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Original Research Article

A Study of Thyroid Function Tests as a Prognostic Marker in Patients with Cirrhosis

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Abstract

Background: In this study, we wanted to evaluate thyroid function tests in patients with cirrhosis and assess the severity of liver dysfunction in relation to the interpretation of thyroid function and its use as a prognostic marker.

Materials and Methods: This was a cross-sectional study conducted among two hundred patients with cirrhosis admitted to the medical ward and attending the outpatient department at Government Vellore Medical College, Adukkamparai, Vellore, for one year (May 2021 to April 2022)

Results: Age distribution was mainly between 40-49 years of age among males and between 20-39 years of age among females. The most common aetiology for cirrhosis among male patients was alcoholism. Among the females, autoimmune hepatitis, Hepatitis B, Wilson disease and cryptogenic cirrhosis were some of the commoncauses. The most common risk factor for Non-Alcoholic Fatty Liver Disease was found to be obesity. As the Child-Pugh score increases from A through B and C, the derangements in bilirubin, INR, degree of ascites, hepatic encephalopathy and serum albumin levels also worsen. Thyroid dysfunction was more pronounced in patients belonging to Child-Pugh C, less pronounced in Child-Pugh B patients and was absent in patients belonging to Child-Pugh A.

Conclusion: As the severity of cirrhosis increases, from Child-Pugh A, B, and C, the thyroid dysfunction becomes more pronounced with the majority of patients having alow FT4 and high TSH. Hence, the usefulness of Thyroid Function Tests as a prognostic markerin patients with cirrhosis has been explored and positive results have beenobtained. So, it is essential to perform a thyroid function test in all patients with cirrhosis especially those with higher Child-Pugh Score.

Keywords: Child-Pugh Score, Thyroid Function, Cirrhosis

Background

Cirrhosis is a final common pathway for a variety of chronic liver diseases. It is a pathologic entity characterized by widespread hepatic fibrosis and the replacement of normal liver architecture by regenerative nodules. The rate of progression of chronic liver disease to cirrhosis will be variable, from a few weeks in patients with complete biliary obstruction to decades in patients with chronic Hepatitis C.

The liver cell type involved in liver fibrosis is the hepatic stellate cell. In normal liver, the hepatic stellate cells lie in the space of Disse [1]. On activation, the hepatic stellate cells transform into myofibroblasts [2]. Activation increases the expression of smooth muscle actin. For the development of liver fibrosis, the stellate cell generates various forms of the matrix, which leads to liver fibrosis [2]. Fibronectin is the earliest form of matrix produced by stellate cells.

Matrix deposition leads to further hepatic stellate cell activation and changes in the hepatic angioarchitecture [3]. In addition to the hepatic stellate cell, portal fibroblasts [4] may also result in the myofibroblast phenotype to form a collagen matrix.

Clinically, cirrhosis is either "compensated" or "decompensated". Decompensation means cirrhosis along with one or more of the following features: jaundice, ascites, hepatic encephalopathy (HE), or variceal bleeding.

Ascites is the usual first sign [5]. Compensated cirrhotic patients have none of these features. The thyroid gland produces two hormones, thyroxine (T4) and triiodothyronine (T3). Acting through thyroid hormone receptors α and β, they play a role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis. T4 is secreted in about twenty-fold excess over T3. Both are bound to plasma proteins, including thyroxine-binding globulin, transthyretin and albumin [6].

The liver plays a crucial role in the metabolism of thyroid hormones, as it is involved in the peripheral conversion of tetraiodothyronine (T4) to T3 by Type 1 deiodinase [7]. Type I deiodinase is the major enzyme in the liver. The liver is also involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid-binding globulin [8]. Thyroid diseases may affect liver function and liver diseases modulate thyroid hormone metabolism [9]. Patients with chronic liver disease can have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism can have abnormal liver function tests, which return to normal as the thyroid condition improves.

Till now, available studies showed a change in serum level of thyroid hormones as decreased total T3 and free T3 concentration which is associated with the severity of liver dysfunction. But no study has mentioned FT4 and thyr oid-stimulating hormone (TSH) levels with the severity of liver cirrhosis. Serum T4 levels remain normal or slightly low, serum TSH levels remain normal or slightly raised. These changes in thyroid function tests are well established that some people have advocated its use as a sensitive index of liver function in patients with cirrhosis [10].

T3 and T4 are reduced due to impaired hepatic deiodination and defective hepatocellular uptake. T4 level decreases, because of decreased production of thyroid-binding globulin and due to the action of peripheral binding inhibitors [11].

Although studies in varied populations differ in their findings with respectto the type and degree of thyroid dysfunction in cirrhosis, it is found to have low FT3 in the face of a normal TSH and clinical euthyroidism. Not only an indicator of thyroid dysfunction but FT3 level has also been correlated with the degree of liver dysfunction [12].

The study of thyroid function tests will throw a light on the functional aspects of liver disease and gives a better understanding of chronic liver disease and their relationship with thyroid function and helps in the management of chronic liver diseases. So, this study was done to highlight the association between thyroid function tests and the severity of liver function in cirrhosis of the liver by using Child-Turcotte Pugh scoring.

Aims and Objectives

To evaluate thyroid function tests in patients with cirrhosis and assess the severity of liver dysfunction in relation to the interpretation of thyroid function and its use as a prognostic marker.

Materials and Methods

This was a cross-sectional study conducted among two hundred patients with cirrhosis admitted to the medical ward and attending the outpatient department at Government Vellore Medical College, Adukkamparai, Vellore, over one year (May 2021 to April 2022)

Inclusion Criteria for the Cases

1. Patients aged more than 12 years
2. Males and females
3. Patients who were willing for the study with symptoms, signs, biochemicaland radiological features of liver cirrhosis irrespective of the cause.

Exclusion Criteria for the Cases

1. Age less than 12 years
2. Renal failure
3. Nephrotic syndrome
4. Pregnancy
5. History of thyroid disorders
6. Patients on drugs known to alter the thyroid function
7. Sepsis
8. Patients not willing for the study.

Study Procedure

After obtaining written and informed consent from the participants, the diagnosis of cirrhosis was confirmed based on radiological evidence of altered liver echoes and portal hypertension in Portal venous Doppler. The patient was assessed clinically for hepatic encephalopathy and graded based on the West-Haven grading system. The ascites was also graded as mild, moderate and severe based on ultrasound. Biochemical parameters like total bilirubin, serum albumin and coagulation profile were done. Tests like 24-hour urinary copper, serum ceruloplasmin, serum ferritin, ANA, Anti - SMA, Anti LKM 1, Anti LC 1, and Viral Hepatitis panel were done in the appropriate setting. Echocardiography was done in patients suspected of having cardiac cirrhosis. Based on the above, a Child-Turcotte Pugh score was obtained and patients were graded as A, B and C.

Fasting Thyroid Function Tests were done on each of these patients by electrochemiluminescence immunoassay and the results were compared. The alteration in TFT was compared with the severity of cirrhosis and its use as a prognostic marker was assessed.

Results

Among the 200 patients, 18.5% were females (n=37) and 81.5% were males (n=163). Among the 163 male patients, 0.7% belonged to the age group of less than 20 years (n=1), 31.1% belonged to the age group of 20-39 years (n=46), 40.5% belonged to the age group of 40-49 years (n=60), 27.7% belonged to the age group of 50-59 years (n=41) and 9.2 % belonged to the age group of more than 60 years (n=15). The majority of the male patients with cirrhosis belonged to the age group of 40-49 years.

Table 1: Aetiology of cirrhosis among males and females

Etiological Distribution	Sex

		Male		Female		Total	
		N	n %	n	n %	n	n %
Aetiology	AI Hepatitis	1	0.6%	6	16.2%	7	3.5%
	Alcoholic	57	35.0%	3	8.1%	60	30.0%
	Cardiac	1	0.6%	0	0.0%	1	0.5%
	Cryptogenic	39	23.9%	6	16.2%	45	22.5%
	Hemochromatosis	1	0.6%	4	10.8%	5	2.5%
	Hepatitis B	18	11.0%	6	16.2%	24	12.0%
	Hepatitis C	22	13.5%	2	5.4%	24	12.0%
	NAFLD	14	8.6%	2	5.4%	16	8.0%
	PBC	0	0.0%	2	5.4%	2	1.0%
	WILSON	10	6.1%	6	16.2%	16	8.0%
	Total	163	100.0%	37	100.0%	200	100.0%

Among the 37 female patients, 11.1% belonged to the age group of less than 20 years (n=4), 58.3% belonged to the age group of 20-39 years (n=21), 22.2 % belonged to the age group of 40-49 years (n=8), 8.3 % belonged to the age group of 50-59 years (n=3) and 2.7% belonged to more than 60 years (n=1). The majority of female patients belonged to the age group of 20-39 years.

Among the male patients, alcoholism (n=57) was the most common aetiology contributing to 35 % followed by cryptogenic (n=39) contributing to nearly 23.9%. Other causes included hepatitis C (n=22) contributing to nearly 13.5%, hepatitis B (n=18) contributing 11%, NAFLD (n=14) contributing to 8.6% and Wilsons disease (n=10) contributing to 6.1%. Minor causes included autoimmune hepatitis, cardiac cirrhosis and hemochromatosis each contributing to 0.6 % (n=1).

Among the female patients, 16.2% (n=6) were found to have autoimmune hepatitis. Hepatitis B, Wilson's disease and cryptogenic causes. 10.8% of patientswere found to have hemochromatosis (n=4), 8.1% of patients were found to have a background of alcoholism (n=3) and 5.4 % of patients were found to have hepatitis C, NAFLD and Primary Biliary Cirrhosis (n=2).

Among the 16 patients, 14 were males and 2 were females. The major risk factor was obesity (n=4) contributing to nearly 28.6%, followed by Type 2 Diabetes (n=3) contributing to 21.40%. Other risk factors included Type 2 Diabetes mellitus with dyslipidemia (n=2) which contributed to nearly 14.30%, and various combinations of Type 2 diabetes, dyslipidemia, obesity, and systemic hypertension contributed to 7.1% of the various risk factors.

Among the 200 patients, 52.5% had a bilirubin value of more than or equal to 4.5 mg/dl (n=105), 21.5% had bilirubin values between 2.5 -3.4 mg/dl (n=43), 16.5 % had bilirubin values between 3.5-4.4 mg/dl (n=33) and 9.5% had bilirubin values of less than 2.5 mg/dl (n=19).

75 % of patients had albumin levels above 3g/dl, 23% of patients had albumin levels between 2-2.9 g/dl and 2% had albumin levels of less than 2g/dl. All 4 of the patients whohad albumin less than 2 g/dl belonged to Child-Pugh class C.

All 6 patients in Child-Pugh A had an INR of less than 1.6. Among Child-Pugh B, 62 patients had INR less than 1.6, 11 patients had INR between 1.6 – 2.4 and none of them had an INR of more than 2.5. Among Child-Pugh Class C, only 30 patients had an INR of less than 1.6. 86 patients had INR between 1.6 - 2.4 and 5 patients had INR of more than 2.5. Overall, among the study population, 49 % had mild coagulation dysfunction with INR less than 1.6. 48.5% had INR between 1.6-2.4 and 2.5 % had INR more than 2.5.

56% patients had only mild ascites (n=112), 36.5% had moderate ascites (n=73) and 7.5% did not have ascites at all (n=15).

All 6 patients in Child-Pugh A did not have hepatic encephalopathy. Among 73 patients in Child-Pugh B, 52 patients did not have hepatic encephalopathy, 16 patients had stage 1 encephalopathy and 5 patients had stage 2 encephalopathy. Among Child-Pugh C, 14 patients did not have encephalopathy, 66 patients were in stage 1 encephalopathy, 27 patients were instage 2 encephalopathy, 11 patients were in stage 3 and 3 patients were in stage 4 encephalopathy.

60.5 % of the patients belonged to Child-Pugh C, 36.5 % of the patients belonged to Child-Pugh B and only 3% belonged to Child-Pugh A.

The derangement in TSH and Free T4 was statisticallysignificant with a p-value of < 0.01 among Child-Pugh class B. The derangement in TSH and Free T4 was statisticallysignificant with a p-value of < 0.01 among Child-Pugh Class C.

Among the Child-Pugh class A, all 6 hada normal thyroid status. Among the Child-Pugh class B, 71.2% (n=52) were euthyroid and 28.8% (n=21) were having thyroid dysfunction. Among Child-Pugh Class C, 74.4% (n=90) had thyroid dysfunction and only 25.6% (n=31) had normal thyroid function.

Among CTP-C, 62.8% had hypothyroidism (n=76), 11.6% had subclinical hypothyroidism (n=14) and 25.6% had normal thyroid function (n=31). Among CTP -B, 15.1 % had hypothyroidism (n=11), 13.7% had subclinical hypothyroidism (n= 10) and 71.2% had normal thyroid function (n=52). Among CTP -A, 100 % had normal thyroid function (n=6).

The decrease in Free T4 was comparatively more among the female patients (Mean = 0.7027) as compared to male patients. (Mean = 0.8204). The lowest valuesof FT4 were observed in the age group of less than 20 years (Mean = 0.646). FT4 levels were found to be the highest in the age group of 20-39 years.

Table 2:

	Bilirubin Values in CTP A, B, C	**CTP**							
		A		**B**		**C**		**Total**	
		n	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**
Total Bilirubin	<2.5	6	100.0%	12	16.40%	1	0.80%	19	9.50%
	2.6 to 3.4	0	0.00%	29	39.70%	14	11.60%	43	21.50%
	3.5 to 4.4	0	0.00%	9	12.30%	24	19.8%	33	16.5%
	More than or Equal to4.5	0	0.00%	23	31.50%	82	67.8%	105	52.5 %
	Total	6	100.0%	73	100.00%	121	100.0%	200	100.0%
Bilirubin values among CTP A, B, C									
	Albumin Levels in CTP A, B, C	**CTP**							
		A		**B**		**C**		**Total**	
		n	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**
Albumin	< 2	0	0.00%	0	0.00%	4	3.30%	4	2.00%
	2.1 to 2.9	0	0.00%	2	2.70%	44	36.4%	46	23.0%
	More than or equal to 3	6	100.0%	71	97.30%	73	60.3%	150	75.0%
	Total	6	100.0%	73	100.0%	121	100.0%	200	100.0%
Albumin levels in CTP A, B, C									

		CTP							
Sl. No.	**Coagulopathy**	**A**		**B**		**C**		**Total**	
		n	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**
1	< 1.6	6	100.00 %	62	84.90 %	30	24.80 %	98	49.00 %
2	1.6 to 2.4	0	0.00%	11	15.1%	86	71.1%	97	48.5%
3	More than or equal to 2.5	0	0.00%	0	0.00%	5	4.10%	5	2.50%
	Total	6	100.0%	73	100.0%	121	100.0%	200	100.0%
Coagulopathy among CTP -A, B, C									

Table 3: Various stages of Hepatic encephalopathy in CTP -A, B, C

		CTP							
		A		**B**		**C**		**Total**	
		n	**n %**	**n**	**n %**	**n**	**n %**	**n**	**n %**
HE	Stage 1	0	0.00%	16	21.90%	66	54.50%	82	41.00%
	Stage 2	0	0.00%	5	6.80%	27	22.30%	32	16.00%
	Stage 3	0	0.00%	0	0.00%	11	9.10%	11	5.50%
	Stage 4	0	0.00%	0	0.00%	3	2.50%	3	1.50%
	None	6	100.00%	52	71.20%	14	11.60%	72	36.00%

Table 4: Correlation of FT4 and TSH among CTP – A, B, C

		TSH	**FT4**
TSH	Pearson Correlation	1	.087
	P-Value		.870
	N	6	6
FT4	Pearson Correlation	.087	1
	P-Value	.870	
	N	6	6
a. CTP = A			
Thyroid function test in CTP A			
		TSH	**FT4**
TSH	Pearson Correlation	1	-.603**
	P-Value		<0.001
	N	73	73
FT4	Pearson Correlation	-.603**	1
	P-Value	<0.001	
	N	73	73
**Correlation is significant at the 0.01 level (2-tailed).			
a. CTP = B			
Thyroid function test in CTP B			
		TSH	**FT4**
TSH	Pearson Correlation	1	-.515**
	P-Value		<0.001
	N	121	121
FT4	Pearson Correlation	-.515**	1

	P-Value	<0.001	
	N	121	121
**Correlation is significant at the 0.01 level (2-tailed).			
a. CTP = C			
Thyroid function test in CTP – C			

Table 5: Degree of thyroid dysfunction and CTP scoring

		CTP							
		A		B		C		Total	
		N	n %	N	n %	n	n %	n	n %
Thyroid Status and CTP Co Relation	Euthyroid	6	100.0%	52	71.2%	31	25.6%	89	44.5%
	Hypothyroidism	0	0.0%	11	15.1%	76	62.8%	87	43.5%
	Subclinical Hypothyroidism	0	0.0%	10	13.7%	14	11.6%	24	12.0%
	Total	6	100.0%	73	100.0%	121	100.0%	200	100.0%

Table 6:

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max	F Value	P-Value
					Lower Bound	Upper Bound				
Male	163	.8204	.57804	.04528	.7310	.9098	.01	1.60	1.261	0.263
Female	37	.7027	.56461	.09282	.5145	.8910	.01	1.60		
Total	200	.7986	.57600	.04073	.7183	.8790	.01	1.60		
Sex correlation with free T4										
	N	**Mean**	**Std. Deviation**	**Std. Error**	**95% Confidence Interval for Mean**		**Min**	**Max**	**F Value**	**P Value**
					Lower Bound	**Upper Bound**				
< 20	5	.6460	.57748	.25826	-.0710	1.3630	.01	1.10	0.264	0.901
20 to 39	67	.8373	.54324	.06637	.7048	.9698	.01	1.60		
40 to 49	68	.7637	.60226	.07304	.6179	.9095	.01	1.60		
50 to 59	44	.8255	.61517	.09274	.6384	1.0125	.01	1.60		
More than 60	16	.7594	.53430	.13357	.4747	1.0441	.02	1.40		
Total	20	.7987	.57600	.0407	.7183	.8790	.01	1.60		

	0			3						
Age-wise correlation of FT4										

Discussion

In a study by Patrik S Kamath *et al*. on MELD, it was found to have similar results which showed low free T3 and low total T3 in patients with decompensated liver disease. In studies by Deepika *et al*. and Kayacetin *et al* the levels of FT3 were significantly low in cirrhosis patients.

Studies done by NK Paitra *et al* showed a prevalence of 62 % hypothyroidism in cirrhotic cases (50). Out of 24 cases of Child A, 21(87%) had normal TSH and 3 (12%) had high TSH. Out of 45 cases of Child B, 35(77%) hada high TSH and 10 (22%) had normal TSH and out of 31 cases of Child C, 26 (83%) had high TSH and 5 (16%) had normal TSH. The study demonstrated that as the severity of cirrhosis increases from child pugh A to C, serum level of TSH started to rise above the normal level, the p value was 0.001 which was statistically significant. These findings were similar to the studies done by Nitesh Kumar *et al*. and Punker *et al* and A. Antonelli *et al*. T3 was found to be low in cases with decompensatedliver disease with child B and child C, these findings were in accordance with the studies done by Mansor *et al*.

Malik, Hodgson *et al*, in their study of cirrhotic patients, found a low free T3 along with an elevated rT3. Penteado KR *et al* observed a low T3 in groups having MELD >18, which normalised after liver transplantation. Shakoor and colleagues, Agiasotelli D and colleagues also found lower levels of free T3 values in liver cirrhosis.

Mobin *et al*. found that in all cirrhotic patients, 76.3% had low serum T3 levels, 14.47% had low serum T4 levels, and 2.63% had raised TSH levels. In several studies, the common abnormalities of thyroid function tests observed were low T3 levels, raised rT3 levels, and normal TSH levels. There are numerous causes for these abnormalities, including alteration in plasma level of thyroid binding proteins, alteration in the binding of T4 and T3 to their carrier protein, impairment of hepatic clearance of reverse T3 (rT3), hyperglucagonemia, along with the reduced extrathyroidal conversion of T4 to T3. In cirrhotic patients, there is extensive hepatic inflammation and fibrosis, and hence there is inhibition of type 1 (D1) deiodinase enzymes. This leads to decreased conversion of T4 to T3. Since the type 2 (D2) deiodinase enzymes remain active, most of the T4 is converted into rT3 leading to increased rT3 levels and low FT4 levels.

Conclusion

As the severity of cirrhosis increases, from Child-Pugh A, B, and C, the thyroid dysfunction becomes more pronounced with the majority of patients having alow FT4 and high TSH. Hence, the usefulness of thyroid function tests as a prognostic markerin patients with cirrhosis has been explored and positive results have been obtained. So, it is essential to perform a thyroid function test in all patients with cirrhosis especially those with higher Child-Pugh Score.

Limitations of the Study

- The results were mainly obtained from a small group ofpatients.
- Patients recruited here may not be the representation of the entirepopulation.
- The duration of cirrhosis was not considered in this study.
- The sample did not include paediatric patients.
- The effect of treatment modality could not be compared since many patients had lost follow-up from treatment.

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