mean levels of FT3, FT4, and TSH were significantly higher and mean levels of FT3 and FT4 were significantly lower, respectively, and that these levels also correlated with the severity of liver disease.[4] Higher Child Pugh ratings were linked to lower mean free T3 levels in patients in a different study trial, however there was no significant relationship found between free T4 and TSH levels.

According to a different also conducted in India in 2017, more severe liver injury is linked to low free T3 and T4 levels.[10]

The most common reason for low free T3 levels in liver disease is reduced Type I deiodinase, which causes peripheral T4 to T3 conversion to be reduced.[11]

The precise relationship between the degree of liver cirrhosis and thyroid function test has not yet been determined in our population.

Thyroid hormone function test study will help manage chronic liver disease by shedding light on the functional components of the disease and improving understanding of how thyroid function tests relate to chronic liver disease. The objective of our study was to determine the correlation between thyroid function test and severity of liver dysfunction in cirrhosis of liver.

Methods:

A hospital based cross-sectional observational study was conducted in the Department of Gastroenterology and Medicine at Sir Salimullah Medical College Mitford Hospital, Dhaka. Total 328 patients were aged between

18 to 70 years irrespective of sexes with clinical, biochemical, and or diagnostic imaging (ultrasonography, Upper GIT Endoscopy and fibroscan) evidence of liver cirrhosis who attended in both indoor and outdoor facilities of the department of Gastroenterology and Medicine of SSMC MH, also patients who were referred to department of Gastroenterology for endoscopy of upper GIT, EVL procedure and fibroscan between August 2022 to July 2023 were enrolled in this study by purposive sampling method. Patient with sepsis, cardiac failure, renal failure, nephrotic syndrome, any malignancy, any chronic disease(except liver cirrhosis), pregnancy, with prior history of thyroid disease (Any known documented thyroid disease or history suggestive of thyroid disease) or taking medication that may affect the activity and metabolism of thyroid hormones were excluded from this study. After selection of participants according to the inclusion and exclusion criteria, detailed history and physical examination, drug history were taken as per predesigned questionnaire. S.billirubin , prothrombin time with INR, S.Albumin, thyroid function test: TSH, FT3, FT4 were done in each patient. Severity of liver dysfunction was graded by using Child Pugh Scoring. According to Child Pugh Scoring, severity of liver cirrhosis was categorized as A, B, C group. All the data were collected in separate case record form by researcher himself.Prior to beginning analysis, the data were evaluated for accuracy, consistency, and completeness after collection. The data analysis was done with SPSS version 24. (IBM Corp., Armonk, NY). A level of P<0.05 was used to determine statistical significance. An analysis of exploratory data was done in order to characterize the study population. Categorical variables were summarized using frequency tables, while continuous variables were summarized using metrics of central tendency and dispersion such as mean, median, percentiles, and standard deviation. The chi-square method was used to evaluate categorical data. One way ANOVA test was used to compare the TFT level with CPS categories and Post-hoc test was done by Bonfrroni test whenever p-value was <0.05.

Results:

In this study, there were 328 participants who satisfied the selection criteria. Majority (62.2%) of the patients were aged between 41 to 60 years followed by 30.2% were above 60 years and 7.6% were 40 years or below. Mean age of the patients was 52.9±9.6 years.

Among all, 58.8% (n=193) of the patients were male and 41.2% (n=135) were female. According to Child Pugh score 31.1% had disease severity score A, 24.1% had B and 44.8% had C. Among all, 53.4% had Ascites, 25.9%v had Encephalopathy, 11% had Hematemesis, 9.8% had melena and 11% had jaundice which is shown in Table I.

Table-I

Distribution of the patients according to clinical parameter (n=328)

Clinical parameter	Frequency (n)	Percentage (%)
Encephalopathy	85	25.9
Ascites	175	53.4
Hematemesis	36	11
Melena	32	9.8
Jaundice	36	11

Multiple answers considered.

In Class A, 6% had FT3 level <3.5fmol/l and 94% had 3.5 to 8.56 fmol/l, in Class B, 46.8% had <3.5fmol/l and 53.2% 3.5 to 8.56 fmol/l and in Class C, 89.8% had <3.5fmol/l and 10.2% had 3.5 to 8.56 fmol/l. FT3 level significantly decreases with the increasing number of disease severity score which is depicted in Table II.

Table II

Distribution of the patients according to FT3 level in different stage of disease (n=328)

FT3 level (fmol/l)	Class A n(%)	Class B n(%)	Class C n(%)	p-value
<3.5	7 (6)	37 (46.8)	132 (89.8)	<0.001
3.5 to 8.56	95 (94)	42 (53.2)	15 (10.2)	

p-value was determined by* Chi-square test. within parenthesis percentage over column in total.

In Class A, 7% (n=7) had FT3 level <3.5fmol/l and 93% (n=95) had 3.5 to 8.56 fmol/l, in Class B, 46.8% (n=37) had <3.5fmol/l and 53.2% (n=42) 3.5 to 8.56 fmol/l and in Class C 80.8% (n=132) had <3.5fmol/l and 10.2% (n=15) had 3.5 to 8.56 fmol/l. FT3 level significantly decreases with the increasing number of disease severity score.

In Class A, 26.5% had FT4 level <8.5fmol/l and 73.5% had 8.56 to 25.6 fmol/l, in Class B, 25.3% had <8.5fmol/l and 74.7% had 8.56 to 25.6 fmol/l and in Class C, 37.4% had <8.5fmol/l and 62.6%had 8.56 to 25.6 fmol/l. FT4 level decreases with the increasing number of disease severity score but these finding was statistically insignificant (Table III).

Table-III

Distribution of the patients according to FT4 level in different stage of disease (n=328)

FT4 level (fmol/l)	Class A n(%)	Class B n(%)	Class C n(%)	p-value
<8.56	27(26.5)	20(25.3)	55(37.4)	0.083
8.56 to 25.6	75(73.5)	59(74.7)	92(62.6)	

p-value was determined by* Chi-square test. within parenthesis percentage over column in total.

In Class A, 26.5% (n=27) had FT4 level <8.5fmol/l and 73.5% (n=75) had 8.56 to 25.6 fmol/l, in Class B, 25.3% (n=20) had <8.5fmol/l and 74.7% (n=59) had 8.56 to 25.6 fmol/l and in Class C, 37.4% (n=55) had <8.5fmol/l and 62.6% (n=92) had 8.56 to 25.6 fmol/l. FT4 level decreases with the increasing number of disease severity score but these finding was statistically insignificant.

In Class A, 88.2% had TSH level 0.3 to 5 μIU/ml and 11.8% had >5 μIU/ml, in Class B, 59.5% had 0.3 to 5 μIU/ml and 40.5% had >5 μIU/ml and in Class C, 69% had 0.3 to 5 μIU/ml and 53% had >5 μIU/ml. TSH level significantly increases with the increasing number of disease severity score (Table IV).

Table-IV

Distribution of the patients according to TSH level in different stage of disease (n=328)

TSH level (μIU/ml)	Class A n(%)	Class B n(%)	Class C n(%)	p-value
0.3 to 5	90(88.2)	47(59.5)	69(47)	<0.001
>5	12(11.8)	32(40.5)	78(53)	

p-value was determined by* Chi-square test. within parenthesis percentage over column in total.

In Class A, 88.2% (n=90) had TSH level 0.3 to 5 μIU/ml and 11.8% (n=12) had >5 μIU/ml, in Class B, 59.5% (n=47) had 0.3 to 5 μIU/ml and 40.5% (n=32) had >5 μIU/ml and in Class C, 69% (n=47) had 0.3 to 5 μIU/ml and 53% (n=78) had >5 μIU/ml. TSH level significantly increases with the increasing number of disease severity score.

Mean FT3 level significantly decreases and TSH level significantly increases with increases number of disease severity score. (Table V).

Table-V

Association of thyroid function test with severity of liver function test (n=328)

Thyroid function test	Class A Mean±SD	Class B Mean±SD	Class C Mean±SD	p-value
FT3 level (3.5-8.56fmol/l)	5.3±1.5	3.5±1.7$^{\alpha}$	3±1.3$^{\alpha}$	<0.01
FT4 level (8.56-25.6fmol/l)	10±2.2	9.6±-2.1	9.4±2.5	0.192
TSH level (.3-5μIU/ml)	3.3±1.3	5.3±2.1$^{\beta}$	5.5±1.8$^{\beta}$	<0.01

Serum bilirubin level and prothrombin time were significantly increased and albumin level significantly decreases with increasing severity of disease. (Table VI).

Table-VI

Association of Biochemical marker with severity of liver function test (n=328)

Biochemical marker	Class A Mean±SD	Class B Mean±SD	Class C Mean±SD	p-value
Serum bilirubin (mg/dl)	1.4±0.3	1.7±0.2	2.2±1.4$^{\alpha\beta}$	0.006
Serum albumin (mg/dl)	3.5±0.8	3.1±-0.4	2.9±0.6$^{\$\#}$	<0.01
Prothrombin time (sec)	12±2	19±2	22±3$^{\gamma}$	<0.01

p-value was determined by Post-Hoc analysis of Bonferroni by One Way ANOVA test.
$^{\alpha}$denotes significant difference between Class A vs Class C regarding serum bilirubin level.
$^{\beta}$denotes significant difference between Class B vs Class C regarding serum bilirubin level.
$^{\$}$denotes significant difference between Class A vs Class B and Class C regarding serum albumin level.
$^{\#}$denotes significant difference between Class B vs Class C regarding serum albumin level.
$^{\gamma}$denotes significant difference between Class A vs Class C regarding prothrombin time.

Discussion:

A total of 328 patients with cirrhosis of liver was enrolled in our study. In our study, Mean age of the patients was 52.9±9.6 years with 62.2% were aged between 41 to 60 years.

A previous study in India had the mean age of 43 ± 14 years among the patients.[4] Another study also revealed that 63% of the patients were aged between 41 to 60 years.[1]

In our study, Male predominant was observed among the patients with 58.8% which was consistent with the previous study where, 71% were male.

The majority of the patients that were enrolled in the previously mentioned study trial were men. Another study conducted in Bangladesh also revealed that cirrhosis of liver is more common in male than female patient.[10]

In our study, According to Child-Pugh score majority (44.8%) of the patients were in class C followed by 31.1% were in class A and 24.1% were in class B. According to the study most of the patients presented in advanced stage with decompensated liver cirrhosis.

In a study based on the Child Pugh score, class A included 15% patients, class B included 26%, and class C included 59% patients.[10] A study conducted in India revealed that patients were classified according to Child Pugh scoring according to which 24% cases were Child A and 45% cases were Child B and 31% cases were Child C.[1]

In our study, class B was found relatively low due to a smaller number of patients was admitted in the hospital in this stage during the study period.

Among all, 53.4% had Ascites, 25.9% had Encephalopathy, 11% had Hematemesis, 11% had jaundice and 9.8% had Melena.

According to a research in Bangladesh, the majority of patients (49.4%) had ascites, which was followed by peripheral edema (24.7%), gastrointestinal hemorrhage (27%), encephalopathy (21.3%), and jaundice (3.4%).[13] A study conducted in Sweden revealed that out of 1317 patients of cirrhosis, ascites was present in 43% cases followed by variceal bleeding in 6% and overt encephalopathy in 4% cases.[14]

In our study, it was shown that as the severity of liver disease increases from Child Pugh grade A to C, the percentage of patients , having decreased level of serum FT3 and FT4 level increased and raised TSH level also increased . FT3 and TSH level showed statistically significant.

A previously mentioned study conducted in India in 2023, revealed that there was significant inverse correlation between serum level of FT3 and FT4 with severity of cirrhosis is very much similar to our study, where FT3 level decreased in 4% of patients who were categorized in CPS A, 91% in CPS B, 92%% in CPS C. FT4 level decreased in 9.3% of patients who were categorized in CPS A, 33.3% in CPS B, 57.4% in CPS C and S.TSH increased in 10% of patients who were categorized in CPS A,31% in CPS B,58.2% in CPS C.[6]

A study conducted in 2019, revealed that there was significant inverse correlation between serum level of FT3, and FT4 with severity of cirrhosis[9] is similar to our study, where FT3 level decreased in 26% of patients who were categorized in CPS A, 52% in CPS B,84.6% in CPS C .S.TSH increased in 15% of patients who were categorized in CPS A,69% in CPS B,88% in CPS C.

An already mentioned study in India found that TSH levels were inversely correlated with the severity of liver disease, with increased levels of S. TSH seen in 12.5 percent of CPS A cases, 77 percent of CPS B cases, and 83.8 percent of CPS C cases (p-.01). Additionally, FT3 was low in the majority of CPS B (75.5 percent) and CPS C (96.78 percent) cases. There was no statistically significant correlation with FT4.[1] These findings are very much similar to our study.

In our study, we found that, mean FT3 level was significantly decreased and mean S.TSH significantly increased with increases number of diseases severity score from CPS A-C.

In the previously mentioned study conducted in Nepal in 2019, according to Child Pugh score (CPS) 56.36% patients were in Class C, 31.82% patients were in Class B. Correlation between different CPS categories was found to be statistically significant with the mean score of FT3 and mean score of FT4.[7] On the contrary, in our study, mean FT4 level was not significant.

A previous study suggested that mean FT3 and FT4 levels were significantly decreased and mean TSH levels were significantly increased in liver cirrhosis patients and level of FT3, FT4, and TSH also correlate with the severity of liver disease. Most common abnormality seen was low FT3(71%),low FT4(21%),high TSH(20%).[4]

In a different research, higher Child Pugh scores were shown to be associated with lower mean free T3 levels but there was no such statistical correlation between free T4 and TSH levels.[10] On the contrary, in our study we found statistically significant correlation between S.TSH and severity of cirrhosis.

According to a study already mentioned, more severe liver injury is linked to low free T3 and T4 levels. The most prevalent explanation for the low free T3 levels

in liver illness is that there is less Type I deiodinase present, which results in less peripheral T4 to T3 conversion.[15]

Conclusion:

This study assessed the correlation between thyroid function test (TFT) abnormalities and severity of liver disease.FT3 level is inversely correlated with severity of cirrhosis (Low FT3 level is associated with more severe disease), S.TSH level is directly correlated (High TSH is associated with more severe disease). Data from this study depicted that mean FT3 level significantly decreases and TSH significantly increases with the increasing disease severity by Child Pugh score, making it a possible biomarker that is associated with disease severity and help identify patients with worse prognosis.

Limitations of the study:

This study was conducted in a single center study. One major limitation of the study was the smaller sample size.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Sir Salimullah Medical College Mitford Hospital (Ref: 59.14.1100.031.18.001.23.135). Written informed consent was taken from all the patients before taking part of the study.

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Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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