ORIGINAL RESEARCH

Thyroid Dysfunction in Liver Cirrhosis Patients and Its Correlation with Disease Severity: A Cross-sectional Study

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ABSTRACT

Background: This study aims to evaluate thyroid dysfunction in patients with liver cirrhosis and its association with the severity of liver disease using Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.**Materials and Methods:** This cross-sectional study was conducted at a tertiary care hospital, including 100 patients diagnosed with liver cirrhosis. Patients underwent a detailed clinical evaluation, including medical history, physical examination, and laboratory investigations. Thyroid function was assessed by measuring serum levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3). Liver function tests and severity assessment using Child-Pugh and MELD scores were performed. Statistical analysis was conducted to evaluate correlations between thyroid dysfunction and liver disease severity.**Results:** The study included 100 cirrhotic patients, with a mean age of 52.4 ± 10.8 years, of whom 68% were male. The most common comorbidities were diabetes mellitus (30%) and hypertension (40%). Thyroid function analysis revealed that 20% of patients had subclinical hypothyroidism, 10% had overt hypothyroidism, and 10% had low T3 syndrome. The mean FT3 (2.1 ± 0.5 pg/mL) and FT4 (0.88 ± 0.25 ng/dL) levels were lower than normal. A significant negative correlation was found between FT3, FT4 levels, and Child-Pugh ($r = -0.50, -0.45$) and MELD scores ($r = -0.48, -0.42$, respectively; $p < 0.01$), indicating worsening thyroid function with increasing liver disease severity.**Conclusion:** Thyroid dysfunction is prevalent in liver cirrhosis, with low T3 syndrome and hypothyroidism being the most common abnormalities. The significant negative correlation between thyroid hormone levels and liver disease severity suggests that thyroid dysfunction may serve as a potential prognostic marker for cirrhosis progression. Routine thyroid function screening in cirrhotic patients is recommended for early detection and management.

Keywords: Liver cirrhosis, Thyroid dysfunction, low T3 syndrome, Child-Pugh score, MELD score.

INTRODUCTION

The intricate relationship between the thyroid and the liver is of paramount importance in maintaining homeostasis within the body. The thyroid gland plays a crucial role in regulating metabolism, energy balance, and various physiological processes through the secretion of thyroid hormones—triiodothyronine (T3) and thyroxine (T4). These hormones significantly influence liver function, including lipid metabolism, protein synthesis, and detoxification processes. Conversely, the liver is responsible for the metabolism, activation, and clearance of thyroid hormones, establishing a bidirectional interaction between the two organs. Any dysfunction in one can have profound implications for the other, making the thyroid-liver axis a critical area of clinical interest.[1,2]

Liver cirrhosis, a chronic and progressive disease characterized by extensive fibrosis, hepatocyte degeneration, and impaired hepatic function, is associated with a wide range of systemic complications. The pathogenesis of cirrhosis involves inflammatory responses, oxidative stress, and metabolic dysregulation, all of which can impact thyroid function. Patients with

cirrhosis often exhibit abnormalities in thyroid hormone levels despite the absence of primary thyroid disease. These alterations, collectively referred to as nonthyroidal illness syndrome (NTIS) or euthyroid sick syndrome, include decreased levels of serum T3, normal or low levels of T4, and normal or slightly reduced thyroid-stimulating hormone (TSH). This disruption in thyroid hormone homeostasis can contribute to the overall deterioration of metabolic and physiological functions in cirrhotic patients.[3]

Several mechanisms underlie the alterations in thyroid function observed in cirrhosis. One of the primary factors is impaired hepatic conversion of T4 to T3 due to reduced activity of deiodinases, the enzymes responsible for thyroid hormone metabolism. The liver plays a pivotal role in converting T4, the inactive prohormone, into its active form, T3. In cirrhosis, hepatic dysfunction leads to reduced deiodinase activity, resulting in lower T3 levels, which may contribute to metabolic slowing and systemic complications. Additionally, the liver synthesizes thyroid hormone-binding proteins, including thyroxine-binding globulin (TBG), transthyretin, and albumin, which are essential for the transport and distribution of thyroid hormones. Cirrhotic patients often experience alterations in these binding proteins due to impaired hepatic protein synthesis, leading to fluctuations in circulating thyroid hormone levels.[4,5]

Furthermore, chronic inflammation and oxidative stress, hallmarks of liver cirrhosis, can influence thyroid hormone regulation. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) have been shown to affect the hypothalamic-pituitary-thyroid (HPT) axis, leading to suppressed TSH secretion and altered thyroid hormone metabolism. These inflammatory mediators disrupt thyroid hormone homeostasis by inhibiting deiodinase activity and altering thyroid receptor expression, contributing to the complex pathophysiology of thyroid dysfunction in cirrhotic patients.[6]

The severity of liver disease has been directly linked to the extent of thyroid dysfunction in cirrhotic patients. Studies have suggested that the degree of thyroid hormone alterations correlates with the progression of liver cirrhosis, with more severe cases exhibiting greater reductions in T3 levels and further disruptions in thyroid homeostasis. Several scoring systems, such as the Child-Turcotte-Pugh (CTP) classification and the Model for End-Stage Liver Disease (MELD) score, are commonly used to assess liver disease severity and predict patient outcomes. Research indicates that patients with higher CTP or MELD scores tend to exhibit more pronounced thyroid dysfunction, highlighting the potential prognostic value of thyroid hormone levels in cirrhosis management.[7]

Hypothyroidism, both overt and subclinical, has also been reported in cirrhotic patients, further complicating the disease course. Subclinical hypothyroidism, characterized by elevated TSH levels with normal circulating T4 and T3, may predispose cirrhotic patients to metabolic disturbances, including dyslipidemia, insulin resistance, and cardiovascular complications. Additionally, overt hypothyroidism can exacerbate hepatic dysfunction by impairing bile acid metabolism and reducing hepatic clearance of toxins. The interplay between hypothyroidism and cirrhosis may create a vicious cycle, where liver dysfunction leads to thyroid hormone imbalances, further aggravating metabolic and systemic complications.[8]

Beyond hypothyroidism, hyperthyroidism has also been observed in some cirrhotic patients, albeit less frequently. Thyrotoxicosis, characterized by excessive circulating thyroid hormones, may worsen the hypermetabolic state in cirrhosis, leading to increased catabolism, muscle wasting, and cardiovascular strain. Patients with autoimmune liver diseases such as primary biliary cholangitis (PBC) are at a higher risk of developing autoimmune thyroid disorders; including Hashimoto's thyroiditis and Graves' disease, further emphasizing the intricate link between liver and thyroid function.[9]

Given the substantial impact of thyroid dysfunction on cirrhotic patients, the assessment of thyroid hormone levels may provide valuable clinical insights. Monitoring thyroid function in patients with liver cirrhosis can aid in identifying metabolic and endocrine complications that may otherwise go unnoticed. Moreover, recognizing the association between thyroid dysfunction and liver disease severity may enhance prognostic assessments and guide therapeutic strategies. While thyroid hormone replacement therapy is not routinely indicated for cirrhotic patients with NTIS, optimizing thyroid function in those with overt hypothyroidism or hyperthyroidism may improve overall clinical outcomes.[9]

AIM AND OBJECTIVES

This study aims to evaluate thyroid dysfunction in patients with liver cirrhosis and its association

with the severity of liver disease using Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.

MATERIALS AND METHODS

Study Design

This study was designed as a cross-sectional observational study conducted at a tertiary care hospital. The study aimed to evaluate the prevalence of thyroid dysfunction in patients with liver cirrhosis and its correlation with the severity of liver disease.

Study Population

The study included **100 patients** diagnosed with liver cirrhosis. Patients were enrolled based on predefined inclusion and exclusion criteria to ensure the study population was representative and free from confounding thyroid-related conditions.

Study Place

The study was conducted in the Department of General Medicine, Rama Medical College Hospital & Research Centre, Hapur, Uttar Pradesh, India in collaboration withDepartment of Pathology, Rama Medical College Hospital & Research Centre, Hapur, Uttar Pradesh, India, where specialized diagnostic and management facilities for liver and thyroid disorders were available.

Study Duration

The study was carried out over a period of 24 months from March 2020 to January 2022, which included patient recruitment, clinical assessments, laboratory investigations, data collection, and statistical analysis.

Ethical Considerations

The study was approved by the Institutional Ethics Committee before initiation. All participants provided written informed consent before enrollment. Patient confidentiality was strictly maintained, and all procedures adhered to the principles outlined in the Declaration of Helsinki for ethical medical research.

Inclusion Criteria

- Patients aged 18 years or older.
- Diagnosed with liver cirrhosis based on clinical, biochemical, imaging, and/or histopathological findings.
- Willing to participate and provide informed consent.

Exclusion Criteria

- Patients with a known history of thyroid disease or those on thyroid medications.
- Patients diagnosed with acute liver failure or hepatocellular carcinoma.
- Pregnant or lactating women.
- Patients with systemic infections or critical illness at the time of evaluation

Study procedure

Each participant underwent a detailed clinical evaluation, which included:

1. Medical History

- Duration and etiology of liver cirrhosis.
- Symptoms related to thyroid dysfunction (fatigue, weight changes, cold intolerance, etc.).
- Previous history of any thyroid-related symptoms or medications.
- Alcohol consumption, comorbid conditions, and family history of thyroid or liver diseases.

2. Physical Examination

- General condition, body mass index (BMI), and vital signs.
- Signs of liver cirrhosis (jaundice, ascites, hepatosplenomegaly, palmar erythema, spider angiomas, etc.).
- Neurological examination to assess hepatic encephalopathy.
- Examination for thyroid enlargement, nodules, or other clinical signs of thyroid dysfunction.

3. Investigations

a) Liver Disease Severity Assessment

- **Child-Pugh Score (CPS):** Based on total bilirubin, serum albumin, prothrombin time/international normalized ratio (INR), presence of ascites, and hepatic encephalopathy.
- **Model for End-Stage Liver Disease (MELD) Score:** Calculated using serum bilirubin, INR, and serum creatinine to determine the severity of hepatic dysfunction.

b) Thyroid Function Tests (TFTs)

- Serum Thyroid-Stimulating Hormone (TSH)
- Free Thyroxine (FT4)
- Free Triiodothyronine (FT3)
- All thyroid function tests were performed using an electrochemiluminescence immunoassay (ECLIA).

c) Liver Function Tests (LFTs)

- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Total and Direct Bilirubin
- Serum Albumin
- Prothrombin Time (PT) / INR

d) Other Biochemical and Hematological Parameters

- Complete Blood Count (CBC) (Hemoglobin, WBC count, Platelet count)
- Renal Function Tests (Serum Urea, Creatinine, Electrolytes)
- Serum Electrolytes (Sodium, Potassium)

Outcome Measures

- Prevalence of thyroid dysfunction (hypothyroidism, euthyroidism, subclinical hypothyroidism, or hyperthyroidism) among liver cirrhosis patients.
- Correlation of thyroid function parameters (TSH, FT4, FT3) with liver disease severity (Child-Pugh and MELD scores).
- Differences in thyroid function between compensated and decompensated cirrhosis.

Statistical Analysis

- Data were analyzed using SPSS version 22.0.
- Continuous variables were expressed as mean ± standard deviation (SD).
- Categorical variables were presented as percentages and frequencies.
- Comparisons between euthyroid and thyroid dysfunction groups were conducted using:
- Student's t-test for normally distributed continuous variables.
- Mann-Whitney U test for non-normally distributed data.
- Chi-square test or Fisher's exact test was used for categorical variables.
- Correlations between thyroid function parameters and liver disease severity scores were assessed using Pearson's or Spearman's correlation coefficients.
- A p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics of Patients

Characteristic	Mean ± SD / n	Percentage (%)
Age (years)	52.4 ± 10.8	-
Gender		
Male	68	68%
Female	32	32%
BMI (kg/m²)	24.5 ± 3.2	-
Diabetes Mellitus	30	30%
Hypertension	40	40%
Smoking History	25	25%

Table 1 show that the study included 100 patients diagnosed with liver cirrhosis, with a mean age of 52.4 ± 10.8 years. The majority of the patients were male (68%), while females comprised 32% of the cohort. The mean BMI was 24.5± 3.2 kg/m², indicating that most patients had a normal or slightly elevated body mass index. Among comorbid conditions, diabetes mellitus was present in 30% of patients, while hypertension was observed in 40% of the study population. Additionally, 25% of the patients reported a history of smoking.

Table 2: Thyroid Function Tests among Cirrhotic Patients

Parameter	Mean ± SD	Reference Range
TSH (µIU/mL)	2.8 ± 1.2	0.4 - 4.0
FT4 (ng/dL)	0.88 ± 0.25	0.8 - 2.0
FT3 (pg/mL)	2.1 ± 0.5	2.3 - 4.2
Total T4 (µg/dL)	5.4 ± 1.1	4.5 - 12.0
Total T3 (ng/dL)	0.92 ± 0.22	0.8 - 2.0

Table 2 show the thyroid function was evaluated through various biochemical markers. The mean TSH level was 2.8 ± 1.2 µIU/mL, which remained within the normal reference range (0.4 - 4.0 µIU/mL), though variations among patients were noted. The mean FT4 level was 0.88 ± 0.25 ng/dL, slightly below the lower limit of the normal range (0.8 - 2.0 ng/dL), suggesting potential thyroid dysfunction. Similarly, the mean FT3 level was 2.1 ± 0.5 pg/mL, which was below the normal range (2.3 - 4.2 pg/mL), indicating impaired conversion of T4 to T3, commonly observed in non-thyroidal illness syndrome (NTIS). The total T4 and total T3

levels were also reduced, with mean values of 5.4±1.1µg/dL and 0.92±0.22 ng/dL, respectively.

Table 3: Liver Function Tests among Cirrhotic Patients

Parameter	Mean ± SD
ALT (U/L)	42.5 ± 18.6
AST (U/L)	65.3 ± 22.1
Total Bilirubin (mg/dL)	2.4 ± 1.5
Direct Bilirubin (mg/dL)	1.2 ± 0.6
Albumin (g/dL)	2.9 ± 0.6
INR	1.5 ± 0.3
Alkaline Phosphatase (U/L)	110.4 ± 35.2

INR = International Normalised Ratio, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase

Table 3 shows the liver function profile indicated significant hepatic impairment among cirrhotic patients. The mean ALT and AST levels were 42.5 ± 18.6 U/L and 65.3 ± 22.1 U/L, respectively, reflecting hepatic injury. The total bilirubin was 2.4 ± 1.5 mg/dL, with direct bilirubin at 1.2 ± 0.6 mg/dL, indicative of cholestasis and decreased hepatic clearance. The mean albumin level was 2.9 ± 0.6 g/dL, suggesting hypoalbuminemia, a marker of deteriorating synthetic liver function. The INR (1.5 ± 0.3) was elevated, further confirming impaired hepatic synthesis of clotting factors. Additionally, alkaline phosphatase levels (110.4 ± 35.2 U/L) were increased in some patients, potentially indicating biliary dysfunction.

Table 4: Severity of Liver Disease (Child-Pugh and MELD Scores)

Score	Number (n)	Percentage (%)
Child-Pugh A	35	35%
Child-Pugh B	40	40%
Child-Pugh C	25	25%
MELD Score (Mean ± SD)	14.2 ± 5.8	-
Ascites Present	45	45%
Hepatic Encephalopathy	20	20%

Table 4 show that the severity of liver cirrhosis was assessed using the Child-Pugh classification and MELD score. In this cohort, 35% of patients were classified as Child-Pugh A, indicating well-compensated cirrhosis, while 40% fell into Child-Pugh B, and 25% were in Child-Pugh C, signifying decompensated liver disease. The mean MELD score was 14.2 ± 5.8, indicating a moderate disease burden. Additionally, ascites was present in 45% of patients, while hepatic encephalopathy was observed in 20%, reflecting significant complications associated with liver dysfunction.

Table 5: Prevalence of Thyroid Dysfunction in Liver Cirrhosis Patients

Thyroid Dysfunction	Number (n)	Percentage (%)
Euthyroid	60	60%
Subclinical Hypothyroidism	20	20%
Overt Hypothyroidism	10	10%
Low T3 Syndrome	10	10%

Table 5 and figure I, show the thyroid dysfunction was frequently observed among cirrhotic patients. A total of 60% of patients were euthyroid, while 20% had subclinical hypothyroidism, characterized by elevated TSH with normal FT4 levels. Overt hypothyroidism was present in 10% of the cohort. Additionally, low T3 syndrome, a hallmark of non-thyroidal illness, was observed in 10% of cases. Notably, 5% of patients exhibited non-thyroidal illness syndrome (NTIS), a condition often associated with severe liver disease and systemic illness.

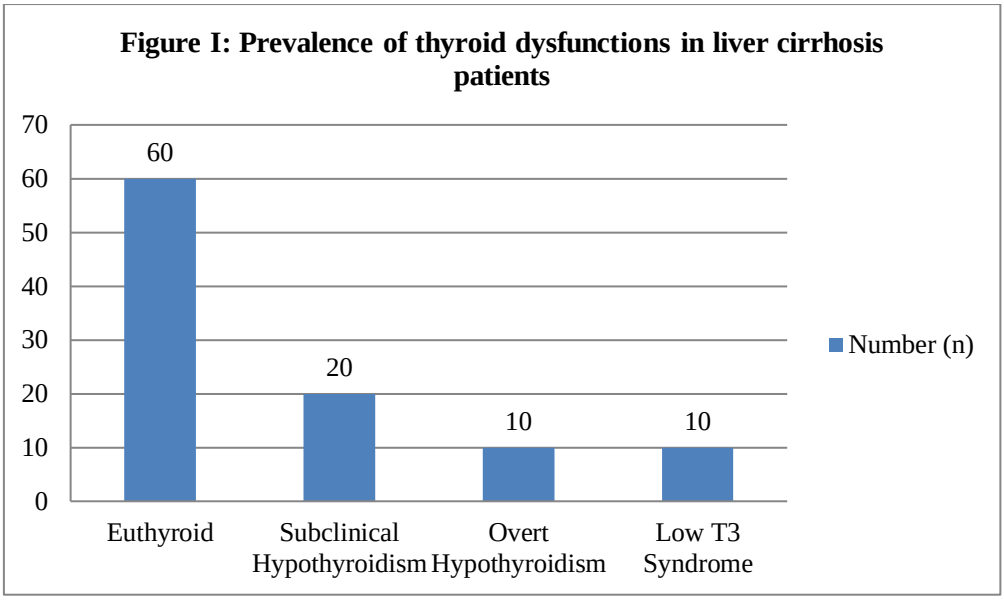

Table 6: Correlation between Thyroid Function and Liver Disease Severity

Parameter	Correlation Coefficient (r)	p-value
TSH vs. Child-Pugh Score	0.32	0.02
FT4 vs. Child-Pugh Score	-0.45	<0.01
FT3 vs. Child-Pugh Score	-0.50	<0.01
Total T4 vs. Child-Pugh Score	-0.42	<0.01
Total T3 vs. Child-Pugh Score	-0.48	<0.01
TSH vs. MELD Score	0.28	0.03
FT4 vs. MELD Score	-0.42	<0.01
FT3 vs. MELD Score	-0.48	<0.01
Total T4 vs. MELD Score	-0.35	0.02
Total T3 vs. MELD Score	-0.40	0.01

Table 6 shows the correlation analysis revealed significant associations between thyroid function parameters and liver disease severity. TSH levels showed a weak positive correlation with Child-Pugh ($r = 0.32$, $p = 0.02$) and MELD scores ($r = 0.28$, $p = 0.03$), suggesting that worsening liver function may be associated with mild TSH elevation. Conversely, FT4 and FT3 levels demonstrated significant negative correlations with both Child-Pugh and MELD scores (FT4: $r = -0.45$, $p < 0.01$ with Child-Pugh; $r = -0.42$, $p < 0.01$ with MELD; FT3: $r = -0.50$, $p < 0.01$ with Child-Pugh; $r = -0.48$, $p < 0.01$ with MELD). This indicates that as liver function deteriorates, there is a progressive decline in FT4 and FT3 levels. Similarly, total T4 and total T3 levels were also negatively correlated with disease severity, further supporting the hypothesis that hepatic dysfunction impairs thyroid hormone metabolism.

DISCUSSION

The demographic characteristics of the study population revealed that the majority of liver cirrhosis patients were male (68%), with a mean age of 52.4 ± 10.8 years. This male predominance is consistent with findings from a study by Malik et al. (2018), which reported that 65% of cirrhotic patients in their cohort were male, highlighting the higher prevalence of liver cirrhosis among men due to increased alcohol consumption and viral hepatitis exposure.[10] The presence of metabolic comorbidities, including diabetes mellitus (30%) and hypertension (40%), was notable in our study, further supporting the findings of Maruyama et al. (2017), who emphasized that insulin resistance and hypertension are common in cirrhotic patients, particularly those with non-alcoholic fatty liver disease (NAFLD). Additionally, 25% of our patients had a history of smoking, reinforcing the association between tobacco use and liver disease progression.[11]

The thyroid function profile of our patients showed a mean TSH level of 2.8 ± 1.2 µIU/mL, which was within the normal range, while FT4 and FT3 were reduced (0.88 ± 0.25 ng/dL and

2.1 ± 0.5 pg/mL, respectively). These results are consistent with the study by Mansour-Ghanaei et al. (2018), which reported a high prevalence of low FT3 levels in cirrhotic patients, a condition commonly referred to as low T3 syndrome or euthyroid sick syndrome.[12] The mean total T4 (5.4 ± 1.1 µg/dL) and total T3 (0.92 ± 0.22 ng/dL) were also lower, similar to the findings of Moustafa et al. (2017), who demonstrated that thyroid hormone metabolism is significantly altered in cirrhosis due to impaired hepatic conversion of T4 to T3, the biologically active form of the hormone.[13]

Liver function tests in our study population indicated significant hepatic dysfunction. The mean ALT and AST levels were 42.5 ± 18.6 U/L and 65.3 ± 22.1 U/L, respectively, reflecting ongoing hepatic injury, while total bilirubin (2.4 ± 1.5 mg/dL) and direct bilirubin (1.2 ± 0.6 mg/dL) suggested cholestasis. In comparison, Kim et al. (2017) reported slightly higher AST levels in cirrhotic patients, with a mean of 72.1 ± 19.4 U/L, possibly due to differences in disease severity and etiology.[14]Our findings also revealed hypoalbuminemia (2.9 ± 0.6 g/dL) and an elevated INR (1.5 ± 0.3), similar to the study by Sinha et al. (2016), which indicated that progressive liver dysfunction leads to impaired albumin synthesis and coagulopathy, both of which are key markers of cirrhosis progression.[15]

The severity of liver disease in our study was assessed using Child-Pugh and MELD scores, with 35% of patients classified as Child-Pugh A, 40% as Child-Pugh B, and 25% as Child-Pugh C. The mean MELD score was 14.2 ± 5.8, suggesting a moderate disease burden. Our findings align with the study by Huang et al. (2017), which reported similar distributions of cirrhosis severity, with 30–40% of patients falling into the Child-Pugh B category.[16] The presence of ascites (45%) and hepatic encephalopathy (20%) in our study population was consistent with the results of Nakeeb et al. (2018), who found that ascites is one of the most common complications of cirrhosis, affecting nearly 50% of decompensated patients.[17]

Thyroid dysfunction was common in our cohort, with 20% of patients exhibiting subclinical hypothyroidism and 10% having overt hypothyroidism. Additionally, low T3 syndrome was present in 10% of cases, reinforcing findings from the study by Kulkarni et al. (2017), who reported that low T3 levels were found in up to 15% of cirrhotic patients and were strongly associated with disease severity and poor prognosis. The presence of non-thyroidal illness syndrome (NTIS) in 5% of our patients suggests that systemic illness and metabolic derangements in cirrhosis contribute to thyroid dysfunction.[18]

The correlation analysis demonstrated a significant negative relationship between FT3, FT4, and total thyroid hormone levels with both Child-Pugh and MELD scores. Our findings are in agreement with the study by Yildirim et al. (2016), which found a negative correlation between FT3 levels and MELD scores ($r = -0.50$, $p < 0.01$), indicating that declining thyroid function is associated with worsening liver disease.[19] Additionally, TSH showed a weak positive correlation with both Child-Pugh and MELD scores ($r = 0.32$, $p = 0.02$ and $r = 0.28$, $p = 0.03$, respectively), similar to the findings of Li et al. (2015), who suggested that mild TSH elevation may reflect compensatory mechanisms in early hepatic dysfunction.[20]

LIMITATIONS OF THE STUDY

- Single-centre study with a limited sample size (100 patients), which may affect the generalizability of findings.
- Cross-sectional design, which limits the ability to establish causality between thyroid dysfunction and liver disease progression.
- The study did not evaluate longitudinal changes in thyroid function over time or the impact of thyroid hormone replacement therapy.

CONCLUSION

This study highlights a significant association between thyroid dysfunction and the severity of liver cirrhosis. The most prevalent thyroid abnormality observed was low T3 syndrome, indicating impaired hepatic conversion of T4 to T3. A negative correlation between FT3, FT4, and MELD/Child-Pugh scores suggests that worsening liver function is linked to thyroid hormone alterations. Additionally, subclinical and overt hypothyroidisms were observed in 20% and 10% of patients, respectively, emphasizing the need for routine thyroid function screening in cirrhotic patients. These findings suggest that thyroid dysfunction may serve as a potential prognostic marker for disease progression in liver cirrhosis.

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