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Original Research Article

A Study on Evaluation of Thyroid Function Test in Patients with Chronic Liver Disease

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Abstract:

Introduction: Chronic liver disease (CLD) is marked by inflammation and tissue damage in the liver that lasts for a long time, causing fibrosis and cirrhosis. CLD can be caused by a number of things, such as viral hepatitis, non-alcoholic fatty liver disease, and autoimmune liver diseases. Because the liver breaks down and makes thyroid chemicals, it is very important to understand how the thyroid works in people with CLD.

Materials and Methods: This cross-sectional study at Darbhanga Medical College and Hospital examined 100 CLD patients, excluding those who had thyroid hormone medication or alcohol-related liver illness. Thyroid function assays (FT3, FT4, TSH) and clinical indicators such bilirubin, albumin, prothrombin time, and ascites severity were assessed. SPSS 20 was used for statistical analysis, with a p-value of < 0.05.

Results: The study found a substantial inverse relationship between CLD severity and serum FT3 levels ($p < 0.001$). As illness severity rose, FT4 levels fell, but less so ($p < 0.001$). TSH levels did not show a significant correlation with CLD severity ($p = 0.351$). Higher bilirubin levels and prolonged prothrombin time were significantly associated with lower FT3 and FT4 levels, but not with TSH. Ascites and hepatic encephalopathy severity also inversely correlated with FT3 and FT4 levels.

Conclusion: The study highlights the prevalence of thyroid hormone abnormalities in CLD patients and their correlation with severity of disease, advocating for regular thyroid function monitoring in CLD management to improve patient outcomes.

Keywords: Chronic Liver Disease, Thyroid function, Thyroid hormones, Liver-thyroid axis, Disease severity.

Introduction

CLD affects clotting factor and protein synthesis, metabolic by-product detoxification, and bile excretion over six months or more. Chronic liver disease's repetitive inflammation, tissue destruction, and regeneration cause fibrosis and cirrhosis. The final stage of chronic liver disease (CLD), cirrhosis, disrupts the liver's architecture, causes nodules, reorganizes blood vessels, forms new ones, and deposits extracellular matrix [1].

Cirrhosis and fibrosis recruit stellate cells and fibroblasts, while hepatic stem cells regenerate parenchyma. Due to its ubiquity, CLD etiologies, symptoms, and treatment must be understood. Extended alcohol use, some drugs and chemicals (including acetaminophen and methotrexate), and persistent viral hepatitis can induce CLD [2]. In CLD, hepatic fibrosis, tissue architectural distortion, and regenerative nodule development progress. Although acute fibrosis can be repaired, it usually becomes permanent and can lead to cirrhosis if left untreated. Environmental, host, and underlying etiologies affect fibrosis development. The slowest rate of fibrosis progression is primary biliary cirrhosis, while HIV-HCV coinfection is the fastest. Age and genetics both affect fibrosis [3]. Activated hepatic stellate cells (HSCs) deposit extracellular matrix to cause hepatic fibrosis after long-term liver injury.

These typically quiescent cells collect ECM and become fibrogenic myofibroblasts after long-term liver injury. Histopathology says stellate cells help produce collagen in diseased conditions. Chronic liver injury activates these cells to become myofibroblasts and produce ECM. Different reasons cause different liver fibrosis patterns. Alcoholic liver disease and adult non-alcoholic fatty liver disease cause centrilobular perivenular and sinusoidal fibrosis, while persistent viral infections cause portal enlargement and periportal fibrosis. Jaundice, skin abnormalities, endocrine

disruptions, hemorrhagic tendencies, general health decline, portal hypertension, and hepatic encephalopathy are indications of chronic hepatocellular failure [4]. Liver dysfunction is indicated by jaundice, prolonged prothrombin time, and decreased albumin. After minor symptoms in compensated chronic liver disease (CLD), decompensated cirrhosis causes ascites, encephalopathy, gastrointestinal bleeding, and pre-coma. Nodules and diffuse liver fibrosis indicate cirrhosis. Liver activities include metabolism of carbohydrates, proteins, and lipids, generation of anticoagulant and clotting factors, bilirubin metabolism, and vitamin and mineral storage.

Objective

1. To investigate thyroid hormone abnormalities in individuals with CLD.
2. To determine if there is a correlation between the severity of chronic liver disease and these anomalies.

Review of Literature

Most CLD cases in India are caused by non-alcoholic fatty liver disease, viral hepatitis, and excessive alcohol drinking. CLD advances silently until ascites, spontaneous bacterial peritonitis, liver disease, or portal hypertension-induced variceal hemorrhage occur [5]. The thyroid gland's role in tissue metabolism and development affects several organ systems. The liver produces thyroid hormone-binding proteins and contributes to peripheral thyroid hormone metabolism and excretion. This association makes thyroid dysfunction studies in CLD patients crucial.

Child-Pugh grading was developed to estimate surgical risks in portosystemic shunt surgery for variceal hemorrhage patients. Higher scores imply illness severity. The tests include total serum albumin, bilirubin, prothrombin time, ascites, and hepatic encephalopathy. We rank each measure from 1 to 3 [6]. The Child-Pugh score divides patients into Class B (7-9 points), Class A (6 points), and Class C (10–15 points). Due to subjective criteria, the Child-Pugh score is extensively used yet limited.

The Model for End-Stage Liver Disease (MELD) score can predict TIPS survival using objective parameters such total bilirubin, creatinine, and INR. Predicting cirrhotic patient outcomes using Child-Pugh or MELD scores is limited by subjective characteristics and laboratory INR variations.

The thyroid and liver have a complex relationship. Thyroid hormones regulate liver cell metabolism, which is essential for their development and function. How the liver breaks down thyroid hormones affects the endocrine system [7]. Thyroid dysfunction and liver disease alter thyroid hormone metabolism. Normal T4, low T3, and elevated rT3 are symptoms of sick euthyroid syndrome, which arises in prolonged illness due to thyroid hormone metabolism anomalies. Deiodinase activity and thyroid-binding protein levels affect these changes.

In Primary Biliary Cirrhosis (PBC) and chronic autoimmune hepatitis, autoimmune thyroid disease is more common. Elevated thyroid-binding globulin can mask PBC patients' autoimmune hypothyroidism. Hepatitis C patients on interferon may develop thyroid dysfunction. Check thyroid function when receiving interferon [8].

Even though most CLD patients have normal thyroid function, thyroid hormone concentration abnormalities are common. These treatment- and disease-specific modifications emphasize the significance of comprehensive thyroid function testing in CLD care [9]. To better understand thyroid function in CLD patients, this study excludes alcohol-related cases to avoid confounding effects on the hypothalamo-pituitary-thyroid axis.

Materials and Method

Study Area: Located in Darbhanga (Bihar), this cross-sectional study was carried out at the Department of Physiology at Darbhanga Medical College and Hospital in Laheriasarai. Participants with a history of chronic liver illness are sought after through the General Medicine patients' department and ward.

Sample Size: 100 Patients.

Study Period: one and half year.

Inclusion Criteria: All patients who are 14 years old and older.

Exclusion Criteria:

- Individuals with a history of thyroid dysfunction and previous administration of thyroid hormone.
- People with alcoholic liver illness.

Study Design: Cross Sectional Study.

Statistical Methods:

We compare the number of patients and percentage of patients between groups. Spearman's Rank Correlation Coefficient captures continuous variable association. SPSS 20 was utilized for analysis. A p -value less than 0.05 is measured important at an alpha level of 5%.

Result and Analysis

Table 1: Age group

		Child	PUGH Class		Total	Overall	
		Class A	Class B	Class C		p Value	Significance
AGE IN YEAR	16-30	6(21.43)	8(16.33)	3(13.04)	17(17)	0.648	Not significant
	31-45	12(42.86)	18(36.73)	7(30.43)	37(37)		
	46-60	6(21.43)	15(30.61)	11(47.83)	32(32)		
	>60	4(14.29)	8(16.33)	2(8.7)	14(14)		
Total		28(100)	49(100)	23(100)	100(100)		

Out of 28 kid class A patients, 6 (21.43%) were 16-30 years old, 12 (42.86%) were 31-45 years old, 6 (21.43%) were 46-60 years old, and 4 (14.29%) were over 60.In kid class B, 8 (16.33%) of 49 patients were 16-30 years old, 18 (36.73%) were 31-45 years old, 15 (30.61%) were 46-60 years old, and 8 (16.33%) were above 60.Three (13.04%) of 23 kid class C patients were 16-30 years old, seven (30.43%) were 31-45 years old, 11 (47.83%) were 46-60 years old, and 2 (8.7) were beyond 60.

Table 2: Gender

		CHILD PUGH CLASS			Total	Overall	
		Class A	Class B	Class C		p -Value	Significance
SEX	F	14(50)	18(36.73)	5(21.74)	37(37)	0.127	Not significant
	M	14(50)	31(63.27)	18(78.26)	63(63)		
Total		28(100)	49(100)	23(100)	100(100)		

Analyses included 100 patients. Of these 100 cases, 28 were kid class A (28%).14 (50%) of these 28 individuals were male and 14 (50%) female. There were 49 (49%) cases in child Pugh B. Thirteen people were male (63.27%) and 18 were female (36.73%).The 23 class A youngsters had 18 male (78.26%) and 5 female (21.74%) patients.CLD-1 included 28 patients, 14 male and 14 female (50/50).Out of 72 CLD stage-2 patients, 49 (68.06%) were male and 23 (31.94%) were female.

Table 3: Child PUGH class

CHILD PUGH	CLASS	FT3 pg/ml	FT4 ng/dl	TSH MIU/L
Class A	Mean	3.06	1.47	2.54
	Std. Deviation	0.78	0.31	1.06
Class B	Mean	1.98	1.42	2.72
	Std. Deviation	0.86	0.27	2.14
Class C	Mean	1.37	1.08	3.41
	Std. Deviation	0.82	0.29	1.72
Overall	p Value	<0.001	0.298	0.351
	Significance	Significant	Not Significant	Not Significant
A Vs. B	p- Value	<0.001	0.556	0.658
	Significance	Significant	Not Significant	Not Significant
A Vs. C	p- Value	<0.001	<0.001	0.036
	Significance	Significant	Significant	Significant
B Vs. C	p- Value	0.006	<0.001	0.042
	Significance	Significant	Significant	Significant

Child Pugh class A had a mean FT3 score of 3.06 ± 0.78, while class B had 1.98 ±0.86 and class C had 1.37 ± 0.82. A p- value of < 0.001 indicates statistical significance. Regarding CLD, CLD-1 patients had a mean free FT3 of 3.06 ± 0.78, while CLD-2 patients had 1.79 ±0.89, with a significant p- value of <0.001.The foregoing results show that serum FT3 levels decrease considerably with liver disease development and are inversely associated to disease severity.

Child Pugh class A has a mean FT4 value of 1.47±0.31, while child class B has a value of The average free T4 value in kid class C is 1.08 ± 0.29, while the mean is 1.42 ±0.21. The overall p-value is 0.29, with p-values of 0.556, <0.001, and <0.001 for B vs C, A vs B, and A A large p- value exists between child B and C. In CLD class, CLD-1 has an average FT4 of 1.47±0.31 and CLD-2 has a mean of 1.31±0.32, with a statistically significant p -value of 0.020. From the aforementioned data, FT4 levels decline with disease severity, albeit less than FT3.

The mean TSH levels in kid A were 2.54 ±1.06, in child B they were 2.72 ± 2.14, and in child C they were 3.41 ±1.72. Statistically, p=0.351 is insignificant. In CLD stage, CLD-1 had mean TSH

2.54 ±1.06 and CLD-2 had mean TSH 2.94±2.03, with p -value of 0.920, indicating no statistical significance. Thus, liver disease severity does not affect TSH.

Table 4: Bilirubin

	BILIRUBIN (mg/dl)	FT3 pg/ml	FT4 ng/dl	TSH MIU/L
<2	Mean	2.51	1.46	2.77
	Std. Deviation	0.94	0.27	1.74
2-3	Mean	1.85	1.36	2.73
	Std. Deviation	0.85	0.29	2.16
>3	Mean	1.49	1.02	3.14
	Std. Deviation	1.12	0.30	1.48
	p Value	<0.001	<0.001	0.161
	Significance	Significant	Significant	Not Significant

Out of 100 patients, 54 had bilirubin levels <2mg/dl, 28 had 2-3mg/dl, and 18 had >3mg/dl. The mean FT3 level was 2.51 ± 0.94 in patients with bilirubin levels below 2mg/dl. At bilirubin levels of 2-3 mg, the mean FT4 level was 1.85±0.85, while at levels >2 mg/dl, it was 1.49±1.2. A P- value of <0.001 indicates statistical significance. This shows that FT3 inversely correlates with bilirubin in chronic liver disease patients. The mean FT4 value was 1.46±0.27 for bilirubin <2mg/dl, 1.36±0.29 for 2-3mg/dl, and 1.02±0.30 for >2mg/dl. A P- value of <0.001 indicates statistical significance. FT4 levels fall as bilirubin levels rise in CLD patients, indicating a statistically significant negative association. The mean TSH levels were 2.77±1.74, 2.73±2.16, and 3.14±1.48 in individuals with bilirubin levels <2mg/dl, 2-3mg/dl, and >3mg/dl, respectively. Non-significant p -value is 0.161. Thus, blood bilirubin does not affect TSH levels in CLD patients.

Table 5: Albumin

Albumin	(gm/dl)	FT3 pg/ml	FT4 ng/dl	TSH MIU/L
>3.5	Mean	2.33	1.41	3.08
	Std. Deviation	1.01	0.41	2.70
2.8-3.5	Mean	2.31	1.44	2.43
	Std. Deviation	1.07	0.29	1.47
<2.8	Mean	1.87	1.23	3.23
	Std. Deviation	0.96	0.30	1.79
	p Value	0.073	0.008	0.051
	Significance	Not Significant	Significant	Not Significant

In 100 individuals, 13 have albumin >3.5gm/dl, 48 have 3.5-2.8, and 39 have less than 2.8. Albumin, FT3, FT4, and TSH are related.

In patients with albumin levels >3.5gm/dl, 3.5-2.8gm/dl, and <2.8gm/dl, mean FT3 levels are 2.33 ±1.01, 2.31 ±1.07, and 1.87. Statistically, p=0.073 is insignificant. Thus, mean FT3 and albumin levels decrease in CLD patients, but the decline is statistically insignificant. In patients with albumin levels >3.5gm/dl, 3.5-2.8gm/dl, and <2.8gm/dl, mean FT4 levels were 1.41 ±0.41, 1.44 ±0.29, and 1.23.Statistically significant p -value is 0.008.

TSH levels in patients with albumin >3.5gm/dl, 3.5-2.8gm/dl, and <2.8gm/dl were 3.08 ±2.70, 2.43 ±1.47, and 3.23±1.79. Statistically, p=0.051 is insignificant.

Table 6: PT prolongation

PT prolongation in sec		FT3 pg /ml	FT4 ng /dl	TSH MIU /L
<4	Mean	2.49	1.44	2.43
	Std. Deviation	0.98	0.29	1.43
4-6	Mean	1.74	1.28	4.23
	Std. Deviation	0.71	0.27	2.73
>6	Mean	1.22	1.11	3.02
	Std. Deviation	0.76	0.34	1.51
	p- Value	<0.001	0.001	0.020

Out of 100 patients, 66 had PT prolongation <4 sec, 16 have 4-6 sec, and 18 have >6 sec. Prothrombin time (PT) follows FT3, FT4, and TSH trends in this study. FT3 mean was 2.49 ±0.98, 1.74 ±0.71, and

1.22 ± 0.76 for individuals with PT prolongation in second <4,4-6, and >6. The p-value is less than 0.001, indicating statistical significance. In CLD patients, prothrombin time demonstrations a substantial inverse connection with FT3. Patients with PT prolongation in second <4,4-6, and >6 had mean FT4 values of 1.44±0.29, 1.28±0.27, and 1.11±0.34.

A statistically significant p -value is 0.001. Prothrombin time also inversely affects FT4 in CLD patients.PT prolongation patients had mean TSH levels of 2.43±1.43, 4.23±2.73, and 3.02±1.51 in the second <4,4-6, and >6 groups. Statistically significant p- value is 0.020.

Table 7: Ascites

Ascites		FT3 pg /ml	FT4 ng /dl	TSH MIU /L
None	Mean	2.64	1.46	2.62
	Std. Deviation	1.00	0.26	1.40
Mild	Mean	2.24	1.38	2.71
	Std. Deviation	0.92	0.37	1.79
Moderate to severe	Mean	1.66	1.25	3.06
	Std. Deviation	0.76	0.33	2.14
	p- Value	<0.001	0.007	0.758
	Significance	Significant	Significant	Not Significant

Ascites is scored either mild (2 point), no (1 point), or moderate to severe (3 point). 40 patients have grade 1, 16 grade 2, and 44 grade 3 ascites.

For FT3 level, the mean values were 2.64±1, 2.24±0.92, and 1.66±0.88 at ascites points of one, two, and three.

A p -value of < 0.001 indicates significant statistical significance. With increasing ascites, FT3 drops dramatically. The mean FT4 level was 1.46±0.26, 1.38±0.37, and 1.25±0.33 at ascites points of one, two, and three. P -value < 0.007 indicates statistical significance. It means FT4 inversely affects ascites severity. TSH levels had mean values of 2.62±1.40, 2.71±1.79, and 3.06±2.14 at ascites points of one, two, and three. The p-value is < 0.758, indicating no statistical significance. Thus, TSH does not affect ascites severity.

Table 8: Hepatic encephalopathy

Hepatic encephalopathy		FT3 pg /ml	FT4 ng /dl	TSH MIU /L
None	Mean	2.44	1.43	2.62
	Std. Deviation	0.96	0.29	1.62
Suppressed by medication	Mean	1.49	1.22	3.80
	Std. Deviation	0.76	0.31	2.52
Not Suppressed by medication	Mean	0.88	0.98	2.84
	Std. Deviation	0.41	0.27	1.57
	p- Value	<0.001	0.001	0.150
	Significance	Significant	Significant	Not Significant

Hepatic encephalopathy points are one when no encephalopathy, two when treatment suppresses it, and three when not. Among 100 patients, 75 have no HE, 16 have point 1 and 9 have point 2. Hepatic encephalopathy in CLD patients is correlated with FT3, FT4, and TSH. Patients with hepatic encephalopathy points one, two, and three had mean FT3 values of 2.44 ±0.96, 1.49±0.76, and 0.88±0.41. The p-value is <0. 001. This is statistically significant. Hepatic encephalopathy inversely affects FT3 level, which is statistically significant. Patients with hepatic encephalopathy points one, two, and three had mean FT4 values of 1.43±0.29, 1.22±0.31, and 0.98±0.27, respectively. The p-value is 0.001.This is statistically significant. Hepatic encephalopathy shows a statistically significant inverse connection with FT3 level. Patients with hepatic encephalopathy points one, two, and three had mean TSH values of 2.62±1.62, 3.80±2.52, and 2.84±1.57, respectively. Value of p is 0.150. This is not statistically significant. Hepatic encephalopathy and TSH levels are not statistically related.

Table 9:

Correlations					
			FT3 pg/ml	**FT4 ng/dl**	**TSH MIU/L**
Spearman's rho	.Globulin	Correlation Coefficient	-0.216	-0.068	0.262
		Sig. (2-tailed)	0.031	0.499	0.008
	AST	Correlation Coefficient	-0.435	-0.405	0.064
		Sig. (2-tailed)	0.000	0.000	0.524
	ALT	Correlation Coefficient	-0.363	-0.386	0.065
		Sig. (2-tailed)	0.000	0.000	0.522
	Bilirubin	- — Correlation Coefficient	-0.397	-0.431	0.030
		Sig. (2-tailed)	0.000	0.000	0.765
	Albumin	Correlation Coefficient	0.272	0.231	-0.171
		Sig. (2-tailed)	0.006	0.021	0.089
	p time prolongation in second	Correlation Coefficient	-0.467	-0.308	0.234
		Sig. (2-tailed)	0.000	0.002	0.019

Discussion

Thyroid hormones impact liver and bilirubin metabolism. Thyroid problems often coincide with liver damage or chemical test irregularities and autoimmune liver diseases including primary biliary cirrhosis and hypothyroidism. Abnormal thyroid testing can accompany liver disease. This study found an inverse relationship between FT3 and liver disease severity. CLD-1 patients exhibited a mean free T3 of 3.06 ±SD ±0.78, while CLD-2 patients had 1.79, SD ±0.89. The difference among groups was significant (p-value < 0.001).

Study results show normal FT4 levels in CLD-1 patients (SD±0.31, mean-1.47) and significant drop in CLD-2 patients (SD±0.29, mean F4 level 1.31). Value of p: 0.20. There was no significant link among TSH levels and liver disease severity (SD ±1.6; mean TSH 2.54 in CLD-1 group, SD ±2.03, mean TSH 2.94 in CLD-2 group). Negligible P - value is 0.92.

In contrast to previous investigations, liver disease severity did not increase blood TSH levels. It may be because we severely rejected people with primary thyroid issues. We omitted the patient with alcohol-related chronic liver illness since alcohol inhibits almost all thyroid gland activities including the HPT axis. This study's strengths include measuring thyroid functioning at different steps of liver disease and excluding individuals with alcoholic liver disease, which impairs the hypothalamo-thyroid axis.

Serum FT3 is knowingly associated with prothrombin time, bilirubin, ascites, and hepatic encephalopathy grade in CLD patients (p < 0.001). PT, serum bilirubin, ascites severity, and HE grading are inversely linked. Despite thyroid function test abnormalities in chronic liver disease patients, euthyroidism is usually sustained, perhaps due to low-normal FT3. Furthermore, liver dysfunction severity appears to correspond with serum FT3 levels.

An adaptive hypothyroid condition with low free T3 levels may sustain liver function and protein storage by reducing hepatocyte basal metabolic rate. Liver function (e.g. coagulation profile) was improved in patients with hypothyroidism due to intrinsic thyroid illness of different causes during cirrhosis, according to a recent study. Control subjects did not experience this improvement. Hypothyroidism reduces cirrhosis loss. Thus, FT3 levels are low. Chronic liver disease lowers FT3, making it a good CLD severity indicator. This study suggests thyroid condition testing for all cirrhotic individuals since chronic liver disease worsens thyroid problems.

Limitations

- The study sample is limited.
- This is not etiological research. To identify thyroid dysfunction with chronic liver disease, etiology-based studies should be done.
- The study is cross-sectional and lacks patient follow-up.
- This study is not community-based. Hospital analysis of tertiary care center. So selection bi-os are possible.
- We did not assess total thyroid hormone or reverse T3 (rT3). rT3 costs plenty. If we measured those hormones, we could better analyze and explain the results.

Conclusion

Our study found an inverse connection between CLD severity regardless of origin and FT3 and FT4.This adverse relationship is stronger for FT3 than FT4.TSH and liver disease severity are not significantly related.

We recommend baseline thyroid function testing for all chronic liver disease patients. An etiology study may assist explain chronic liver disease

thyroid dysfunction. Our current work shows that FT3 can be utilized to assess chronic liver disease severity.

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