Original Research Article

# A study on thyroid profile in chronic liver disease patients admitted in a rural tertiary care hospital of West Bengal, India

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## Abstract

**Introduction**: Abnormal thyroid function tests occur in various non-thyroidal illnesses, like chronic liver disease(CLD), where no pre-existing hypothalamic-pituitary and thyroid gland dysfunction is present. Available studies reported decreased T3 and fT3 in most cases. But a limited study reported the association of fT4, rT3 and TSH level with severity of CLD. Aim is to measure thyroid functions in patients with CLD and to assess the severity of liver dysfunction in relation with thyroid functions a in tertiary care hospital. **Methods**: 100 patients of CLD were included. Blood sample was analysed for Thyroid profile (TSH, FT4, FT3, total T3 and rT3), Serum LFT, Serum creatinine, Prothrombin time, INR and USG of Hepatobiliary apparatus. Results were analysed to find out the correlation of thyroid profile with the severity of liver dysfunction according to Child–Turcotte–Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score. **Results**: Majority of the patient had low FT3 (90 %), Normal FT4 (58%), Normal TT3 (57%), high rT3 (57 %), and a normal TSH (72%). High TSH, low FT4, low FT3, low Total T3 (TT3) and high rT3 correlated with the severity of liver disease as per CTP score. High TSH, low FT3 and low total T3 correlated with the MELD score. **Conclusion**: This study showed the existence of several abnormalities in thyroid function test in CLD, although euthyroidism was maintained in the majority. Low FT3 and low TT3 might be used as a predictor of severity in CLD.

**Keyword:** Chronic liver disease, Thyroid profile (TSH, FT4, FT3, Total T3, rT3), CTP score, MELD score.



## Introduction

The Liver plays an important role in the metabolism of thyroid hormone. Abnormal findings on thyroid function tests occur in various non-thyroidal illnesses (NTI), like chronic liver disease, where no pre-existing hypothalamic-pituitary and thyroid gland dysfunction is present. Thyroid function test result becomes completely normal after recovery of patients. The most prominent changes are low serum triiodothyronine (T3) and elevated reverse T3 (rT3). For this reason, this syndrome is named “low T3 syndrome” and also “euthyroid sick syndrome”. Based on the duration and severity of the NTI, TSH, FT4, FT3, and total T3(TT3) levels in serum are also affected in variable degrees. As the severity of the NTI increases, serum level of T3 and T4 also decrease, but levels gradually start to become normal as the patient recovers[2].

There are various theory about thyroid hormone abnormality in chronic liver disease. The liver plays an important role in the metabolism of thyroid hormones, involved in thyroid hormone conjugation and excretion. So, liver pathology can cause thyroid hormone level abnormality. Also, patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism[3]. But the most important mechanism of TFT abnormality in the settings of NTIS is impaired peripheral deiodination of T4 to T3, which is mediated by deiodinase enzyme. Liver is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to T3 by Type 1 deiodinase. Type I deiodinase is responsible for approximately 30%–40% of extrathyroidal production of T3. As Type 1 and Type 2 deiodinase enzyme activity diminishes; deiodination of T4 to T3 is decreased. Type III deiodinase becomes activated in muscle and liver, results in decreased T3 and T4 and most importantly, increased rT3[1,2].Thyroid function test abnormality also may occur due to changes in secretion of thyroid hormone by the thyroid gland, effects on the hypothalamic-pituitary-thyroid axis, effects on metabolism of the hormones in peripheral tissue, due to inhibitory effect of thyroid hormone – proteins binding or a combination of these effects[2].

There is also some other theory. Some inhibitor can be present both in the serum and in body tissues and it might inhibit binding of hormone to nuclear T3 receptors, prevent binding of T4 with various binding protein like TBG, Transthyretin, and albumin and also prevent uptake of thyroid hormones by various cells. So, the hormones cannot act

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properly. (2) It was also proposed that cytokines play an important role in NTI. They found that Pro-inflammatory cytokines are often increased in NTI and have been found to correlate inversely with thyroid hormone levels in the critically ill patients[4, 6, 7] and also in patients suffering from chronic diseases[4, 5, 8, 9]. Some theory proposed that serum factors, such as bilirubin, NEFA, furanoic acid, hippuric acid, and indoxyl sulphate, which are found to be present in various NTIs, inhibit transport of thyroid hormones, thus producing abnormality of thyroid hormones. (2) Liver produces all three of the binding proteins, ie, TBG, TBPA, and albumin, so in presence of Liver disease, production of these binding proteins is affected. As a result, thyroid hormone transport in blood is significantly affected, and it contributes to the abnormal TFT. In some situation, systemic diseases that alter Thyroid hormone metabolism, also aggravate the situation due to use of medications that also affect TH metabolism[4, 10, 11].

As for present evidence of Thyroid hormone levels in CLD**, Nilesh Kumar Patira et al**. found that TSH level increases and serum albumin level, T3, FT3, and FT4 level reduce as the severity of cirrhosis increases[18]. **Arnaldo Moura Neto et al.** found that in cases of cirrhosis, the most common finding was low TT3 and FT3 and elevated rT3. Free T4 may be increased; while TT4 can be decreased. TSH is usually normal or mildly increased, but the patients have a euthyroid clinical presentation .The serum relation TT3/rT3 is inversely associated with the severity of the disease[4]. **P. Punekar et al**. found that the mean FT3 and FT4 levels were significantly decreased and mean TSH levels were significantly increased in liver cirrhosis patients compared to healthy controls. Level of FT3, FT4, and TSH also correlated with the severity of liver disease. Level of FT3 can be used as prognostic marker for liver cirrhosis patients[3].

Available studies reported decreased T3 and fT3 in most cases. But a limited study reported the association of fT4, rT3 and TSH level with severity of CLD. To the best of our knowledge, there is no study on similar topic from rural areas of West Bengal, India.

**Aims of the Study**

To evaluate the Thyroid functions and to assess the severity of liver dysfunction in relation with thyroid functions in patients with chronic liver disease admitted in Midnapore Medical College.

**Objective of the study**

To Investigate Thyroid profile (TSH, FT4, FT3, TT3, rT3) of chronic liver disease cases and to find out the correlation of thyroid profile with severity of liver dysfunction according to Child–Turcotte–Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score.

**Material and Method**

Study was conducted among 100 patients of chronic liver disease admitted in General Medicine, Midnapore Medical College and Hospital and those fulfilling the inclusion and exclusion criteria during the study period from January 2019 to June 2020. It was an observational, cross sectional, hospital based and single centre study. The protocol for the study was approved by the Institutional Ethical Committee.

**Inclusion criteria**

1) Patients between the ages of 18 – 85 years who voluntarily participated 2) Patients with clinical, biochemical and radiological evidence of chronic liver disease were included.

**Exclusion criteria**

1) Patients with upper gastro- intestinal bleeding 2) Patients with acute hepatic encephalopathy 3) Patients with renal failure 4) Pregnant Women 5) Prior H/O thyroidal illness or Patients on thyroid medications already 6) patient on medication that may interfere with thyroid hormone metabolism and function.

**Sample Size**

In recent study, prevalence of low FT3 in cases of cirrhosis of liver was average 50% (3). Taking this data as reference, the sample size was determined by the formula as 4PQ/E2 (P = Prevalence in previous study, Q = 100 – P, E = Type 2 error = 20% of prevalence) = 4×50×(100 – 50)÷(10×10)= 100 patients with chronic liver disease.

**Investigation**

1) Thyroid profile (TSH, FT4, FT3, TT3, rT3) 2) Serum LFT 3) Serum creatinine 4) Prothrombin time 5) INR 6) USG of Hepatobiliary apparatus 7) Ascitic fluid study

**Analyser and Method**

All the Thyroid function tests were analysed by cobas e411 thyroid immune analyser by Roche diagnostics by electrochemiluminescence method.

The normal ranges for thyroid functions in our laboratory are as follows TSH - 0.27 – 4.2 µIU/ml, FT4 - 1.0 – 1.6 ng/dl, FT3 - 2.6 – 4.4 pg/ml, Total T3 - 80 – 220 ng/dl, rT3 -10 – 24 ng/dl.

**Statistical Analysis**

Data collected during the study was entered in Microsoft Excel spread sheet, analysed statistically using Microsoft Excel and SPSS latest software package. Appropriate statistical tests like Chi-square test, ANOVA and t test was applied. Data were expressed with respect to 'p' value, mean and standard deviation. A statistical value <0.05 was considered as significant. Student's t-test was used to compare the variables between data from case and normal group. As there was no control in the study, data of test report of normal cases collected from various studies done before, and data was matched according to age and sex. To compare data between more than 2 groups, p value (One way ANOVA) was calculated. The results were expressed in the form of tables.

**Results**

Out of the 100 patient, 86 were male and 14 were female with a male female ratio of 43:7. Mean age with standard deviation for all patients were 49.9 ± 13.58, for males - 50.08 ± 13.62, and for females - 48.79 ± 13.80. Majority of patients belonged to 45 – 55 age groups. 97 patients were suffering from Alcoholic Cirrhosis (84 male and 13 female) and 3 patients were suffering from Post-Viral Cirrhosis (2 male and 1 female).

**TABLE 1: Mean, SD and p value of Thyroid Function Test of all patients**

| | TSH | FT4 | FT3 | Total T3 | rT3 |
|---|---|---|---|---|---|
| **Case** | 3.51±2.27 | 1.27±0.45 | 1.56±0.55 | 87.23±17.45 | 25.78±4.89 |
| **P value** | 0.16 | <0.0001 | <0.0001 | 0.01 | <0.0001 |

**TABLE 2: Distribution of study population according to serum values of Thyroid hormones**

| | Low | Normal | High |
|---|---|---|---|
| **TSH (µIU/ml)** | 1 | 72 | 27 |
| **FT4 (ng/dl)** | 24 | 58 | 18 |
| **FT3 (pg/ml)** | 90 | 10 | 0 |
| **Total T3 (ng/dl)** | 43 | 57 | 0 |
| **rT3 (ng/dl)** | 0 | 43 | 57 |

**TSH** value ranged from 0.396 to 11.92 µIU/ml. Mean TSH was 3.51 ±2.27 µIU/ml (P = 0.16) (Table 1). 1% case had low TSH, 72% cases had normal TSH, and 27% cases had high TSH (Table 2).

**FT4** value ranged from 0.467 to 2.64 ng/dl. Mean value of FT4 among cases was 1.27 ± 0.45 ng/dl (P = <0.0001) (Table 1). 24 cases had low FT4, 58 cases had normal FT4, 18 cases had high FT4 (Table 2).

**FT3** value ranged from 0.739 to 2.86 pg/ml. Mean serum FT3 among cases was 1.56±0.55 pg/ml (P = <0.0001) (Table 1). 90 case had low FT3, 10 cases had normal FT3 (Table 2).

**TT3** value ranged from 0.61 to 115 ng/dl. Mean serum TT3 among cases was 87.23±17.45 ng/dl (P = 0.01) (Table 1). 43 case had low Total T3, 57 cases had normal Total T3 (Table 2).

**rT3** value ranged from minimum of 17 to maximum of 35 ng/dl. Mean value of rT3 among cases was 25.78±4.89 ng/dl (P = <0.0001) (Table 1). 43 cases had normal rT3, 57 cases had high rT3 (Table 2).

**TABLE 3: Comparison of Thyroid Functions Test in all cirrhotic patients according to CTP classification of severity of liver disease**

| Thyroid profile | CTP Classification | | | |
|---|---|---|---|---|
| | Class A n=16 | Class B n=47 | Class C n=37 | P (one way ANOVA) |
| **TSH** | 2.20±1.25 | 2.52±1.48 | 5.34±2.30 | <0.0001 |
| **FT4** | 1.37±0.20 | 1.33±0.49 | 1.15±0.45 | 0.13 |
| **FT3** | 1.80±0.55 | 1.65±0.55 | 1.35±0.48 | 0.006 |
| **Total T3** | 95.75±16.75 | 91.17±15.47 | 78.54±16.86 | 0.0003 |
| **rT3** | 23.94±5.11 | 24.72±4.77 | 27.92±4.26 | 0.002 |

By **CTP** classification (table 3), 16% cases were found to be Class A, 47% cases to be Class B, and 37% cases to be Class C. On comparing the mean serum levels of **TSH** in Child A, B, and C, the lowest levels were among the Child A group (2.20 ± 1.25), followed by the Child B group (2.52 ± 1.48), and the Child C group (5.34 ± 2.30). Lowest levels of mean serum **FT4** were among the Child C group (1.15 ± 0.45), followed by the Child B group (1.33 ± 0.49), and the Child A group (1.37 ± 0.20). The lowest levels of serum **FT3** were observed among the Child C group (1.35 ± 0.48), followed by the Child B group (1.65 ± 0.55), followed by the Child A group (1.80 ± 0.55). The Child C group had lowest serum **TT3** (78.54 ± 16.86), followed by the Child B group (91.17 ± 15.47), followed by the Child A group (95.75 ± 16.75). The mean serum **rT3** was lowest in the Child A group (23.94 ± 5.11), followed by the Child B group (24.72 ± 4.77), and followed by the Child C group (27.92 ± 4.26).

**TABLE 4: Comparison of Thyroid Functions Test in all cirrhotic patients according to MELD classification of severity of liver disease**

| Thyroid profile | MELD Score | | | | |
|---|---|---|---|---|---|
| | ≤9 n=29 | 10 – 19 n=43 | 20 – 29 n=21 | 30 – 39 n=7 | P(one way ANOVA) |
| **TSH** | 1.78±0.89 | 3.66±1.88 | 4.69±2.54 | 6.31±2.56 | <0.0001 |
| **FT4** | 1.29±0.40 | 1.26±0.42 | 1.25±0.49 | 1.32±0.71 | 0.98 |
| **FT3** | 1.63±0.58 | 1.60±0.54 | 1.52±0.57 | 1.20±0.22 | 0.28 |
| **Total T3** | 95.93±14.78 | 86.49±16.11 | 81.90±18.87 | 71.71±15.79 | 0.001 |
| **rT3** | 22.69±4.50 | 26.33±4.29 | 28.24±4.67 | 27.86±4.95 | 0.0001 |

By **MELD** classification (table 4), 29% cases were found to have a score of ≤9, 43% cases had a score of 10 - 19, 21% cases had 20 - 29, and 7% cases were found to score 30 – 39. On comparing the mean serum levels of **TSH** in MELD Score, the lowest levels were among the ≤9 group (1.78 ± 0.89), followed by the 10 - 19 group (3.66 ± 1.88), followed by the 20 - 29 group (4.69 ± 2.54), followed by the 30 - 39 group (6.31 ± 2.56). Mean serum levels of **FT4** was lowest among the 20 - 29 group (1.25 ± 0.49), followed by the 10 - 19 group (1.26 ± 0.42), followed by the ≤9 group (1.29 ± 0.40), followed by the 30 - 39 group (1.32 ± 0.71). On comparing the mean serum levels of **FT3** in MELD Score the lowest levels were among the 30 - 39 group (1.20 ± 0.22), followed by the 20 - 29 group (1.52 ± 0.57), followed by the 10 - 19 group (1.60 ± 0.54), followed by the ≤9 group (1.63 ± 0.58). 30 - 39 group had lowest mean serum levels of **TT3** (71.71 ± 15.79), followed by the 20 - 29 group (81.90 ± 18.87), followed by the 10 - 19 group (86.49 ± 16.11), followed by the ≤9 group (95.93 ± 14.78) Whereas mean serum **rT3** was lowest in the ≤9 group (22.69 ± 4.50), followed by the 10 - 19 group (26.33 ± 4.29), followed by the 30 - 39 group (27.86 ± 4.95), followed by the 20 - 29 group (28.24 ± 4.67).

**Discussion**

Most of our cases were from rural area. None of the participant had symptoms of hypothyroidism or hyperthyroidism. There were more male patients because CLD is more common in male, and alcoholism, a major cause for CLD, also more common in male. Most common aetiology of CLD was Alcoholic liver disease.

Majority of the patient had low FT3 (90 %), Normal FT4 (58%), Normal TT3 (57%), high rT3 (57 %), and a normal TSH (72%). FT3, FT4 and TT3 were significantly decreased in CLD cases. rT3 was significantly increased in CLD cases. **P. Punekar et al** found that Cirrhosis patients had statistically significant lower level of FT3 (P < 0.0001) and FT4 (P < 0.0001) but had higher level of TSH (P < 0.0001) compared with the controls. Level of FT3, FT4, and TSH also correlated with the severity of liver disease. The results of our study for FT3 and FT4 levels were consistent with P. Punekar et al, but contradicted for TSH levels. This difference may be due to sample size, age, sex, severity of liver disease and regional variation of thyroid disorders patients[3]. **Sudhir Kumar Verma et al** found low fT3, fT4 and slightly raised TSH in most of the patients that is consistent with our study[14].Low serum **FT4** also correlated with the severity of liver disease (P value = 0.13). These results were consistent with P. Punekar et al. (3) and Sanjay Neeralagi et al (16), but contradicted with Sudhir Kumar Verma et al[14].

Levels of low **FT3** also correlated with the severity of liver disease(P value = 0.006). These results were consistent with P. Punekar et al[3]., El-Feki MA[9], Sanjay Neeralagi[16] and Sudhir Kumar Verma et al[14]. Similarly low **TT3** also correlated with the severity of liver disease (P value = 0.0003) and high **rT3** correlated with the severity of liver disease as per Child–Turcotte–Pugh score (P value = 0.002).Levels of low **TT3** also correlated with the severity(P value = 0.001), whereas high **rT3** had no corelation with the severity of liver disease (P value = 0.0001).As per **CTP** classification (Table 3), 16% patients were in CTP score Class A, 47% patients in Class B, 37% patients in Class C. High **TSH** also correlated with the severity of liver disease as per Child–Turcotte–Pugh score (P value = <0.0001). These results were consistent with Sanjay Neeralagi et al but contradicted with P. Punekar et al[4] and Sudhir Kumar Verma et al[14].As per **MELD** classification (Table 4), 29% patients were in MELD score ≤9 group, 43% patients in[10-19] group, 21% patients in

[20 – 29] group, and 7% patients in [30 – 39] group. High **TSH** correlated with the severity of liver disease (P value = <0.0001). These results were consistent with P. Punekar et al[3] but contradicted by Sudhir Kumar Verma et al[14]. Levels of low **FT4** did not correlate with the severity of liver disease (P value = 0.98) but low **FT3** correlated with the severity (P value = 0.28). These results were consistent with Sudhir Kumar Verma et al[14] and Taş A et al[17]. So, High TSH, low FT4, low FT3, low TT3 and high rT3 correlated with severity of CLD cases as per CTP score. High TSH, low FT3 and low TT3 also correlated with severity of CLD cases as per MELD score. This study showed the existence of several abnormalities in thyroid function test in chronic liver disease, although euthyroidism was maintained in majority of patients. Low FT3 and Low TT3 might be used as a predictor of the severity of CLD.

**Limitation**

In spite of every sincere effort, our study had few shortcomings. The sample size was small. Only 100 cases are not sufficient for this kind of study. This study was needed to be done on a larger scale to obtain more statistically significant outcomes. This study was done in a single Centre. This study was carried out in a tertiary care hospital, so hospital bias cannot be ruled out. There was also lack of long term follow up and outcome.

**Conclusion**

This study showed the existence of several abnormalities in thyroid function test in chronic liver disease, although euthyroidism was maintained in the majority. So, TFT can be used as marker of the severity of CLD. Patients with CLD should be evaluated with TFT periodically to reduce the morbidity and mortality.

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