Section: Biochemistry

Original Research Article

THYROID DYSFUNCTION IN PATIENTS WITH ALCOHOLIC LIVER DISEASE AND ITS ASSOCIATION WITH SEVERITY OF LIVER DISEASE

Bhavita Patel[1], Harshit Malkan[2], Mahesh G Solu[3], Sajiya Patel[4]

[1]Associate Professor, Department of Biochemistry, Dr Kiran C Patel Medical College and Research Institute, Bharuch, India.
[2]Intern Doctor, Department of Medicine, Dr Kiran C Patel Medical College and Research Institute, Bharuch, India.
[3]Professor and Head of Department, Department of Medicine, Dr Kiran C Patel Medical College and Research Institute, Bharuch, India.
[4]Junior Doctor, Department of Medicine, Dr Kiran C Patel Medical College and Research Institute, Bharuch, India.

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Corresponding Author:
Dr. Harshit Malkan,
Intern Doctor, Department of Medicine, Dr Kiran C Patel Medical College and Research Institute, Bharuch, India.
Email: hm1912003@yahoo.com

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ABSTRACT

Background: Alcoholic liver disease (ALD) is a leading cause of chronic liver disease globally, with India experiencing rising prevalence rates. The liver plays a crucial role in thyroid hormone metabolism, and thyroid dysfunction is commonly observed in patients with chronic liver disease. However, limited data exists on the relationship between thyroid dysfunction and severity of alcoholic liver disease in Indian patients.

Materials and Methods: This case-control study was conducted at Civil Hospital, Dr. Kiran C Patel Medical College and Research Institute, Bharuch, from October 2024 to June 2025. A total of 100 patients with alcoholic liver disease (cases) and 100 healthy controls were enrolled. Thyroid function tests including TSH, free T3, and free T4 were measured using electrochemiluminescence immunoassay. Liver disease severity was assessed using Child-Pugh classification. Statistical analysis was performed using SPSS version 20.0, with Student's t-test for continuous variables and chi-square test for categorical variables.

Results: The mean age of cases was 51.2 ± 7.3 years with 93% males. Cases showed significantly higher TSH levels (5.06 ± 1.72 vs 2.40 ± 0.79 mIU/L, $p<0.001$), lower free T3 levels (3.30 ± 1.03 vs 5.48 ± 0.96 pmol/L, $p<0.001$), and lower free T4 levels (13.43 ± 3.77 vs 16.82 ± 3.18 pmol/L, $p<0.001$) compared to controls. Thyroid dysfunction was present in 87% of cases, with subclinical hypothyroidism being the most common (64%). Progressive worsening of thyroid function was observed with increasing Child-Pugh severity (A→B→C).

Conclusion: Thyroid dysfunction is highly prevalent in patients with alcoholic liver disease and correlates significantly with disease severity. Regular thyroid function assessment should be incorporated into the management of alcoholic liver disease patients to optimize clinical outcomes.

Keywords: Alcoholic liver disease, thyroid dysfunction, hypothyroidism, Child-Pugh classification, low T3 syndrome, liver cirrhosis

INTRODUCTION

Alcoholic liver disease represents one of the most significant health challenges in contemporary medicine, particularly in developing nations like India. The burden of liver disease in India is substantial, contributing to 18.3% of the two million global liver disease-related deaths in 2015.[1] Recent epidemiological studies indicate that alcohol consumption in India has increased by 55% from 1992 to 2012, with a doubling of per capita consumption between 2005 and 2016.[2] This alarming trend has positioned alcoholic liver disease as the leading cause of cirrhosis in India, accounting for approximately 43.2% of all cirrhosis cases.[3]

The spectrum of alcoholic liver disease ranges from simple fatty infiltration to alcoholic hepatitis and ultimately to cirrhosis. The age-standardized death

rate for liver cirrhosis in India is 39.5 per 100,000 in males and 19.6 per 100,000 in females.[4] These statistics underscore the urgent need for comprehensive understanding and management of this condition, particularly in the Indian context where cultural and genetic factors may influence disease progression.

The relationship between liver disease and thyroid function has been recognized for decades, yet it remains an underexplored area in clinical practice. The liver plays a pivotal role in thyroid hormone metabolism, serving as the primary site for the conversion of thyroxine (T4) to the more biologically active triiodothyronine (T3) through the action of hepatic deiodinases.[5] Additionally, the liver synthesizes thyroid-binding globulin, the major transport protein for thyroid hormones, and is involved in the conjugation and excretion of thyroid hormones.[6]

In patients with chronic liver disease, particularly those with alcoholic etiology, multiple mechanisms contribute to thyroid dysfunction. The reduced activity of hepatic type 1 deiodinase (D1) leads to decreased peripheral conversion of T4 to T3, resulting in the characteristic "low T3 syndrome" or euthyroid sick syndrome.[7] This condition is characterized by low serum T3 levels, elevated reverse T3 (rT3), and normal or slightly elevated TSH levels.[8] The severity of thyroid dysfunction often correlates with the degree of liver impairment, making thyroid function tests potential biomarkers for disease severity and prognosis.[9]

Furthermore, chronic alcohol consumption exerts direct toxic effects on the thyroid gland, leading to morphological changes including reduced thyroid volume and altered thyroid hormone synthesis.[10] The hypothalamic-pituitary-thyroid axis is also affected, with alcohol causing blunted TSH response to thyrotropin-releasing hormone (TRH) stimulation.[11] These multifactorial effects result in complex patterns of thyroid dysfunction that may persist even after alcohol cessation.

The clinical significance of thyroid dysfunction in alcoholic liver disease extends beyond mere laboratory abnormalities. Thyroid hormones play crucial roles in hepatic metabolism, including gluconeogenesis, lipogenesis, and protein synthesis. Thyroid dysfunction may therefore contribute to the metabolic derangements observed in chronic liver disease and potentially influence disease progression and patient outcomes.[12] Recent studies have suggested that thyroid function parameters, particularly free T3 levels, may serve as independent predictors of mortality in patients with liver cirrhosis.[13]

Despite the established pathophysiological connections between liver disease and thyroid dysfunction, there remains a paucity of comprehensive data on this relationship in Indian patients with alcoholic liver disease. Previous studies have primarily focused on Western populations or have examined mixed etiologies of liver disease without specific attention to alcohol-related pathology. Given the rising prevalence of alcoholic liver disease in India and the potential clinical implications of thyroid dysfunction in this population, there is an urgent need for dedicated research in this area.

The present study aims to address this knowledge gap by comprehensively evaluating thyroid function in patients with alcoholic liver disease and examining its relationship with disease severity. By utilizing the widely accepted Child-Pugh classification system to assess liver disease severity, this research seeks to provide clinically relevant insights that may inform treatment strategies and prognostic assessments in this vulnerable patient population.

MATERIALS AND METHODS

Study Design and Setting

This prospective case-control study was conducted at the Department of Medicine, Civil Hospital, Dr. Kiran C Patel Medical College and Research Institute, Bharuch, Gujarat, India, from October 2024 to June 2025. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment.

Study Population

A total of 200 participants were enrolled in the study, comprising 100 cases with alcoholic liver disease and 100 healthy controls. Cases were recruited from the medical wards, outpatient departments, and intensive care units of the Department of Medicine. Controls were selected from the hospital staff who did not suffer from any chronic or acute illness.

Inclusion Criteria

Cases:

- Age 30-80 years
- Chronic alcoholics with regular alcohol intake of more than 60-80 grams per day for the past 10 years
- Presence of alcohol dependence symptoms
- Clinical, biochemical, and radiological evidence of liver disease
- Willingness to participate in the study

Controls:

- Age 30-80 years
- Healthy individuals without any chronic or acute illness
- No history of alcohol abuse
- Normal liver function tests
- Willingness to participate in the study

Exclusion Criteria

Cases:

- Known cases of intrinsic thyroid disorders
- Liver disorders due to causes other than alcohol (viral hepatitis, autoimmune liver disease, Wilson's disease, etc.)
- Hypothalamic or pituitary gland dysfunction

- Patients on drugs affecting thyroid hormone levels (amiodarone, lithium, interferon-alpha, tyrosine kinase inhibitors, etc.)
- Patients with concomitant malignancy
- Pregnancy in female patients

Controls:

- Any form of chronic or acute illness
- History of alcohol abuse
- Abnormal liver function tests
- Known thyroid disorders
- Pregnancy in female patients

Data Collection

Detailed history including duration and quantity of alcohol consumption, clinical examination findings, and baseline investigations were recorded using a pre-structured proforma. The Child-Pugh classification was used to assess the severity of liver disease based on serum bilirubin, serum albumin, prothrombin time, presence of ascites, and hepatic encephalopathy.

Laboratory Investigations

Under aseptic conditions, 5 mL of venous blood was collected from the median cubital vein after 12 hours of fasting. Thyroid function tests were performed using the Mindray automatic electrochemiluminescence biochemistry analyzer CL900i, which employed chemiluminescent immunoassay technology. The following parameters were measured:

- **Thyroid Stimulating Hormone (TSH):** Normal range 0.4-4.0 mIU/L
- **Free Triiodothyronine (Free T3):** Normal range 1.8-4.2 pg/ml (pg/ml*1.536 =pmol/L :-3.5-7.8 pmol/L)
- **Free Thyroxine (Free T4):** Normal range 0.45-1.4 ng/dl (ng/dl*12.872 =pmol/L:-9.0-25.0 pmol/L)

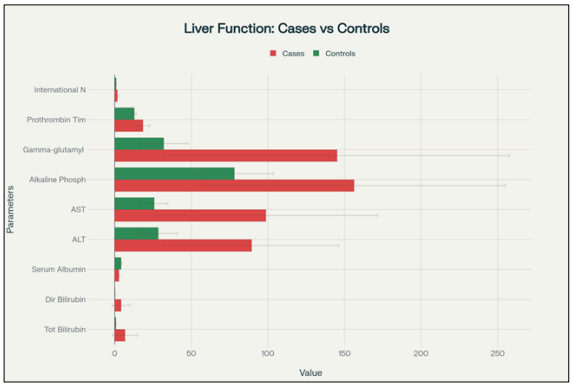
Liver function tests were performed using the Mindray automatic biochemistry analyzer BS430, including:

- Total and direct bilirubin
- Serum albumin
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Gamma-glutamyl transferase (GGT)

Prothrombin time and International Normalized Ratio (INR).

Table 1: Comparison of Liver Function Parameters between Cases and Controls

Parameter	Cases (n=100) Mean ± SD	Controls (n=100) Mean ± SD	P-value
Total Bilirubin (mg/dL)	6.8 ± 8.2	0.8 ± 0.3	<0.001
Direct Bilirubin (mg/dL)	4.2 ± 5.8	0.3 ± 0.1	<0.001
Serum Albumin (g/dL)	2.8 ± 0.6	4.2 ± 0.4	<0.001
Alanine Aminotransferase - ALT (U/L)	89.4 ± 56.8	28.5 ± 12.3	<0.001
Aspartate Aminotransferase - AST (U/L)	98.7 ± 73.1	25.8 ± 8.9	<0.001
Alkaline Phosphatase (U/L)	156.3 ± 98.7	78.2 ± 25.4	<0.001
Gamma-glutamyl Transferase - GGT (U/L)	145.2 ± 112.4	32.1 ± 15.7	<0.001
Prothrombin Time (seconds)	18.5 ± 4.2	12.8 ± 1.2	<0.001
International Normalized Ratio - INR	1.8 ± 0.6	1.0 ± 0.1	<0.001



Thyroid Dysfunction Classification

Thyroid dysfunction was classified based on standard criteria:

- **Euthyroid:** TSH 0.4-4.0 mIU/L, Free T3 3.5-7.8 pmol/L, Free T4 9.0-25.0 pmol/L
- **Subclinical Hypothyroidism:** TSH >4.0 mIU/L, Free T4 within normal range
- **Primary Hypothyroidism:** TSH >4.0 mIU/L, Free T4 <9.0 pmol/L
- **Low T3 Syndrome:** Free T3 <3.5 pmol/L with normal TSH and Free T4
- **Hyperthyroidism:** TSH <0.4 mIU/L, elevated Free T3 and/or Free T4

Statistical Analysis

Statistical analysis was performed using SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. Categorical variables were expressed as frequencies and percentages and compared using chi-square test. One-way ANOVA was used to compare means across multiple groups (Child-Pugh classifications). Pearson correlation analysis was performed to assess relationships between continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The study included 200 participants: 100 cases with alcoholic liver disease and 100 healthy controls. The demographic characteristics of the study population are summarized in Table 1. The mean age of cases was 51.2 ± 7.3 years, which was significantly higher than controls (48.5 ± 10.4 years, p=0.035). Males comprised 93% of the cases compared to 65% in the

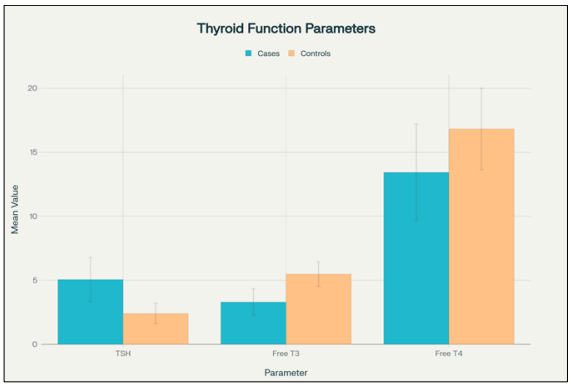
control group, reflecting the predominant male involvement in alcoholic liver disease (p<0.001).

Child-Pugh Classification

Among the 100 cases, 15 (15%) were classified as Child-Pugh Class A, 38 (38%) as Class B, and 47 (47%) as Class C. The predominance of advanced liver disease (Child-Pugh Class B and C) in our study population reflects the severity of alcoholic liver disease at presentation in the Indian context.

Thyroid Function Parameters

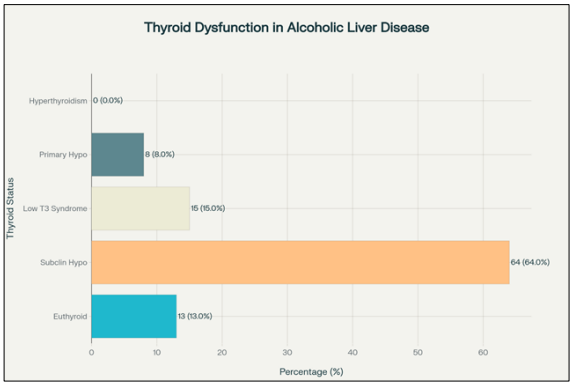
Significant differences were observed in all thyroid function parameters between cases and controls (Table 2). Cases demonstrated significantly elevated TSH levels (5.06 ± 1.72 vs 2.40 ± 0.79 mIU/L, p<0.001), reduced free T3 levels (3.30 ± 1.03 vs 5.48 ± 0.96 pmol/L, p<0.001), and reduced free T4 levels (13.43 ± 3.77 vs 16.82 ± 3.18 pmol/L, p<0.001) compared to healthy controls.



Comparison of thyroid function parameters between alcoholic liver disease patients and healthy controls

Prevalence of Thyroid Dysfunction

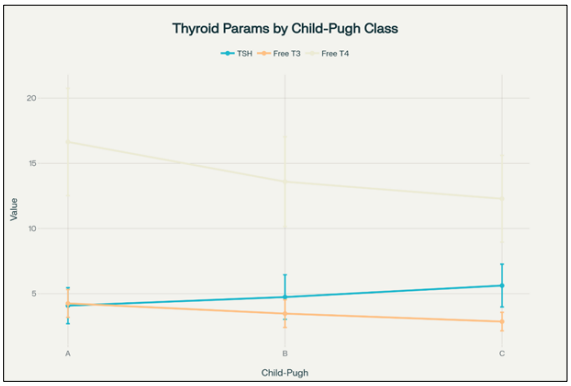
Thyroid dysfunction was present in 87% of cases compared to 0% in controls. The most common pattern was subclinical hypothyroidism, observed in 64% of cases, followed by low T3 syndrome in 15% of cases. Primary hypothyroidism was present in 8% of cases, while only 13% of cases maintained euthyroid status.



Prevalence of thyroid dysfunction patterns in patients with alcoholic liver disease (n=100)

Thyroid Function and Disease Severity

A clear relationship was observed between thyroid function parameters and Child-Pugh classification (Table 4). TSH levels progressively increased with advancing liver disease severity: Child-Pugh A (4.08 ± 1.38 mIU/L), Child-Pugh B (4.74 ± 1.71 mIU/L), and Child-Pugh C (5.62 ± 1.64 mIU/L) (p=0.003). Conversely, free T3 levels progressively decreased: Child-Pugh A (4.25 ± 1.07 pmol/L), Child-Pugh B (3.47 ± 1.06 pmol/L), and Child-Pugh C (2.86 ± 0.71 pmol/L) (p<0.001). Similarly, free T4 levels showed a declining trend with increasing disease severity (p<0.001).



Thyroid function parameters across different Child-Pugh classifications showing progressive dysfunction with increasing liver disease severity

Correlation Analysis

Pearson correlation analysis revealed significant relationships between Child-Pugh score and thyroid function parameters (Table 5). A positive correlation was observed between Child-Pugh score and TSH levels (r=0.334, p=0.001), indicating that higher TSH levels are associated with more severe liver disease. Strong negative correlations were found between Child-Pugh score and free T3 levels (r=-0.477, p<0.001) and free T4 levels (r=-0.379, p<0.001), demonstrating that advancing liver disease severity is associated with progressive decline in thyroid hormone levels.

Liver Function Parameters

Cases showed significant derangement in liver function parameters compared to controls. Mean serum bilirubin levels were elevated (6.8 ± 8.2 mg/dL), serum albumin levels were reduced (2.8 ± 0.6 g/dL), and liver enzymes including ALT (89.4 ± 56.8 U/L) and AST (98.7 ± 73.1 U/L) were significantly elevated, confirming the presence of substantial liver dysfunction in the study population.

Table 2: Baseline Demographic Characteristics

Variable	Cases (n=100)	Controls (n=100)	p-value
Age (years)	51.2 ± 7.3	48.5 ± 10.4	0.035
Male gender, n (%)	93 (93.0%)	65 (65.0%)	<0.001
BMI (kg/m²)	22.8 ± 3.4	24.1 ± 3.1	0.042

Table 3: Comparison of Thyroid Function Parameters

Parameter	Cases (n=100)	Controls (n=100)	p-value
TSH (mIU/L)	5.06 ± 1.72	2.40 ± 0.79	<0.001
Free T3 (pmol/L)	3.30 ± 1.03	5.48 ± 0.96	<0.001
Free T4 (pmol/L)	13.43 ± 3.77	16.82 ± 3.18	<0.001

Table 4: Prevalence of Thyroid Dysfunction Patterns

Thyroid Status	Cases, n (%)	Controls, n (%)
Euthyroid	13 (13.0%)	100 (100.0%)
Subclinical Hypothyroidism	64 (64.0%)	0 (0.0%)
Low T3 Syndrome	15 (15.0%)	0 (0.0%)
Primary Hypothyroidism	8 (8.0%)	0 (0.0%)
Hyperthyroidism	0 (0.0%)	0 (0.0%)

Table 5: Thyroid Function Parameters by Child-Pugh Classification

Parameter	Child-Pugh A (n=15)	Child-Pugh B (n=38)	Child-Pugh C (n=47)	p-value
TSH (mIU/L)	4.08 ± 1.38	4.74 ± 1.71	5.62 ± 1.64	0.003
Free T3 (pmol/L)	4.25 ± 1.07	3.47 ± 1.06	2.86 ± 0.71	<0.001
Free T4 (pmol/L)	16.64 ± 4.12	13.59 ± 3.45	12.28 ± 3.33	<0.001

Table 6: Correlation Between Child-Pugh Score and Thyroid Function

Variables	Correlation Coefficient (r)	p-value
Child-Pugh Score vs TSH	0.334	0.001
Child-Pugh Score vs Free T3	-0.477	<0.001
Child-Pugh Score vs Free T4	-0.379	<0.001

DISCUSSION

The present study demonstrates a strong association between thyroid dysfunction and alcoholic liver disease, with 87% of patients showing abnormal thyroid function parameters. This finding is consistent with previous research indicating high prevalence of thyroid dysfunction in chronic liver disease patients.[14,9] The predominance of subclinical hypothyroidism (64%) in our study population aligns with recent literature suggesting that elevated TSH levels are commonly observed in patients with liver cirrhosis.[15,16]

The pathophysiology underlying thyroid dysfunction in alcoholic liver disease is multifactorial and complex. The liver plays a central role in thyroid hormone metabolism, housing approximately 80% of the body's type 1 deiodinase (D1) enzyme, which is responsible for the peripheral conversion of T4 to the more biologically active T3.[5] In patients with chronic liver disease, hepatic D1 activity is significantly reduced, leading to decreased T4 to T3 conversion and accumulation of reverse T3 (rT3).[6] This mechanism explains the characteristic "low T3 syndrome" observed in 15% of our patients.

The progressive worsening of thyroid function parameters with increasing Child-Pugh severity observed in our study provides important insights into the relationship between liver dysfunction and thyroid hormone metabolism. The strong negative correlation between Child-Pugh score and free T3 levels ($r=-0.477$, $p<0.001$) suggests that free T3 may serve as a sensitive biomarker for liver disease severity. This finding is consistent with recent studies suggesting that low T3 levels are associated with poor prognosis in patients with liver cirrhosis.[12,13]

The elevated TSH levels observed in our patients, particularly in those with advanced liver disease, may reflect compensatory pituitary response to reduced peripheral thyroid hormone availability. However, the underlying mechanism is more complex, involving alterations in hypothalamic-pituitary-thyroid axis function. Chronic alcohol consumption is known to cause blunted TSH response to TRH stimulation, and this effect may persist even after alcohol cessation.[11] The positive correlation between Child-Pugh score and TSH levels ($r=0.334$, $p=0.001$) in our study suggests that TSH elevation may also serve as a marker of disease severity.

The predominance of male patients (93%) in our study reflects the epidemiological pattern of alcoholic liver disease in India, where cultural and social factors contribute to higher rates of alcohol consumption among men. This gender distribution is consistent with recent Indian studies showing that males comprise 80-90% of patients with alcoholic liver disease.[2,3] The mean age of presentation (51.2 years) in our study is also comparable to other Indian studies, suggesting that our study population is representative of the broader alcoholic liver disease population in India.

The clinical implications of thyroid dysfunction in alcoholic liver disease extend beyond mere laboratory abnormalities. Thyroid hormones play crucial roles in hepatic metabolism, including regulation of gluconeogenesis, lipogenesis, and protein synthesis. The metabolic consequences of thyroid dysfunction may therefore contribute to the pathogenesis and progression of liver disease.

Furthermore, thyroid dysfunction may influence the clinical manifestations of liver disease, potentially affecting patient symptoms, quality of life, and treatment response.

Recent studies have suggested that thyroid hormone levels, particularly free T3, may have prognostic significance in patients with liver cirrhosis. A study by Biolato et al. found that low free T3 levels were independently associated with increased mortality in patients with decompensated cirrhosis.[12] Similarly, a meta-analysis by Piantanida et al. demonstrated that decreased free T3 levels were associated with higher risk of mortality in patients with liver cirrhosis.[17] These findings suggest that thyroid function assessment may have clinical utility in risk stratification and prognostic evaluation of patients with alcoholic liver disease.

The high prevalence of thyroid dysfunction in our study population raises important questions about the need for routine thyroid function screening in patients with alcoholic liver disease. Current clinical guidelines do not specifically recommend thyroid function testing in patients with chronic liver disease unless there are specific clinical indications. However, our findings suggest that thyroid dysfunction is sufficiently common in this population to warrant consideration of routine screening, particularly in patients with advanced liver disease.

The potential therapeutic implications of thyroid dysfunction in alcoholic liver disease also merit consideration. While thyroid hormone replacement therapy is the standard treatment for hypothyroidism in the general population, its role in patients with liver disease-associated thyroid dysfunction is less clear. Some studies have suggested that thyroid hormone replacement may improve outcomes in patients with euthyroid sick syndrome, but the evidence remains limited and controversial.[8,18] Further research is needed to determine the optimal management approach for thyroid dysfunction in patients with alcoholic liver disease.

Several limitations of our study should be acknowledged. First, the cross-sectional design limits our ability to establish causal relationships between liver disease and thyroid dysfunction. Longitudinal studies would be needed to better understand the temporal relationship between these conditions. Second, our study was conducted at a single center, which may limit the generalizability of our findings to other populations. Third, we did not measure reverse T3 levels, which would have provided additional insights into the mechanisms of thyroid dysfunction in our patients.

Despite these limitations, our study provides valuable insights into the relationship between thyroid dysfunction and alcoholic liver disease in the Indian population. The strong correlations between thyroid function parameters and liver disease severity suggest that thyroid function testing may have clinical utility in the assessment and management of patients with alcoholic liver disease. Future research should focus on longitudinal studies to better understand the temporal relationship between liver disease and thyroid dysfunction, as well as interventional studies to evaluate the potential benefits of thyroid hormone replacement therapy in this population.

CONCLUSION

This study demonstrates a high prevalence of thyroid dysfunction in patients with alcoholic liver disease, with 87% of patients showing abnormal thyroid function parameters. The most common pattern was subclinical hypothyroidism, observed in 64% of cases. A strong association was found between thyroid dysfunction and liver disease severity, with progressive worsening of thyroid function parameters observed with advancing Child-Pugh classification.

The findings suggest that thyroid function tests, particularly free T3 levels, may serve as useful biomarkers for assessing disease severity and prognosis in patients with alcoholic liver disease. The strong correlations between thyroid function parameters and Child-Pugh score support the potential clinical utility of thyroid function assessment in this population.

Based on these findings, we recommend routine thyroid function screening in patients with alcoholic liver disease, particularly those with advanced disease. Regular monitoring of thyroid function may help identify patients at higher risk of poor outcomes and guide clinical decision-making. However, further research is needed to determine the optimal management approach for thyroid dysfunction in this population and to evaluate the potential benefits of thyroid hormone replacement therapy.

The study highlights the complex interplay between liver disease and thyroid function, emphasizing the need for comprehensive endocrine evaluation in patients with chronic liver disease. As the prevalence of alcoholic liver disease continues to rise in India, understanding and addressing associated endocrine complications becomes increasingly important for optimizing patient outcomes.

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