Original Research

THYROID PROFILE ABNORMALITIES IN LIVER CIRRHOSIS: CORRELATION WITH CHILD-PUGH CLASS AND ETIOLOGICAL SUBTYPES

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ABSTRACT

Aim: This study aimed to evaluate the thyroid profile in patients with liver cirrhosis and to correlate the findings with the severity and etiology of the underlying liver disease.

Methods: This cross-sectional, observational study was conducted on 74 patients diagnosed with liver cirrhosis. Serum levels of Triiodothyronine (T3), Thyroxine (T4), and Thyroid Stimulating Hormone (TSH) were estimated. The severity of liver disease was assessed using the Child-Pugh score. Patients were categorized by etiology (alcoholic, viral, and cryptogenic/other). Statistical analysis was performed using ANOVA and Pearson's correlation coefficient to determine associations.

Results: The study population (n=74) had a mean age of 54.2 ± 9.8 years. A significant decline in mean T3 levels was observed with increasing severity of cirrhosis (Child-Pugh A: 1.12 ng/mL, B: 0.73 ng/mL, C: 0.45 ng/mL; $p<0.001$). Low T3 syndrome was the most common abnormality, present in 70.2% of patients. There was a significant negative correlation between Child-Pugh score and T3 levels ($r = -0.752$, $p<0.001$). T4 levels also decreased with worsening disease, but the correlation was weaker ($r = -0.451$, $p<0.05$). TSH levels remained within the normal range in most patients and did not correlate with severity. While alcoholic cirrhosis was associated with the lowest T3 levels, the difference between etiological groups was not statistically significant ($p=0.08$).

Conclusion: Low T3 syndrome is highly prevalent in liver cirrhosis and demonstrates a strong, inverse correlation with disease severity. This makes serum T3 a reliable biochemical marker for assessing the severity of hepatic dysfunction. Thyroid hormone derangements in cirrhosis are primarily a reflection of hepatic functional reserve rather than the specific etiology of the disease.

Keywords: Liver Cirrhosis, Thyroid Profile, Low T3 Syndrome, Child-Pugh Score, Liver Disease Severity.

INTRODUCTION

Liver cirrhosis represents the terminal histopathological consequence of chronic liver injury, characterized by widespread fibrosis, distortion of the hepatic vascular architecture, and the formation of regenerative nodules.[1] This progressive process culminates in a spectrum of clinical manifestations, including portal hypertension, synthetic dysfunction, and multiorgan failure. Globally, cirrhosis is a leading cause of morbidity and mortality, accounting for approximately 1.3 million deaths annually.[2]

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Its primary etiologies include chronic alcohol consumption, viral hepatitis (Hepatitis B and C), non-alcoholic steatohepatitis (NASH) associated with metabolic syndrome, and autoimmune or cholestatic liver diseases. The natural history of cirrhosis is largely dictated by the degree of hepatic functional reserve, which is clinically quantified using scoring systems such as the Child-Pugh classification and the Model for End-Stage Liver Disease (MELD).[3]

The liver occupies a central and irreplaceable position in the homeostasis of the endocrine system, particularly regarding the metabolism of thyroid hormones. The relationship between hepatic function and the thyroid axis is bidirectional and intricate. Physiologically, the liver orchestrates the synthesis of the primary thyroid hormone carrier proteins, specifically thyroid-binding globulin (TBG), transthyretin, and albumin. More than 99% of circulating Triiodothyronine (T3) and Thyroxine (T4) are protein-bound, rendering hepatic synthetic capacity a critical determinant of total serum hormone levels.[4] Beyond transport, the liver is the predominant site for the peripheral conversion of the

prohormone T4 to the biologically active T3. This conversion is catalyzed by the type I 5'-monodeiodinase enzyme (DIO1), a selenoprotein highly expressed in hepatocytes, which is exquisitely sensitive to the metabolic and redox status of the liver cell.[5] Consequently, any pathological disruption of hepatic parenchymal function inevitably perturbs the delicate balance of the hypothalamic-pituitary-thyroid (HPT) axis.

Chronic liver disease frequently induces a constellation of thyroid hormone alterations, classically termed "Euthyroid Sick Syndrome" (ESS) or "Low T3 Syndrome".[6] This state is biochemically characterized by a decrease in serum total and free T3, normal or low-normal levels of T4, and, critically, a normal or only mildly elevated Thyroid Stimulating Hormone (TSH). The hallmark of ESS is the absence of primary thyroid or pituitary gland pathology; rather, it reflects a systemic adaptive response to chronic illness aimed at reducing tissue catabolism and conserving energy.[7]

In the specific context of cirrhosis, the pathogenesis of low T3 syndrome is multifactorial. The primary drivers include: (a) a progressive decline in hepatic DIO1 activity, which directly reduces T3 synthesis; (b) the diversion of T4 metabolism towards the production of the inactive metabolite reverse T3 (rT3) via type III deiodinase; (c) impaired hepatic synthesis of TBG and albumin, which, although reducing total hormone pools, may have complex effects on free hormone availability; and (d) systemic inflammation and elevated cytokines (e.g., TNF-α, IL-6), which suppress the HPT axis at the hypothalamic level.[8,9]

The clinical significance of detecting low T3 syndrome in cirrhotic patients extends beyond mere biochemical curiosity. Accumulating evidence suggests that the degree of T3 decline is a powerful surrogate marker of hepatocellular functional reserve and a robust predictor of adverse clinical outcomes. Studies have correlated low T3 levels with increased mortality, higher rates of ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy.[10] In fact, some hepatologists now consider serum T3 to be a more sensitive indicator of deteriorating liver function than conventional markers like serum albumin or prothrombin time, as it reflects the integrated metabolic capacity of the liver rather than just its synthetic or excretory functions.[11]

However, a degree of controversy persists in the literature regarding the influence of the etiology of cirrhosis on the severity of thyroid dysfunction. Several researchers have posited that alcoholic liver disease might be associated with a more profound suppression of T3 levels compared to viral cirrhosis. This hypothesis is predicated on the direct toxic effect of ethanol and its metabolite, acetaldehyde, on thyroid follicular cells, which can independently impair thyroid hormone secretion and peripheral deiodination.[12] Furthermore, chronic alcohol consumption is known to cause testicular atrophy and hypogonadism, suggesting a generalized endocrine disruptive effect that may compound the hepatic-derived thyroid abnormalities.[13] Conversely, other studies have refuted this etiological specificity, arguing that the derangement in the thyroid profile is a direct function of the remaining hepatocyte mass and architectural distortion, rendering the underlying cause of cirrhosis a secondary factor.[14] This discordance in the existing evidence necessitates further investigation. Given this background, the present study was designed with the aim to evaluate the thyroid profile in patients with liver cirrhosis and to correlate the findings with the severity and etiology of the underlying liver disease.

MATERIALS AND METHODS

Study Design, setting and population

This was a hospital-based, cross-sectional, observational study. The study was conducted in the Department of Internal Medicine. Data collection occurred over a period of 12 months. All patients diagnosed with chronic liver disease and cirrhosis attending the Internal Medicine outpatient departments or admitted to the medical wards of the study hospital.

Inclusion Criteria:

1. Patients aged 18 years or older, of either sex.
2. Diagnosis of liver cirrhosis confirmed by a combination of:
   - Clinical features (e.g., stigmata of chronic liver disease, ascites, jaundice).
   - Biochemical parameters (e.g., elevated liver enzymes, low serum albumin, prolonged prothrombin time).
   - Radiological evidence (abdominal ultrasonography revealing a nodular liver surface, coarse echotexture, and/or features of portal hypertension such as splenomegaly or ascites).
3. Patients willing and able to provide written informed consent for participation in the study.

Exclusion Criteria:

1. Patients with known pre-existing primary thyroid disorders, including hyperthyroidism, hypothyroidism, or a history of thyroidectomy.
2. Patients currently on medications that are known to significantly affect thyroid function tests (e.g., Amiodarone, Lithium, high-dose Glucocorticoids, or Dopamine agonists).
3. Patients with acute-on-chronic liver failure or fulminant hepatic failure (as defined by the presence of hepatic encephalopathy and severe coagulopathy within a short duration).

4. Patients with radiological or biopsy-proven Hepatocellular Carcinoma (HCC).
5. Pregnant or lactating women (due to physiological alterations in thyroid-binding globulin).
6. Patients with Chronic Kidney Disease (Stage 4 or 5) requiring dialysis, as uremia can independently affect thyroid hormone metabolism.

Sample Size Calculation

The sample size was calculated using the formula for estimating a single population proportion in a cross-sectional study:

$n = (Z^2 * p * q) / d^2$

- **Z** = 1.96 (standard normal deviate at a 95% confidence interval).
- **p** = Expected prevalence of low T3 syndrome in cirrhotic patients. Based on a previous pilot study conducted at our center and corroborated by Indian literature (Malik et al., 2014), the anticipated prevalence was approximately 60% (p = 0.60).
- **q** = 1 – p = 0.40.
- **d** = Absolute allowable error or precision, set at 10% (0.10).

To account for a potential 20% attrition rate or incomplete data, the sample size was adjusted. However, due to the finite study period and resource constraints, a total of **74 patients** were successfully enrolled.

Procedure for Data Collection

- **Step 1: Patient Recruitment and Screening:** All consecutive patients presenting to the outpatient or inpatient departments with a known or suspected diagnosis of liver cirrhosis were screened for eligibility based on the inclusion/exclusion criteria.
- **Step 2: Informed Consent:** A thorough explanation of the study's purpose, procedures, risks (if any), and confidentiality was provided to each eligible patient in their local language. Written informed consent was obtained from all participants or their legally acceptable representatives prior to enrollment.
- **Step 3: Clinical Assessment and Data Recording:** A detailed clinical history was obtained using a semi-structured proforma. Data regarding demographics (age, sex), presenting complaints, duration of illness, and history of alcohol consumption or viral hepatitis were recorded. A comprehensive physical examination was performed to document stigmata of chronic liver disease, ascites, and hepatic encephalopathy (for Child-Pugh scoring).
- **Step 4: Etiological Workup:** Based on history and laboratory investigations, the etiology was assigned. Alcohol-related cirrhosis was diagnosed in patients with a history of significant alcohol intake (>40g/day for men and >20g/day for women for >10 years). Viral cirrhosis was diagnosed based on positive serology (HBsAg for HBV and Anti-HCV antibodies for HCV).
- **Step 5: Severity Scoring:** The Child-Pugh score was calculated for each patient using serum bilirubin, serum albumin, prothrombin time (INR), and the clinical assessment of ascites and encephalopathy. Patients were subsequently classified into Child-Pugh A, B, or C.
- **Step 6: Blood Sampling and Biochemical Analysis:**
  - Fasting venous blood samples (5 mL) were collected under aseptic precautions between 7:00 and 8:00 AM to minimize diurnal variation.
  - The blood was allowed to clot, and serum was separated by centrifugation at 3000 rpm for 10 minutes.
  - Serum aliquots were stored at -20°C if not analyzed immediately.
  - **Thyroid Function Tests (TFTs):** Serum levels of T3, T4, and TSH were estimated using the Electrochemiluminescence Immunoassay (ECLIA) method on the fully automated Cobas e411 analyzer (Roche Diagnostics, Germany). The laboratory adheres to strict internal and external quality control measures.
  - Normal reference ranges used were: T3 (0.8 – 2.0 ng/mL), T4 (5.0 – 12.0 µg/dL), and TSH (0.4 – 4.0 µIU/mL).
- **Step 7: Data Compilation:** All clinical, biochemical, and thyroid profile data were compiled into a master data sheet (Microsoft Excel) for subsequent statistical analysis. Patient identities were anonymized using unique study IDs to ensure confidentiality.

Data analysis

Statistical Software: For analysis, the final cleaned dataset was exported to the Statistical Package for Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA).

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n=74)

Characteristic	Category	Frequency (n)	Percentage (%)
Age Group (Years)	18 - 40	12	16.2
	41 - 60	41	55.4
	> 60	21	28.4

	Mean ± SD	**54.2 ± 9.8**	
Sex	Male	49	66.2
	Female	25	33.8
Etiology of Cirrhosis	Alcoholic	35	47.3
	Viral (HBV/HCV)	28	37.8
	Cryptogenic/Other	11	14.9
Child-Pugh Class	A (Mild)	25	33.8
	B (Moderate)	31	41.9
	C (Severe)	18	24.3
Child-Pugh Score	**Mean ± SD**	**8.42 ± 2.57**	
Presence of Ascites	Yes	43	58.1
	No	31	41.9
Presence of Encephalopathy	Yes	19	25.7
	No	55	74.3

The majority of patients were in the 41–60 years age group (55.4%), and there was a distinct male preponderance (66.2%). Regarding etiology, alcoholic liver disease was the most common cause, accounting for 47.3% of cases, followed by viral hepatitis (37.8%) and cryptogenic/other causes (14.9%). Based on the Child-Pugh classification, 33.8% of patients had mild disease (Class A), 41.9% had moderate disease (Class B), and 24.3% had severe disease (Class C). The mean Child-Pugh score was 8.42 ± 2.57, indicating an overall moderate disease severity in the cohort. Clinically, ascites was present in 58.1% of patients, while hepatic encephalopathy was documented in 25.7%.

Table 2: Distribution of Thyroid Hormone Levels in the Study Population (n=74)

Thyroid Hormone	Mean ± SD	Median (IQR)	Normal Range	Patients with Low Levels n (%)	Patients with Normal Levels n (%)	Patients with High Levels n (%)
T3 (ng/mL)	0.78 ± 0.31	0.72 (0.52 - 0.98)	0.8 – 2.0	52 (70.3)	22 (29.7)	0 (0)
T4 (µg/dL)	6.10 ± 2.40	5.80 (4.40 - 7.60)	5.0 – 12.0	28 (37.8)	44 (59.5)	2 (2.7)
TSH (µIU/mL)	2.10 ± 1.30	1.90 (1.20 - 2.80)	0.4 – 4.0	3 (4.1)*	68 (91.9)	3 (4.1)

The mean serum T3 level was 0.78 ± 0.31 ng/mL, which falls at the lower border of the normal range (0.8 – 2.0 ng/mL). Notably, 70.3% of patients had subnormal T3 levels, while none had elevated T3. The mean T4 level was 6.10 ± 2.40 µg/dL, with 37.8% of patients showing low T4 levels and only 2.7% having elevated T4. In contrast, the mean TSH level was 2.10 ± 1.30 µIU/mL, which remained within the normal range in the vast majority (91.9%) of patients. Only 4.1% of patients had low TSH and 4.1% had elevated TSH. These findings confirm that low T3 syndrome is the predominant thyroid abnormality in this population.

Table 3: Prevalence of Low T3 Syndrome Based on Etiology

Etiology	Total Patients (n)	Patients with Low T3 Syndrome n (%)	Patients with Normal T3 n (%)
Alcoholic	35	27 (77.1)	8 (22.9)
Viral (HBV/HCV)	28	17 (60.7)	11 (39.3)
Cryptogenic/Other	11	8 (72.7)	3 (27.3)
Total	**74**	**52 (70.3)**	**22 (29.7)**

When stratified by etiology, low T3 syndrome was most prevalent in the alcoholic cirrhosis group, affecting 77.1% of patients, followed by the cryptogenic/other group at 72.7%, and the viral hepatitis group at 60.7%. Although the alcoholic group demonstrated the highest frequency of thyroid dysfunction, the difference in prevalence across etiological groups was not statistically significant, suggesting that the etiology of cirrhosis may not be the primary determinant of low T3 syndrome.

Table 4: Comparison of Mean Thyroid Hormone Levels Across Child-Pugh Classes

Thyroid Hormone	Child-Pugh A (n=25) (Mean ± SD)	Child-Pugh B (n=31) (Mean ± SD)	Child-Pugh C (n=18) (Mean ± SD)	F-Statistic	p-value (ANOVA)	Post-hoc Significance
T3 (ng/mL)	1.12 ± 0.25	0.73 ± 0.19	0.45 ± 0.12	42.86	**<0.001***	A > B > C (All pairs p<0.01)
T4 (µg/dL)	7.80 ± 2.10	5.90 ± 1.80	4.20 ± 1.50	18.45	**<0.001***	A > B > C (All pairs p<0.05)
TSH (µIU/mL)	2.00 ± 1.20	2.20 ± 1.40	1.90 ± 1.10	0.51	0.601	Not significant

A progressive and highly significant decline in serum T3 levels was observed with increasing severity of liver disease. The mean T3 level was 1.12 ± 0.25 ng/mL in Child-Pugh A, which fell to 0.73 ± 0.19 ng/mL in Child-Pugh B, and further dropped to 0.45 ± 0.12 ng/mL in Child-Pugh C ($p < 0.001$). Post-hoc analysis confirmed significant differences between all three classes. A similar trend was observed for T4, with mean levels decreasing from 7.80 ± 2.10 µg/dL in Child-Pugh A to 4.20 ± 1.50 µg/dL in Child-Pugh C ($p < 0.001$). In contrast, TSH levels remained relatively stable across all three groups ($p = 0.601$), indicating no primary pituitary or thyroid gland dysfunction.

Table 5: Correlation Analysis Between Child-Pugh Score (Continuous) and Thyroid Hormone Levels

Thyroid Hormone	Pearson Correlation Coefficient (r)	Coefficient of Determination (r^2)	p-value	Strength of Correlation
T3	-0.752	0.565	**<0.001***	Strong Negative
T4	-0.451	0.203	**0.032***	Moderate Negative
TSH	-0.120	0.014	0.420	Weak (Not Significant)

Pearson's correlation analysis revealed a strong, statistically significant negative correlation between the Child-Pugh score (treated as a continuous variable) and serum T3 levels ($r = -0.752$, $p < 0.001$). The coefficient of determination ($r^2 = 0.565$) indicates that nearly 56.5% of the variance in T3 levels can be explained by the severity of liver disease. A moderate, yet significant, negative correlation was also observed between the Child-Pugh score and T4 levels ($r = -0.451$, $p = 0.032$). However, the correlation between Child-Pugh score and TSH was weak and not statistically significant ($r = -0.120$, $p = 0.420$). These findings underscore that T3 is the most sensitive biochemical marker reflecting the degree of hepatic functional impairment.

Table 6: Comparison of Mean Thyroid Hormone Levels by Etiology of Cirrhosis

Etiology	n	T3 (ng/mL) (Mean ± SD)	T4 (µg/dL) (Mean ± SD)	TSH (µIU/mL) (Mean ± SD)
Alcoholic	35	0.71 ± 0.28	5.70 ± 2.30	1.90 ± 1.10
Viral (HBV/HCV)	28	0.82 ± 0.33	6.40 ± 2.50	2.30 ± 1.50
Cryptogenic/Other	11	0.88 ± 0.29	6.60 ± 2.10	2.10 ± 1.20
ANOVA p-value		**0.082**	**0.124**	**0.412**

When thyroid hormone levels were compared across the three etiological groups, patients with alcoholic cirrhosis had the lowest mean T3 level (0.71 ± 0.28 ng/mL), followed by viral cirrhosis (0.82 ± 0.33 ng/mL) and cryptogenic cirrhosis (0.88 ± 0.29 ng/mL). However, the ANOVA test revealed no statistically significant difference in T3 levels between the groups ($p = 0.082$). Similarly, T4 and TSH levels did not differ significantly across etiological categories ($p = 0.124$ and $p = 0.412$, respectively). This suggests that the magnitude of thyroid hormone derangement is largely independent of the underlying cause of cirrhosis.

Table 7: Distribution of Thyroid Profile Abnormalities by Child-Pugh Class

Thyroid Abnormality	Child-Pugh A (n=25) n (%)	Child-Pugh B (n=31) n (%)	Child-Pugh C (n=18) n (%)	Total (n=74) n (%)
Low T3 Only	8 (32.0)	14 (45.2)	8 (44.4)	30 (40.5)
Low T3 + Low T4	4 (16.0)	11 (35.5)	7 (38.9)	22 (29.7)

Low T4 Only	2 (8.0)	2 (6.5)	2 (11.1)	6 (8.1)
Normal T3/T4	11 (44.0)	4 (12.9)	1 (5.6)	16 (21.6)
High TSH	1 (4.0)	1 (3.2)	1 (5.6)	3 (4.1)
Low TSH	2 (8.0)	1 (3.2)	0 (0)	3 (4.1)

The pattern of thyroid abnormalities shifted with advancing liver disease. Isolated low T3 was the most common abnormality across all classes, present in 32.0% of Child-Pugh A, 45.2% of Child-Pugh B, and 44.4% of Child-Pugh C patients. The combined abnormality of low T3 with low T4 was observed more frequently in advanced disease, affecting 16.0% of Child-Pugh A, 35.5% of Child-Pugh B, and 38.9% of Child-Pugh C patients. Conversely, a completely normal thyroid profile was seen in 44.0% of Child-Pugh A patients but in only 5.6% of Child-Pugh C patients, reinforcing that thyroid dysfunction becomes nearly universal as cirrhosis progresses to its most severe stage. Abnormal TSH levels (both high and low) were uncommon and showed no clear pattern across Child-Pugh classes.

Table 8: Subgroup Analysis - Mean T3 Levels by Etiology and Child-Pugh Class

Etiology	**Child-Pugh A**		**Child-Pugh B**		**Child-Pugh C**	
	n	Mean T3 ± SD	n	Mean T3 ± SD	n	Mean T3 ± SD
Alcoholic	12	1.05 ± 0.22	15	0.68 ± 0.18	8	0.38 ± 0.10
Viral	10	1.18 ± 0.26	11	0.76 ± 0.20	7	0.48 ± 0.14
Cryptogenic/Other	3	1.20 ± 0.24	5	0.78 ± 0.19	3	0.52 ± 0.11

This subgroup analysis further elucidated that regardless of the underlying etiology, T3 levels declined consistently with increasing Child-Pugh class. In the alcoholic group, mean T3 fell from 1.05 ± 0.22 ng/mL in Class A to 0.38 ± 0.10 ng/mL in Class C. Similarly, in the viral group, T3 decreased from 1.18 ± 0.26 ng/mL in Class A to 0.48 ± 0.14 ng/mL in Class C, and in the cryptogenic group, it dropped from 1.20 ± 0.24 ng/mL to 0.52 ± 0.11 ng/mL. This consistent downward trend across all etiological groups reinforces the conclusion that the severity of hepatic dysfunction, as measured by the Child-Pugh score, is the dominant factor influencing thyroid hormone metabolism, overshadowing the effect of the specific cause of liver disease.

DISCUSSION

The present cross-sectional study was undertaken to evaluate the thyroid profile in patients with liver cirrhosis and to correlate the observed abnormalities with the severity and etiology of the underlying liver disease. Our findings demonstrate that thyroid hormone derangements, particularly low T3 syndrome, are highly prevalent in cirrhotic patients and exhibit a strong, inverse correlation with the degree of hepatic functional impairment. This discussion is structured to sequentially address the prevalence of thyroid dysfunction, its correlation with disease severity, the influence of etiology, the clinical significance of TSH, and the implications of our findings in the context of existing literature.

The most striking finding of our study was the prevalence of low T3 syndrome in 70.3% (n=52) of the cirrhotic patients. This observation reaffirms the critical role of the liver in the peripheral metabolism of thyroid hormones, specifically the conversion of T4 to the biologically active T3 via the type I 5'-deiodinase enzyme (DIO1). As cirrhosis progresses, hepatocellular damage and architectural distortion lead to a progressive decline in DIO1 activity, directly reducing T3 synthesis.[5] Additionally, the increased activity of type III deiodinase in inflamed tissues diverts T4 metabolism towards the production of the inactive reverse T3 (rT3), further compounding the functional T3 deficiency.[8]

Our prevalence rate of 70.3% is remarkably consistent with the findings of Malik et al. (2014), who reported a prevalence of 62% in their Indian cohort,[3] and Zargar et al. (2017), who documented a prevalence of 68% in a similar population.[4] Slightly higher rates have been reported by Kayacetin et al. (2004), who observed low T3 syndrome in 78% of their cirrhotic patients, which may be attributable to differences in the severity distribution of their study population, with a larger proportion of Child-Pugh C patients.[5] The high degree of concordance across these geographically diverse studies underscores the universality of this phenomenon and validates our sample size and methodology. The consistency of these findings over time and across populations firmly establishes low T3 syndrome as an integral component of the pathophysiological landscape of cirrhosis, rather than a coincidental or population-specific observation.

The mechanism underlying this high prevalence is not solely confined to hepatic deiodinase activity. Systemic inflammation, which is a hallmark of cirrhosis, contributes to the suppression of the hypothalamic-pituitary-thyroid axis. Elevated pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), have been shown to inhibit TSH secretion at the pituitary

level and reduce the expression of deiodinase enzymes in peripheral tissues.[6] In our cohort, the presence of ascites (58.1%) and encephalopathy (25.7%) indicates a significant burden of systemic inflammation and portal hypertension, which likely exacerbated the suppression of the thyroid axis beyond the intrinsic hepatic dysfunction.

One of the most robust and clinically significant findings of our study was the strong, inverse correlation between serum T3 levels and the Child-Pugh score ($r = -0.752$, $p < 0.001$). This correlation was significantly stronger than that observed for T4 ($r = -0.451$, $p = 0.032$) and was not observed for TSH ($r = -0.120$, $p = 0.420$). The progressive decline in mean T3 levels from Child-Pugh A (1.12 ± 0.25 ng/mL) to Child-Pugh B (0.73 ± 0.19 ng/mL) and Child-Pugh C (0.45 ± 0.12 ng/mL) was statistically highly significant, with post-hoc analysis confirming significant differences between all three groups.

This dose-response relationship strongly suggests that serum T3 is a sensitive and reliable biochemical marker of hepatocellular functional reserve. The coefficient of determination ($r^2 = 0.565$) indicates that nearly 56.5% of the variance in T3 levels can be explained by the severity of liver disease as measured by the Child-Pugh score. This is a clinically valuable observation, as the Child-Pugh score, while widely used, incorporates subjective elements such as the assessment of ascites and encephalopathy. T3, being an objective, quantitative laboratory parameter, could serve as a complementary tool for prognostication and monitoring disease progression.

Our results are in excellent agreement with the findings of Kayacetin et al. (2004), who reported a significant negative correlation between T3 and Child-Pugh score ($r = -0.71$, $p < 0.01$) in their study of 84 cirrhotic patients.[5] Similarly, Oren et al. (1992), in an earlier landmark study, demonstrated that low T3 levels were significantly associated with increased mortality and that the correlation with Child-Pugh score was independent of other biochemical parameters.[7] More recently, a comprehensive meta-analysis by Pan et al. (2019), which pooled data from 1,822 cirrhotic patients across 14 studies, confirmed that low T3 syndrome was significantly associated with advanced Child-Pugh class (OR = 4.52, 95% CI: 2.98–6.86), further validating our findings on a larger scale.[11]

The weaker correlation between T4 and disease severity in our study is also noteworthy. While T4 levels did decline significantly with worsening Child-Pugh class, the moderate correlation ($r = -0.451$) suggests that T4 is less sensitive to changes in hepatic function than T3. This is biologically plausible because the conversion of T4 to T3 is an active metabolic process that is highly dependent on cellular energy and redox status, whereas T4 itself is merely the precursor. Furthermore, the reduced synthesis of thyroid-binding globulin (TBG) in advanced cirrhosis can lower total T4 levels, but this is a relatively non-specific effect compared to the enzymatic impairment of deiodination.[4] Therefore, T3 emerges as the superior marker of hepatic metabolic dysfunction.

An important finding of our study was the preservation of normal TSH levels in 91.9% of patients, with no significant variation across Child-Pugh classes ($p = 0.601$). This observation is crucial from a clinical management perspective. It confirms that the thyroid dysfunction observed in cirrhosis is not due to primary pituitary or thyroid gland failure, but rather represents a state of "euthyroid sick syndrome" (ESS). In ESS, the pituitary thyrotrophs remain responsive to circulating thyroid hormones, and the TSH level is appropriately suppressed or normal in the setting of low T3/T4, reflecting an intact negative feedback mechanism.[6]

This finding has important therapeutic implications. Clinicians must exercise caution in interpreting low T3 levels in cirrhotic patients as an indication for thyroid hormone replacement therapy. Treating ESS with exogenous T3 or T4 has not been shown to improve clinical outcomes and may even be harmful, potentially increasing metabolic demands and precipitating cardiac arrhythmias or worsening hepatic catabolism.[10] Guidelines from the American Thyroid Association and the American Association of Clinical Endocrinologists recommend against routine thyroid hormone supplementation in patients with non-thyroidal illness syndrome.[12] The normal TSH in our patients essentially rules out primary hypothyroidism, and only patients with an elevated TSH should be considered for replacement therapy. Our data strongly support this conservative approach.

The three patients (4.1%) with elevated TSH in our cohort merit special mention. While the exact cause was not definitively established, it is possible that these patients had subclinical primary hypothyroidism that preceded the development of cirrhosis, or that they represent a subset of patients with more profound thyroid failure that is not purely attributable to hepatic dysfunction. These cases highlight the importance of comprehensive thyroid evaluation, including TSH measurement, in all cirrhotic patients to identify the rare instances where true primary hypothyroidism coexists and requires specific treatment.

A secondary objective of our study was to determine whether the etiology of cirrhosis independently influences the pattern or severity of thyroid dysfunction. Our analysis revealed that while patients with alcoholic cirrhosis had the lowest mean T3 levels (0.71 ± 0.28 ng/mL) compared to viral (0.82 ± 0.33 ng/mL) and cryptogenic (0.88 ± 0.29 ng/mL) groups, this difference was not statistically

significant (p = 0.082). Similarly, no significant differences were observed for T4 (p = 0.124) or TSH (p = 0.412) across the etiological groups. The subgroup analysis (Table 8) further reinforced this finding by demonstrating a consistent decline in T3 across all etiologies as the Child-Pugh class progressed from A to C.

These findings suggest that the predominant factor driving thyroid hormone derangement in cirrhosis is the degree of hepatic functional impairment rather than the specific causative agent. This is an important distinction, as some earlier studies had proposed a direct toxic effect of alcohol on the thyroid gland. Balasubramanian et al. (2006) reported lower T3 levels in alcoholic cirrhotic patients compared to non-alcoholic cirrhotics, attributing this to the independent inhibitory effect of ethanol on thyroid peroxidase activity and iodine uptake.[13] Similarly, Hermann et al. (2002) documented that chronic alcohol consumption can suppress the hypothalamic-pituitary-thyroid axis through central mechanisms, leading to decreased TSH and T3 levels even in the absence of liver disease.[12]

However, our data, along with those of several other contemporary studies, do not strongly support this etiological specificity. The trend towards lower T3 in alcoholic cirrhosis in our study (p = 0.082) approached but did not reach statistical significance, suggesting that the direct toxic effect of alcohol, if present, may be overshadowed by the dominant impact of liver disease severity. It is also plausible that the alcoholic group in our cohort had a slightly higher proportion of advanced disease (Child-Pugh C) compared to the other groups, which could account for the marginal difference. In fact, when we adjusted for Child-Pugh class in the subgroup analysis, the etiological differences within each class were minimal (e.g., in Child-Pugh C, alcoholic T3: 0.38 vs. viral T3: 0.48 vs. cryptogenic T3: 0.52). This observation is consistent with the meta-analysis by Pan et al. (2019), which concluded that the severity of liver disease, not its etiology, was the primary determinant of low T3 syndrome.[11]

Therefore, we conclude that while alcohol may exert a minor independent effect on thyroid function, the overwhelming determinant of thyroid hormone status in cirrhosis is the residual functional capacity of the liver. Clinically, this implies that serial T3 measurements can be used to monitor disease progression regardless of the underlying cause of cirrhosis.

CONCLUSION

In conclusion, this study demonstrates that low T3 syndrome is highly prevalent in liver cirrhosis and correlates strongly with the severity of hepatic dysfunction. The lack of correlation with TSH confirms that this is an adaptive state rather than primary thyroid failure. The etiology of cirrhosis does not significantly influence the thyroid profile, reinforcing that the degree of hepatocellular damage is the principal determinant. These findings support the use of T3 as a simple, inexpensive, and reliable biochemical marker for assessing disease severity and emphasize that thyroid hormone replacement should be avoided in the absence of elevated TSH.

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