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Relationship of free T3 with Child Pugh Score in patients with chronic liver disease

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Abstract

Introduction: Liver cirrhosis is a leading cause of mortality and morbidity in the world. The liver plays a vital role in both the circulation as well as the metabolism of thyroid hormones. Liver diseases can alter the normal metabolism of the thyroid hormones. Studies have shown that reduction in total T3 and free T3 concentration is associated with severity of hepatic dysfunction.

The aim of our research was to study the relationship of serum free T3 with Child Pugh score in patients with Chronic Liver Disease. Objectives were to assess the level of serum free T3, to calculate the Child Pugh score and to compare and study the correlation between serum free T3 levels and Child Pugh score in patients with chronic liver disease.

Materials and Methods

This Hospital based cross sectional observational study was carried out in the Department of Medicine, Assam Medical College and Hospital, Dibrugarh. Patients with chronic liver disease who attended medicine OPD and those admitted in the department of medicine were taken up for the study. All patients aged above 12 years of age fulfilling the Garcia–Tsao criteria for cirrhosis of liver were included in the study. Exclusion criteria were known cases of thyroid disorder with or without liver cirrhosis, patient with history of cancer, radio or chemotherapy, abdominal surgery, sepsis, congestive heart failure, nephrotic syndrome, chronic kidney disease, pregnancy, personal or family history of thyroid disorders, using drugs that interfere with thyroid metabolism, who did not meet up the inclusion criteria and not giving informed written consent.

Result

Out of total 120 patients 77.5% were male whereas 22.5% were female with the sex ratio 3.4:1. The majority of the subjects in the study group belonged to the age group of 30-39 years. The majority of the subjects belonged to CTP class C (60.8%) followed by CTP class B (28.3%) and CTP class A (10.8%).

The mean free T3 for subjects in CTP class A, CTP class B, CTP class C was 3.63 ± 0.61 ,3.35 ± 0.63 and 2.31 ± 0.60, respectively (p-value <0.001). The result was statistically significant after ANOVA analysis. The mean serum free T3 levels in grade 1 was 2.54 ± 0.50; in grade 2 was 2.31 ±0.74; grade 3 was 1.76 ±0.40 and grade 4 was 1.83 ±0.31. The result was statistically significant after ANOVA analysis. Post hoc analysis was done and there was a statistically significant difference between two individual grades of hepatic encephalopathy (p<0.05) except for grade 1 and grade 2 (p=0.299), grade 2 and grade 4 (p=0.07), grade 3 and grade 4 (p=0.77).

Statistically significant negative correlation between serum free T3 with CTP score (r value: -0.69, p <0.01), total bilirubin (r value: -0.33, p=0.0002), PT (r value: -0.19, p =0.04), INR (r value: - 0.46, p <0.01). There was a statistically significant positive correlation between serum free T3 only with serum albumin (r value: 0.29, p=0.001).

Conclusion: we observed statistically significant negative correlation between serum free T3 and the Child Turcotte Pugh (CTP) score. Serum free T3 can be used as a marker of severity in patients with chronic liver disease.

Keywords: free T3, Child Pugh Score, Chronic Liver Disease]

Introduction

Liver cirrhosis is a leading cause of mortality and morbidity in the world[1]. Chronic liver disease refers to any liver disease persisting for more than 6months. Cirrhosis is the final pathway for a number of chronic liver diseases. It is defined as a pathologic entity characterized by diffused fibrosis and the subsequent replacement of the normal liver architecture by nodules[2]. Cirrhosis can be clinically classified as a “compensated” or “decompensated” state[3]. Decompensation results in ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, hyponatremia and spontaneous bacterial peritonitis. Compensation however, does not include any of these features[3].

The thyroid gland gives rise to two hormones i. e, thyroxine (T4) and triiodothyronine (T3) and these hormones act via the thyroid hormone receptors α and β, and play an important role in cell differentiation during development[4]. They also help in maintaining both thermogenic as well as metabolic homeostasis. T4 is secreted from the thyroid gland about twenty times more than T3. Both T3 as well as T4 are bound to different plasma proteins (thyroxine binding globulin, transthyretin and albumin) [4].

The liver plays a vital role in both the circulation as well as the metabolism of thyroid hormones. The liver produces thyroid binding globulin (TBG), transthyretin and albumin, and is also responsible for the peripheral conversion of free T4 to free T3(which is the active form of thyroid hormone), by the action of Type 1 deiodinase (D1) enzyme. However, selenium independent deiodinase (Type 3 deiodinase=D3) converts thyroxine (T4) to the hormonally inactive reverse T3 (rT3) [5].

In most chronic illness, there is an error in the thyroid hormone metabolism which results in the low T3 syndrome or the sick euthyroid syndrome, which is characterized by a normal total T4, normal or high free T4, low total T3, low free T3 and an elevated rT3. These changes depict a reduction in the deiodinase 1(D1) activity and an increase in the activity of the deiodinase 3 enzyme (D3) [6].

In the same manner, it is reasonable to assume that liver diseases can also alter the normal metabolism of the thyroid hormones. There is a certain pattern of alteration in the thyroid hormones which is different in various

types of liver diseases. Acute viral hepatitis results in increased levels of both total T3 and

T4 [7,8]. This is due to the release of thyroid binding globulin (TBG) into circulation from the dead and necrotic hepatocytes which can then bind to these thyroid hormones released from the liver[7,8]. Throughout the entire disease process, these patients remain clinically euthyroid and TSH is normal. The increase in both T3 and T4 was according to the extent of liver damage however the serum level of these hormones goes back to normal during or after the recovery phase[7].

The progression of liver disease into chronicity leads to a decreased working capacity of the liver. Thus, in chronic liver disease, there are reduced levels of T3, free T3 as well as free T4[9–11].

There is decreased conversion of T4 toT3 due to functional deficiency of Type 1 deiodinase(D1) activity[12].Some studies have shown that the low T3 may actually be an adaptive thyroid response to reduce the basal metabolic rate of hepatocytes in order to preserve liver function [13]. Both T3 and rT3 bind to the same plasma proteins, hence the T3/rT3 ratio provides a parameter of liver function independent of protein binding[14]. Till date, studies have shown that the most frequent thyroid hormone changes were a reduction in total T3 and free T3 concentration, which was also associated with severity of hepatic dysfunction[15].

Hence this study is being undertaken to assess the level of serum free T3 in patients presenting with chronic liver disease and to find out if there is any relation between serum free T3 and Child Pugh score, various other parameters, and also to assess the prognosis, in chronic liver disease.

By comparing serum free T3 with Child-Turcotte-Pugh (CTP) score, we may be able to find out if it can be used as a marker of severity of disease and prognosis in patients with chronic liver disease.

Aims and Objectives

Aim

To study the relationship of serum frees T3 with Child Pugh score in patients with Chronic Liver Disease.

Objectives

1. To assess the level of serum free T3 in patients with chronic liver disease.
2. To calculate the Child Pugh score of patients with chronic liver disease.
3. To compare and study the correlation between serum free T3 levels and Child Pugh score in patients with chronic liver disease.

Materials and Methods

This Hospital based cross sectional observational study was carried out in the Department of Medicine, Assam Medical College and Hospital, Dibrugarh from 1st June 2019 to 31st May 2020.

Study population

All patients with chronic liver disease who attended medicine outpatient department and those admitted in the department of medicine in Assam Medical College & Hospital, during the period of one year were taken up for the study.

Inclusion criteria

All patients aged above 12 years of age irrespective of gender fulfilling the Garcia–Tsao[16]criteria for cirrhosis of liver were included in this study.

Exclusion criteria

Known cases of thyroid disorder with or without liver cirrhosis, history of cancer, radio or chemotherapy,

past history of abdominal surgery, sepsis, congestive heart failure, nephrotic syndrome, chronic kidney disease, pregnancy, personal or family history of thyroid disorders, using drugs that interfere with thyroid

metabolism [such as levothyroxine, propylthiouracil, carbimazole, amiodarone, antiepileptic

(carb amezapine), interferon alfa, mefloquine, steroids, recombinant growth hormone, lithium etc.], patients who did not meet up the inclusion criteria and who did not give an informed written consent.

Sample size

The sample size was calculated and rounded off to be 120, based on the prevalence of thyroid abnormalities in cirrhosis of liver which ranges from 13% to 61%, according to the formula[17]:

$n = z^2pq/L^2$

(Where z=1.96, p stands for prevalence (61%), q = 100-p, L = relative error = 15% of p).

Consent

Informed written consent was taken from the patients or their attendants after explaining about the purpose of the study.

Method of data collection

Data was collected from all CLD patients attending medicine outpatient department or admitted in the medicine wards according to inclusion and exclusion criteria after obtaining Ethical clearance from the Institutional Ethics Committee.

Diagnosis of cirrhosis

Firstly, the diagnosis of liver cirrhosis was made on the basis of the Garcia-Tsao criteria:

Garcia – Tsao criteria[16]

A Non-Histopathological diagnostic criterion for cirrhosis of liver. The case of cirrhosis of liver is defined as a patient having: Clinical signs of hepatocellular dysfunction, Signs of portal hypertension and USG findings suggestive of cirrhosis of liver.

Clinical signs of hepatocellular dysfunction

Jaundice, Neuro logical changes (Hepatic encephalo pathy), Skin changes: spider angiomas, palmar erythema, Endocrine changes: breast atrophy, Gynaecomastia, testicular atrophy.

Signs of portal hypertension

Haematemesis, melaena or gastroesophageal varices by UGI endoscopy, splenomegaly and ascites

Findings in USG abdomen suggestive of cirrhosis of liver

Coarse echotexture, nodular surface, increased caudate to right lobe (C/RL) ratio.

Portal Hypertension: ascites, splenomegaly, varices, portal venous flow rate < 16cm/sec.

Work-up

1. Detailed history and meticulous clinical examination was done for all patients.

2. Complete blood count (CBC) with ESR, Renal function test (RFT), Liver function test (LFT) and PT, INR, Random blood sugar (RBS), Serum electrolytes (Na+, K+) and serum free T3 was done in all patients. USG whole abdomen was done in all cases to look for presence of features suggestive of cirrhosis of liver, portal hypertension and splenomegaly.

Serological tests for detection of infection with hepatitis B and C virus (HBsAg and Anti HCV antibody) were done in all cases. Upper Gastrointestinal endoscopy (Eso phago gastro duodenos copy) was done for presence and grading of gastroesophageal varices.

Child Pugh score was calculated for all patients as a measure of the degree of severity of liver disease. Etiology Specific tests was done only in those patients where it was indicated based on high index of suspicion: Anti-nuclear antibody (ANA), Anti-mitochondrial antibody (AMA), Anti-smooth muscle antibody (ASMA), Anti-Liver Kidney Microsomal 1 antibody (Anti LKM 1), Serum ceruloplasmin,24 hr. urinary copper, Serum Ferritin, Transferrin saturation, HbA1c.

Laboratory investigations

The routine tests were done in the Pathology and Biochemistry Laboratory in Assam Medical College and Hospital, Dibrugarh.

Liver Function Tests

Serum Bilirubin

By dual wavelength End point colorimetric method. Normal reference interval: Total bilirubin: 0.2-1.3mg/dL; Unconjugated:0-1.1 mg/dL; Conjugated: 0-0.3mg/dL

Serum protein

The method of analysis is based on the biuret reaction, which produces a violet complex when protein reacts with cupric ion in an alkaline medium. The amount of colored complex formed is proportional to the amount of total protein in the sample and is measured by reflectance spectrophotometry. Normal reference interval: Protein: 6.3-8.2gm/dl.

Serum Albumin

Albumin binds with bromocresol green dye, and these binding results in a shift in wavelength of the reflectance maximum of the free dye. The colour complex that forms is measured by reflectance spectrophotometry. The amount of albumin-bound dye is proportional to the concentration of albumin in the sample. Normal reference interval- Albumin: 3.5-5g/dL; Globulin: 2.5-3.5g/dL.

AST

In the assay for aspartate aminotransferase, the amino group of L-aspartate is transferred to α-ketoglutarate in the presence of pyridoxal-5-phosphate to produce glutamate and oxaloacetate. The oxaloacetate is converted to pyruvate and carbon dioxide by oxaloacetate decarboxylase. Pyruvate is oxidized to acetyl phosphate and hydrogen peroxide by pyruvate oxidase. The final reaction step involves the peroxidase catalyzed oxidation of a leuco dye to produce a colored dye. The rate of oxidation of the leuco dye is monitored by reflectance spectrophotometry. The rate of change in reflectance density is proportional to enzyme activity in the sample. Normal reference interval: 15-46 U/L

ALT

Alanine aminotransferase catalyses the transfer of the amino group of Lalanine to α-ketoglutarate to produce pyruvate and glutamate. Lactate dehydrogenase then catalyses the conversion of pyruvate and NADH to lactate and NAD+. The rate of oxidation of NADH is monitored by reflectance spectrophotometry. The rate of change in reflection density is proportional to enzyme activity.

Normal reference interval: 13-69 U/L

Alkaline phosphatase

The ALP in the sample catalyses the hydrolysis of the pnitrophenyl phosphate to p-nitrophenol at alkaline ph. The p-nitrophenol is monitored by reflectance spectrophotometry.

The rate of change in reflection density is converted to enzyme activity.

Normal reference interval: 38-126 U/L

GGT

GGT catalyses the transfer of the γ-glutamyl portion of L - γ - glutamyl - pnitroanilide to glycyl glycine, simultaneously producing p-nitroaniline. The rate of change in reflection density is measured and is used to calculate the enzyme activity of GGT. Normal reference interval: 12-58 U/L

Prothrombin Time (PT & INR)

0.2ml of UNIPLASTIN reagent is added to normal citrated plasma and a stop watch was started simultaneously. The clotting mechanism is initiated, forming solid gel clot within specified period of time. The watch was stopped as soon as the first fibrin clot was visible and gel/clot was formed. The results may be

reported as ratio or mean of the double determination of PT of the test in seconds or as a ratio (R) MNPT for reagent Mean of patient plasma PT in seconds

R Or it can be expressed as internationalized normalized ratio (INR)= (R)ISI. Usually plasma of at least 20 normal healthy individuals should be used to establish the Mean PT (MNPT).

Free T3

The radioimmunoassay of free triiodothyronine (T3) is a competition assay based on the principle of labelled antibody. Samples and calibrators were incubated with 125I- labelled monoclonal antibody specific for T3, as tracer, in tubes coated with an analog of T3(ligand). There is a competition between the free T3 of the sample and the ligand for the binding to the labelled antibody. After incubation, the content of tubes is aspirated and bound radioactivity was measured. A calibration curve was established and unknown values were determined by interpolation from the curve.

Normal reference interval: 3.37-5.61 pmol/L

CTP score calculation[26]

The CTP score of each patient was calculated on the basis of 2 qualitative (Ascites and Hepatic Encephalo pathy) and 3 quantitative variables (Albumin, Bilirubin, and INR).

Parameter	Points		
	1 point	2 points	3 points
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	None	Mild	Moderate to severe
Bilirubin(mg/dl)	<2	2-3	>3
Bilirubin in PBC	<4	4-10	>10
Albumin(g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time prolongation (secs prolonged) or INR	< 4s or INR<1.7	4-6s or INR1.7-2.3	>6 or INR >2.3

CTP class A= 5-6 points; CTP class B = 7-9 points; CTP Class C = 10-15 points

Hepatic Encephalopathy Grading

Done as per West Haven Criteria[27].

Ascites grading

Ascites was classified as per the consensus guidelines of the International Ascites club. Mild/ Grade 1: ascites detectable only by ultrasound examination. Moderate/ Grade 2: ascites is manifest by moderate symmetrical distension of abdomen. Severe/ Grade 3: Large or gross ascites with marked abdominal distension.

Statistical Analysis

The data collected was tabulated in Microsoft Excel Worksheet 2010 and computer-based analysis was performed using the Statistical product and service solutions (SPSS) 20.0 software (SPSS, Chicago, Illinois, USA). Results on continuous measurements are presented as mean ± standard deviation and are compared using Analysis of Variance (ANOVA). Where the p-value was found significant ($p<0.05$) among 3 groups, post hoc analysis was done to find out the significance between 2 individual groups. Discrete data are expressed as number (%) and analysed using Chi square test and Fischer's exact test. Pearson's correlation coefficient (r) was used to measure the associations among continuous variables. For all analyses, statistical significance was fixed at 5% level (p value < 0.05).

Results and Observations

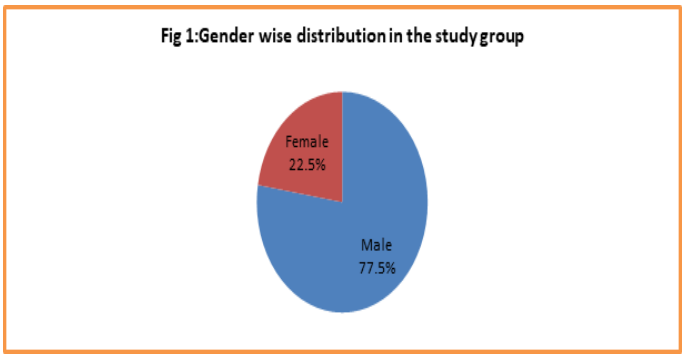
The results and observations of our study are illustrated in the following tables and figures

Table 1: Age distribution of CLD

Age group (In Years)	Number (N=120)	Percentage (%)
13–19	1	0.83
20–29	13	10.83
30–39	33	27.50
40–49	30	25.00
50–59	26	21.67
60–69	11	9.17
70	6.00	5.00
Mean ± *S.D.* = 45.19 ± 13.40		

The table 1 shows that the majority of the subjects in the study group belonged to the age group of 30-39 years (27.5%) followed by in the age group of 40-49 years (25%). The mean age of the whole study group was 45.19 ± 13.40 years.

Fig 1: Gender wise distribution in the study group



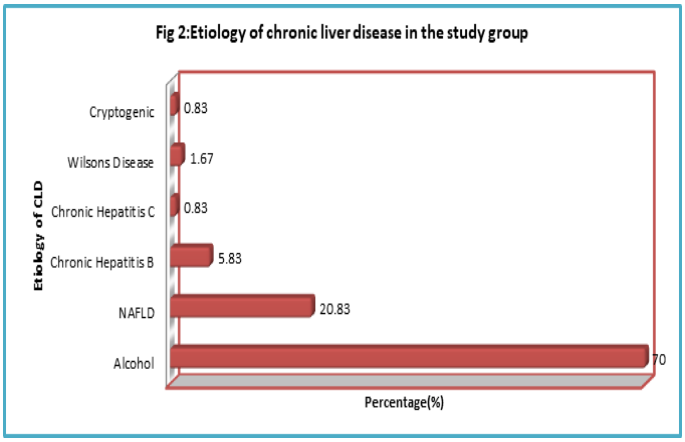
The fig 1 shows the male subjects constituted 77.5% (n=93) of the study group whereas female subjects constituted only 22.5% (n=27). The sex ratio in the study group was 3.4:1.

Table 2: Presenting symptoms and signs in the study group

(A)Clinical Symptoms	Number (n = 120)	Percentage (%)
Fatigue	96	80
Anorexia	86	71.6
Swelling of Feet	98	81.6
Abdominal Distension	105	87.5
Jaundice	50	41.6
Melaena	45	37.5
Altered Sensorium	47	39.1
Hematemesis	25	20.8
Bleeding diathesis	49	40.8
Constipation	52	43.3
(b)Clinical signs:	Number (n = 120)	Percentage (%)
Pedal oedema	98	81.6
Ascites	105	87.5
Splenomegaly	63	52.5
Pallor	45	37.5
Icterus	50	41.6
Asterixis	32	26.6
Parotid Swelling	45	37.5
Gynaecomastia	52	43.3
Loss of axillary/pubic hair	40	33.3
Palmar erythema	31	25.8
Spider naevi	25	20.8

The above table 2 shows the most common symptom was abdominal distension (87.5%) and the most common clinical sign was ascites (87.5%). Other clinical signs and symptoms were swelling of feet (81.6%), fatigue (80%), anorexia (71.6%), constipation (43.3 %), jaundice (41.6%), bleeding diathesis (40.8%), altered sensorium (39.1 %), melena (37.5%), hematemesis (20.83 %), splenomegaly (52.5%), gynecomastia (43.3%), icterus (41.6%), pallor (37.5%), parotid swelling (37.5%), loss of axillary /pubic hair (33.3%), asterixis (26.6%), palmar erythema (25.8%) and spider naevi (20.8%).

Fig 2: Etiology of chronic liver disease in the study group



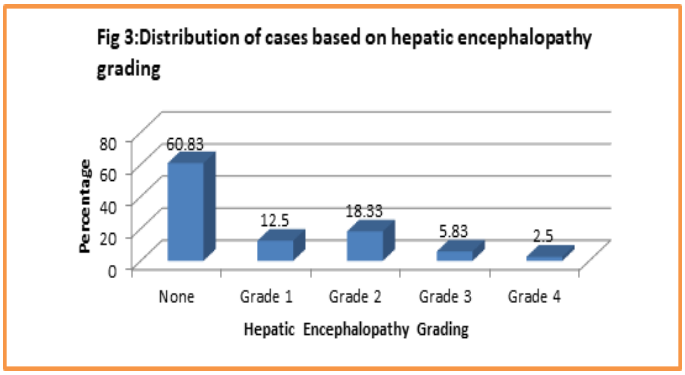
The fig 2 shows the most common cause of CLD was alcohol (70%) followed by non-alcoholic fatty liver disease (20.8%), Chronic hepatits B (5.83%), Wilson's disease, Chronic hepatitis C and cryptogenic.

Table 3: Etiology of chronic liver disease in the study group based on gender

Etiology	Male		Female	
	N=93	Percentage (%)	N=27	Percentage (%)
Alcohol	65	69.89	19	70.37
NAFLD	19	20.43	6	22.22
Chronic Hepatitis B	6	6.45	1	3.70
Chronic Hepatitis C	0	0.00	1	3.70
Wilsons Disease	2	2.15	0	0.00
Cryptogenic	1	1.08	0	0.00

The table 3 shows the most common cause of CLD was alcohol in both males (69.89 %) and females (70.37%). The second most common cause of CLD in both males and females was NAFLD (20.43% in males and 22.22% in females).

Fig 3: Distribution of cases based on hepatic encephalopathy Grading



The Fig 3 shows that most common hepatic encephalopathy was grade 2 hepatic encephalopathy (18.33 %) followed by grade 1 (12.5%) and grade 3(5.83 %).73 subjects (60.83%) in the study group did not have hepatic encephalopathy.

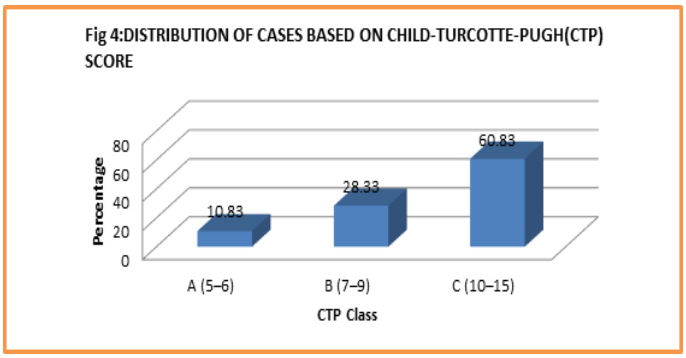
Table 4: laboratory parameters in the study group

Laboratory Parameters	Mean ± S.D.
Hemoglobin (g/dL)	8.47 ± 2.08
TC	7104.92± 2572.76
Platelet Count	1.43± 0.98
Total Protein	6.74± 1.09
Albumin	2.62± 0.62
Globulin	4.12± 1.01
Bilirubin Total	3.93± 4.48
Indirect Bilirubin	1.82± 2.45
Direct Bilirubin	2.11± 2.84
SGOT	107.18± 87.74
SGPT	71.68± 129.13
GGT	191.22± 357.51
ALP	155.76± 89.34
PT	19.39± 11.14
INR	1.76± 0.66
Urea	38.07± 30.33
Creatinine	1.27± 1.06
Na	134.09± 4.94

K	3.99± 0.79
RBS	123.26± 54.35
free T3	2.75± 0.82

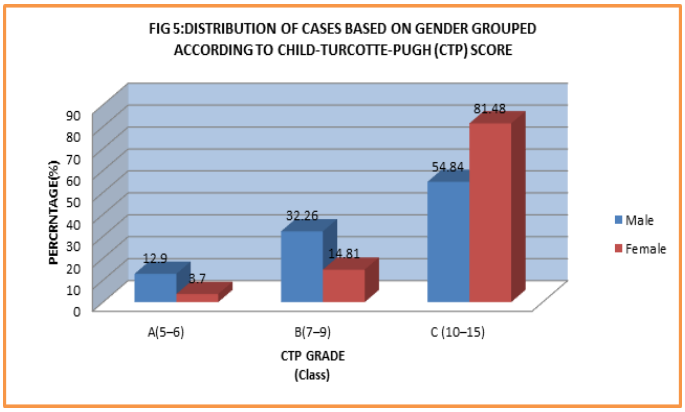
The above table 4 shows the mean total protein was 6.74 ± 1.09 g/dl, mean albumin was 2.62 ± 0.62 g/dl, mean globulin was 4.12 ± 1.01 g/dl, mean total bilirubin was 3.93 ± 4.48 mg/dl, mean direct bilirubin was 2.11 ± 2.84 mg/dl, mean indirect bilirubin was 1.82 ± 2.45 mg/dl. The mean SGOT/AST was 107.18 ± 87.74 U/L, mean SGPT/ ALT was 71.68 ± 129.13 U/L, mean GGT was 191.22 ± 357.51 U/L, mean ALP was 155.76±89.34 U/L, mean PT was 19.39 ± 11.14 secs, mean INR was 1.76 ±0.66, mean free T3 was 2.75±0.82 pmol/L.

Fig 4: Distribution of cases based on Child-Turcotte-Pugh (CTP) score



The above Fig 4 shows majority of the subjects in the study group belonged to CTP class C (60.8%). followed by CTP class B (28.3%) and CTP class A (10.8%) .

Fig 5: Distribution of cases based on gender grouped according to Child-Turcotte-Pugh (CTP) score



The fig 5 shows that 54.8% of all male cases and 81.4% of all female cases fall under CTP class C.

32.26% of all male cases and 14.8% of all female cases fall under CTP class B. Whereas 12.9% of all male cases and 3.7% of all female cases fall under CTP class A.

Table 5: Comparison of mean serum free T3 level in males and females

Gender	Free T3(pmol/L) Mean ± S.D.	Range (Min—Max)	p value
Male	2.76 ± 0.85	1.30 – 5.20	0.714
Female	2.70 ± 0.71	1.50 – 4.50	

The table 5 shows the mean free T3 in male subjects was 2.76 ± 0.85 and the mean free T3 in female subjects was 2.70 ± 0.71 (p=0.714). The results were not statistically significant after ANOVA test was done.

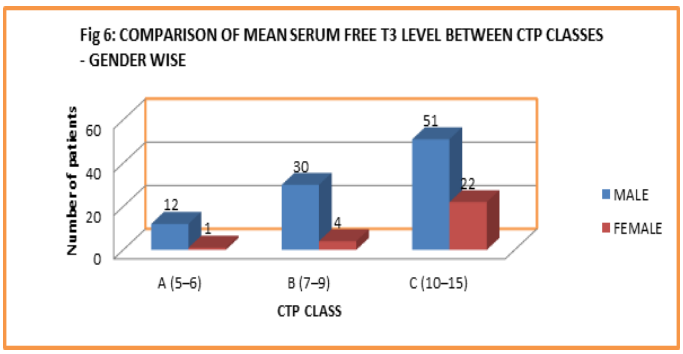
Table 6: Comparison of mean serum free T3 level between the CTP classes

CTP grade (Class)	Number (n=120)	Free T3(pmol/L)		p value
		Mean ± S.D.	Range	
A (5–6)	13	3.63 ± 0.61	2.90 – 5.10	<0.001
B (7–9)	34	3.35 ± 0.63	1.50 – 5.20	
C (10–15)	73	2.31 ± 0.60	1.30 – 3.90	

The table 6 shows the mean free T3 for subjects in CTP class A, CTP class B, CTP class C was 3.63 ± 0.61 ,3.35 ± 0.63 and 2.31 ± 0.60, respectively (p-value <0.001). The result was statistically significant after ANOVA analysis. Post-hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C(p<0.01), and also between CTP class B and CTP class C (p<0.01); but

there was no statistical significance between CTP class A and CTP class B(p=0.16).

Fig 6: Comparison of mean serum free t3 level between CTP classes - gender wise



The fig 6 shows majority of male subjects were grouped under CTP class C (n=51) and the mean

free T3 of male subjects under CTP class C, CTP class B and CTP class A was 2.23 ± 0.61, 3.33 ± 0.63 and 3.59 ± 0.62, respectively (p<0.01).

The result was statistically significant after ANOVA analysis. Post-hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C (p<0.01), and also between CTP class B and CTP class C (p<0.01); but there was no statistical significance between CTP class A and CTP class B(p=0.23). Majority of female subjects were grouped under CTP class C (n=22) and the mean free T3 of female subjects under CTP class C, CTP class B and CTP class A was 2.50 ± 0.56, 3.45 ± 0.72 and 4.10, respectively (p=0.003). The results showed statistically significant difference in the mean free T3 among CTP classes for females, following ANOVA test. Post-hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C(p=0.01), and also between CTP class B and CTP class C (p<0.01); but there was no statistical significance between CTP class A and CTP class B (p= 0.47).

Table 7: Comparison of mean serum free T3 level in various etiologies of chronic liver disease

Etiology	Number (n=120)	Free T3(pmol/L) (Mean ±SD)	p value
Alcohol	84	2.72 ± 0.91	0.823
NAFLD	25	2.89 ± 0.57	
Chronic Hepatitis B	7	2.59 ± 0.45	
Chronic Hepatitis C	1	1.90	
Wilsons Disease	2 2.90 ± 0.28	2 2.90 ± 0.28	
Cryptogenic	1	2.90	

The table 7 shows the mean free T3 in subjects with alcohol related CLD was 2.72 ± 0.91, NAFLD related CLD was 2.89 ± 0.57, Chronic Hepatitis B related CLD was 2.59 ± 0.45, Chronic Hepatitis C related CLD was 1.90, Wilsons Disease related CLD was 2.90 ± 0.28 and Cryptogenic causes of CLD was 2.90 (p=0.823). However, the results were not statistically significant following the ANOVA test.

Table 8: Comparison of mean serum free T3 level between CTP classes (etiology wise)

Etiology	CTP grade (Class)									p value
	A (5–6)			B (7–9)			C (10–15)			
	N=13	Mean free T3	S. D	N=34	Mean free T3	S.D.	N=73	Mean free T3	S.D.	

Alcohol	9	3.82	0.59	22	3.44	0.74	53	2.24	0.63	<0.01
NAFLD	3	3.3	0.46	10	3.22	0.33	12	2.52	0.54	0.003
Hep B	-	-	-	1	2.9	-	6	2.53	0.46	0.816
Hep C	-	-	-	-	-	-	1 1.9	1 1.9	-	-
Wilson's	-	-	-	1	3.1	-	1	2.7	-	-
Cryptogenic	1	2.7	-	-	-	-	-	-	-	-

The table 8 shows that in CTP class A of alcohol related CLD, the mean serum free T3 was 3.82 ± 0.59; in CTP class B, the mean serum free T3 was 3.44±0.74; in CTP class C, the mean serum free T3 was 2.24±0.63 (p<0.01). The result was statistically significant after ANOVA analysis. Post hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C(p<0.01), and also between CTP class B and CTP class C (p<0.01); but there was no statistical significance between CTP class A and CTP class B (p= 0.18).

The table 8 shows that in CTP class A of NAFLD related CLD, the mean serum freeT3 was 3.3±0.46; in CTP class B, the mean serum free T3 was 3.22±0.33; In CTP class C, the mean serum free T3 was 2.52±0.54 (p=0.003). The result was statistically significant after ANOVA analysis. Post hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C(p=0.04), and also between CTP class B and CTP class C (p<0.01); but there was no statistical significance between CTP class A and CTP class B (p= 0.74).

The table 8 shows that there were no cases of CTP class A Chronic Hepatitis B patients. There was only 1 case of Chronic Hepatits B in CTP class B and the mean serum free T3 was 2.9; There were 6 cases of CTP class C Chronic Hepatitis B related CLD, and the mean serum free T3 was 2.53±0.46 (p=0.82). The results were not statistically significant after ANOVA test. The mean free T3 in subjects with Chronic Hepatitis C related CLD was 1.90, Wilsons Disease related CLD was 2.90 ± 0.28 and Cryptogenic causes of CLD was 2.90.

Table 9: Comparison of mean serum free t3 level in hepatic encephalopathy

Hepatic Encephalopathy	Number (n=120)	Free T3(mg/dL) (Mean ±SD)	p value
Grade 1	15	2.54 ±0.50	<0.01
Grade 2	22	2.31 ±0.74	
Grade 3	7	1.76 ±0.40	
Grade 4	3	1.83 ±0.31	
None	73	3.06 ± 0.77	

The above table 9 shows the mean serum free T3 levels in grade 1 was 2.54 ± 0.50; in grade 2 was 2.31 ±0.74; grade 3 was 1.76 ±0.40 and grade 4 was 1.83 ±0.31. The cases without hepatic encephalopathy had serum free T3 of 3.06 ± 0.77 (p<0.01). The result was statistically significant after ANOVA analysis. Post hoc analysis was done and there was a statistically significant difference between two individual grades of hepatic encephalopathy (p<0.05) except for grade 1 and grade 2(p=0.299), grade 2 and grade 4(p=0.07), grade 3 and grade 4(p=0.77).

Table 10: Correlation of free T3 with various parameters

Parameter	r value	p value
CTP Score	-0.69	<0.01
Age	-0.18	0.05
TC	-0.01	0.89
Platelet Count	-0.07	0.46
Albumin	0.29	0.001

Bilirubin Total	-0.33	0.0002
SGOT	-0.01	0.90
SGPT	0.01	0.87
GGT	0.15	0.11
ALP	0.05	0.59
INR	-0.46	<0.01
Hemoglobin	0.03	0.78
Total Protein	0.12	0.18
Globulin	-0.06	0.50
PT	-0.19	0.04

The above table 10 shows a statistically significant negative correlation between serum free T3 with CTP score (r value: -0.69, p <0.01), total bilirubin (r value: -0.33, p=0.0002), PT (r value: -0.19, p=0.04), INR (r value: - 0.46, p <0.01). There was a statistically significant positive correlation between serum free T3 only with serum albumin (r value: 0.29, p=0.001).

Discussion

Age distribution in the study group

In our study, the majority of the subjects (27.5%) belonged to the age group of 30-39 years followed by the age group of 40-49 years (25%). The mean age of the whole study group was 45.19 ± 13.40 years.

The mean age observed by different researchers were 43± 14 years (Punekar et al [36],41±13.7 years (Verma et al[37]).

In a study by Joeimon et al [38], the age of study population was in the range of 25-60 years.

In a case control study by Kaya cetin et al[39], 15 patients with hepatic encephalopathy due to non-alcoholic cirrhosis had a mean age of 51 ± 8.74 years (range 37–75 years), 33 nonalcoholic cirrhotic patients without encephalopathy had a mean age of 55 ±7.71 (range 36–74 years). El-Sawy et al[40] found the mean age 54.5 ± 17.5 years (range 37–72 years). In a case control study by Deepika et al [41], the mean age of case groups were 44 ±13.7 years and that of the control group were 45±15.7 years. In a study done by El-Feki et al [42], the mean age of those patients with liver cirrhosis was 51.8± 8.2 and without liver cirrhosis was 47.5±8.8. Patira et al[43] observed that 72% patients belonged to the age group of 41-60 yrs, 18% patients were below 40 years.

Gender wise distribution in the study group

In our study, majority of the patients with chronic liver disease were males (77.5%) and the sex ratio was 3.4:1. Kharb et al [44] observed that, out of 25 patients, there were only 8 females (one postmenopausal) and rests were males (17). The sex ratio in this study was 2.1:1. In a study by El feki et al[42], the non-cirrhotic group of patients included 9 males (60%) and 6 females (40%). The cirrhotic group however consisted of 30 males (66.7%) and 15 females (33.3%). The sex ratio was 1.5:1 among non-cirrhotic patients and 2:1 among cirrhotic patients. In a study by Kayacetin et al[39], out of 15 patients with hepatic encephalopathy secondary to non-alcoholic cirrhosis 8 were males and 7 were females (Sex ratio: 1.14:1). Out of 33 non-alcoholic cirrhotic patients without encephalopathy 22 were males and 11 were females (Sex ratio: 2:1). Verma et al[37] found 73 males and 29 females and the sex ratio was 2.5:1. In a study by Joeimon *et al*[38], out of 111 patients, 80 were males and 31 were females and the sex ratio was 2.6:1. In a study by Patira et al[43], 78% patients were male and 22%were female. The sex ratio was 3.5: 1.

Presenting symptoms and signs in the study group

In our study, the most common symptom in the study group was abdominal distension (87.5%) and 81.6% of the subjects in the study group had swelling of feet, 80% had fatigue, 71.6% had anorexia, 43.3 % had constipation, 41.6% had jaundice, 40.8% had bleeding diathesis, 39.1 % had altered sensorium, 37.5% had melaena, and only 20.83 % presented with hematemesis.

The most common clinical sign was ascites (87.5%) followed by pedal edema (81.6%), splenomegaly (52.5%), gynecomastia (43.3%), icterus (41.6%), pallor (37.5%), parotid swelling (37.5%), loss of axillary /pubic hair (33.3%), asterixis (26.6%), palmar erythema (25.8%) and spider naevi (20.8%)

In a study by Punekar et al[36], the most common presentation was ascites (74%). Other complications included anemia (87%), coagulation abnormality (65%), thrombocytopenia (53%), hepatic encephalopathy (38%), jaundice (32%), upper gastrointestinal bleed (34%), azotemia (17%), pleural effusion (16%), sepsis (22%), shock (14%) and constipation (49%). In a study by Verma et al[37], the most common presentation was ascites [with mild ascites (52.94%) and severe ascites (17.65%)] and hepatic encephalopathy (29.41%) and bleeding varices (20.59%). In a study by Huang et al[45], patients presented with ascites was (47.27%) [out of which mild ascites (5.97%) and severe ascites (41.3%)] followed by portal vein thrombosis (20%) and hepatic encephalopathy (2.86%).

Etiology of chronic liver disease (CLD)

In our study, the most common cause of CLD in the study group was alcohol (70%) followed by non-alcoholic fatty liver disease (NAFLD) accounting for 20.8% of the cases. Other causes of CLD in our study included Chronic Hepatitis B, Wilson's disease, Chronic hepatitis C and cryptogenic causes accounting for 5.83% ,1.67% ,0.83%and 0.83% respectively. The most common cause of CLD in both male and female subjects was alcohol, accounting for 69.89 % in males and 70.37% in females. The second most common cause of CLD in both males and females was NAFLD (nonalcoholic fatty liver disease) , accounting for 20.43% in males and 22.22% in females. Chronic hepatitis B accounted for 6.45% and 3.7% in males and females respectively. Chronic hepatitis C was found in only 1 female subject (3.7%). Wilson's disease was found in only 2 male subjects (2.15%). There was only one cryptogenic cause of CLD which was found in 1 male subject.

In a study by Chaudhary et al [46], the most common cause of cirrhosis was ethanol ingestion which was found in 97 (88.18%) patients. Chronic hepatitis B infection was the second most common cause which was seen in 8 (7.27%) patients followed by chronic hepatitis C infection in 3 (2.73%) patients. The cause of cirrhosis was unknown in 2 (1.81%) patients.

Patira *et al*[43] found that the etiology of liver cirrhosis was alcohol (70%), HBV (26%), and had HCV (4%)

Hepatitis B (44.94%) was the most common cause of CLD in a study done by Huang et al[45].

In a study done by Kharb *et al*[44], the most common cause of CLD was Hepatitis B. Among 50 subjects with CLD, 29 were hepatitis B virus (HBV)-related cirrhosis, 8 were hepatitis C virus (HCV)-related cirrhosis, 3 had HBV and HCV co-infection, and 10 had cryptogenic cirrhosis with probable autoimmune etiology in six. The patients with history of alcohol intake were excluded in this study. In a study by Punekar et al[36], alcohol was found to be the most common etiology (46%) followed by hepatitis B (19%), hepatitis C (3%), Wilson disease (1%), and others. Vincken et al[47] found that 76% had alcoholic liver cirrhosis, while 17% had chronic hepatitis C related liver cirrhosis. In four other cases, chronic hepatitis B and non-alcoholic steatohepatitis were the causes of cirrhosis.

In a study by Verma et al[37], the most common cause of liver cirrhosis was alcohol comprising of 34(33.3%) patients followed by 29(28.43%) patients who had cryptogenic cirrhosis, 28 (27.45%) patients had hepatitis B related cirrhosis and 11 (10.78%) patients had hepatitis C related cirrhosis.

Alcohol was found to be the most common etiology of CLD in our study as well as the majority of the above-mentioned study. Other causes of CLD however, was variable depending upon risk factors, co-morbidities as well as regional variation.

Laboratory parameters in the study group

In our study, the mean Hemoglobin (Hb) was 8.47±2.08 g/dl, mean total count was 7104.9±2572.76 cells/ μL, mean platelet count (PC) was 1.43 ± 0.98 cells/μL. The mean total protein was 6.74 ± 1.09 g/dl, mean albumin was 2.62 ± 0.62 g/dl, mean globulin was 4.12 ± 1.01 g/dl, mean total bilirubin was

3.93 ± 4.48 mg/dl, mean direct bilirubin was 2.11 ± 2.84 mg/dl, mean indirect bilirubin was 1.82 ± 2.45 mg/dl. The mean SGOT/AST was 107.18 ± 87.74 U/L, mean SGPT/ ALT was 71.68 ± 129.13 U/L, mean GGT was 191.22 ± 357.51 U/L, mean ALP was 155.76 ± 89.34 U/L, mean PT was 19.39 ± 11.14 secs, mean INR was 1.76 ±0.66, and mean free T3 was 2.75±0.82 pmol/L.

Chaudhary et al[46] in their study found that the mean Hemoglobin (g/dl) was 9.37±2.72, mean TLC (/cu.mm) was 10380±801.76 ,mean Platelet count (/Cu.mm) was 98227.27±36206, mean INR was 1.59±0.59, mean total Protein (mg/dl) was 6.45±0.68 , mean albumin(mg/dl) was 3.31±0.39, mean total Bilirubin (mg/dl) was 4.20±4.07 ,mean AST (IU/L) was 158.77±89.42 , mean ALT (IU/L) was 85.73±78.23, mean Alkaline phosphatase (IU/L) was 250.75 ±106. In a study by Hammam et al[48], 72 patients with liver cirrhosis due to chronic HCV infection were selected. The cases were then grouped into group I, II and III (Based on Child Turcotte Pugh class). Group I included 24 patients with compensated cirrhosis (Child's grade A). Group II included 24 patients with decompensated cirrhosis (Child's grade B or C) without encephalopathy and group III included 24 patients with decompensated cirrhosis (Child's grade B or C) with encephalopathy. In groups I,II and III the mean Hb(gm/dl) was 12.1 ± 2.0 , 10.1 ± 2.4 and 11.1 ± 2.2 respectively; mean WBC(cells x103/ml) was 6.1 ± 2.1 ,7.1 ± 3.5 , 9.9 ± 5.8 respectively; mean platelet count (cellsx103/ml) was 94.6 ±28.2,91.3 ± 30 ,110.3 ± 38.9 respectively ; mean total bilirubin (mg/dl) was 0.9 ± 0.4 ,2.6 ± 1.4 ,3.7 ± 2.5 respectively ; mean direct bilirubin(mg/dl) was 0.3 ± 0.2,1.1 ± 0.8 ,1.8 ± 1.5 respectively; mean albumin (g/dl) was 3.6 ± 0.5,2.4 ± 0.3 ,2.5± 0.5 respectively; mean ALT (IU/ml) was 47.8 ± 32.5 ,46.2 ± 28.3 ,80.4 ± 126 respectively ; mean AST(IU/ml)was 51.4 ± 25.4 ,63 ± 45.9 , 131.7 ± 214.7 respectively; mean INR was 1.16 ± 0.14 ,1.7 ± 0.5 ,1.6 ± 0.4 respectively ; mean PT(sec) was 13.5 ± 0.7,16.3 ± 3.8 , 16.1 ± 2.7 respectively. In a study by Punekar et al[36], the mean Hb was 8.05±2.2, mean TLC was 8744±6134, mean Platelets was 1.17±0.78, mean Bilirubin was4.75±5.21, mean SGOT was 106.03±105, mean SGPT was 57.99±62.4, mean Protein was 6.14±0.84, mean Albumin was 2.*61*±0.71, mean Globulin was 3.53±0.75, mean PT was 25±13.86, mean INR was 1.67±0.58.

In our study anemia, hypoalbuminemia, raised liver enzymes, hyperbilirubinemia and raised PT was present. These findings were consistent with the findings of Chaudhury *et al*, as well as Punekar *et al*. However, our findings were not in agreement with those of Hamman *et al*, most probably due to equal distribution of cases to various CTP classes in their study.

Age distribution in the study group based on Child Turcotte Pugh (CTP) class

In our study, the mean age of CTP class A, B and C was 36.69±11.15 years, 44.44 ± 11 years and 47.05±14.27 respectively (p=0.03). The result following ANOVA test showed statistically significant difference in the mean age among CTP classes.

In a study by El-Sawy et al[40], the mean age of patients belonging to CTP class A, B and C was 56.5 ± 9.5 years (range 37–56 years), 50.5 ± 7.5 years (range 43–58 years), 49.5 ± 8.5 years range 41–58 years), respectively. In a case control study by Kharb *et al*[44], the mean age in patients with acute hepatitis was 35±12.7 years, in patients with CLD 1(CTP class A), CLD2 (CTP class B and C) the mean age was 40.5±10.6 years and 44.0±9 years respectively and those who underwent liver transplantation the mean age was 44±10 years. In a case control study by Kayacetin et al[39],The patients with CTP class A had a mean age of 51.33 ± 8.81 years (range37–65 years), CTP class B had a mean age of 52.72 ±7.80years (range 44–75 years) and CTP class C had a mean age of 57.21 ±9.40 years (range 51–72 years).In a study by El-Feki *et al*[42], where 60 patients with chronic hepatitis C (CHC) infection were selected, those patients with liver cirrhosis (n=45) were again subdivided based on their CTP score. The mean age

of patients with CTP class A, B and C was 49.9±8.5, 49.3±8.9 and 56.2±5, respectively. In a study by Neeralagi et al[49], out of the patients included in Child A group, mean age of subjects was 40.3 ± 9.5 years, in Child B, mean age of subjects was 42.2 ± 10.6 years and in Child C, mean age of subjects was 44.1 ± 11.4 years. There was no statistically significant difference in the mean age with among various Child Pugh classes.

Hence, it is seen that in both our study as well as the above-mentioned studies, the severity of liver dysfunction (based on CTP class) was more in older aged patients as compared to younger patients and most of the patients with CLD were in the age group of 30-40 years.

Gender wise distribution in the study group (Based on CTP class)

In our study, among those who fall under CTP class C, 51 were males (accounting for 54.8% of all males cases) and 22 were females (accounting for 81.4% of all female cases). Among those who fall under CTP class B, 30 were males (accounting for 32.26% of all males cases) and 4 were females (accounting for14.8% of all female cases). Among those who fall under CTP class A, 12 were males (accounting for 12.9% of all males' cases) and 1 was female (accounting for 3.7% of all female cases). The sex ratio for CTP class A, B and C was 12:1 ,7.5:1 and 2.3: 1 respectively.

In a study by Kharb *et al*[44], out of 25 patients, there were only 8 females (one postmenopausal) and rests were males (17). The sex ratio in patients having Acute hepatitis, CLD2(CTP B and CTP C) and Liver Transplantation 3.8: 1 ,14: 1 and 9:1 respectively. The patients belonging to CLD (CTP A class) consisted only of males. In a study by El-Feki et al[42], the non-cirrhotic group of patients included males (60%) and female (40%). The cirrhotic group however consisted of 66.7% males (and 33.3% females. Based on the Child Turcotte Pugh score, there was equal division of male (66.7%) subjects amongst CTP classes, 10 males each in CTP A, B and C. There was also equal division of females (33.3%) amongst CTP classes, 5 females each in ever CTP class (Sex ratio was 2:1 in all CTP classes). In a study by Hammam et al[48], 72 patients with liver cirrhosis due to chronic HCV infection were selected, out of which 40 were males and 32 were females. The sex ratio was 1.2:1. The cases were then grouped into group I,II and III(Based in Child Turcotte Pugh class). Group I included 24 patients with

compensated cirrhosis (Child's grade A). Group II included 24 Patients with decompensated cirrhosis (Child's grade B or C) without encephalopathy and group III included 24 Patients with decompensated cirrhosis (Child's grade B or C) with encephalopathy. In group I , there were 14 males and 10 females(sex ratio: 1.4:1) , in

group II there were 9 males and 15 females (sex ratio : 0.6:1)and in group III there were 17 males and 7 females(sex ratio : 2.4:1).

Patient distribution and relationship of serum free T3 with the different classes of Child Turcotte Pugh Score (CTP)

In our study majority of the subjects belonged to CTP class C (60.8%) followed by CTP class B (28.3%) and CTP class A(10.8%).

We found out that the mean serum free T3 for subjects in CTP class A, CTP class B and CTP class C was 3.63 ± 0.61 ,3.35 ± 0.63 and 2.31 ± 0.60, respectively. The lowest levels of serum free T3 was found in CTP class C, followed by CTP class B and then CTP class A. With an increase in the CTP class there was a decrease in the mean serum free T3.

There was a statistically significant difference in the mean serum free T3 among the patients in various CTP classes (p-value <0.001). Post hoc analysis also showed statistically significant difference in the mean serum free T3 levels between all CTP classes except CTP class A and CTP class B(p=0.16). There was also statistically significant negative correlation between the mean free T3 with the CTP score (r value: -0.69, p<0.01). Hence, the free T3 levels correlate well with the severity of the disease as evidenced by the decreasing trend of free T3 levels with increase in the CTP score.

In a study by El-Feki et al [42], on evaluation of serum level of thyroid hormones in patients with Chronic Hepatitis C Virus (CHC) infection, 60 patients with chronic hepatitis C were selected and grouped into those with cirrhosis (n=15) and those without cirrhosis (n=45). The 2nd group was classified

according to the Child-Turcotte-Pugh scoring system into CTP A (15 patients), CTP B (15 patients), and CTP C (15 patients). On comparing the mean serum levels of Free T3 in CTP A, B, and C, the lowest levels were among the CTP C group (1.4 ± 1.0), followed by the CTP B group (1.9 ± 1.0), while the CTP A group was within the normal range (2.5 ± 0.6). There was a statistically significant difference in the free T3 level between the groups (except between CTP A and B, p = 0.078).In a case control study done by Punekar *et al* [36], a total of 100 cases of patients having liver cirrhosis was selected and they were classified according to Child Turcotte Pugh (CTP) score. Only 1 patient belonged to CTP class A, 37 patients belonged to CTP class B and 62 patients belonged to CTP class C. The mean serum free T3 for subjects in CTP class A was 1.9(n=1), CTP class B was 2.20 ± 0.55 and CTP class C was 1.8 ± 0.53, (p-value =0.002). The lowest serum free T3 was found in CTP class C group. Prevalence of low free T3 correlated with the severity of liver disease as per Child Turcotte Pugh score (CTP). In a case control study by Kharb *et al* [44], which assessed the thyroid and gonadal function in liver diseases, the cases were grouped into–Acute hepatitis(n=25), CLD 1(20 patients grouped into CTP class A) and CLD 2(30 patients grouped into CTP class B and C) and 10 patients who had undergone

Liver transplantation. The mean serum free T3 for cases in CLD 1 was 3.1 ± 0.4, in CLD 2 was 2.8 ± 0.4. In the study, thyroid dysfunction was present in 16% of the cases. Non thyroidal illness (sick euthyroid syndrome) was the most common which was present in patients with acute hepatitis as well as CLD. Serum total T3 was low in all types of liver disease, however free T3 was significantly lower in cases with CLD 2 when compared (CTP class B and C).

In a case control study by Kayacetin *et al*[39],15 patients with hepatic encephalopathy due to non-alcoholic cirrhosis and 33 non-alcoholic cirrhotic patients without encephalopathy were classified according to the Child

Turcotte Pugh (CTP)score. There were 9 patients in CTP A, 11 patients in CTP B and 13 patients in CTP C. The mean serum free T3 level in CTP A, B and C was 2.40±0.79, 2.36±0.56, 1.61±0.38(p<0.05). Compared to controls, patients with hepatic encephalopathy and decompensated cirrhotic patients (Child C group) showed a significant decrease in free T3 levels (2.76 ± 0.45 in control group vs 1.15±0.25 and 1.61±0.38 for mean free T3 respectively; p <0.05). Decompensated cirrhotic patients (Child C) had significantly lower serum free T3 levels than Child A and Child B groups (p<0.05). There was a significant inverse correlation between serum free T3 concentrations and the severity of liver dysfunction. In a study by Verma *et al*[37], 102 patients with liver cirrhosis were selected and the mean free T3 level in patients with cirrhosis was 2.32±0.17. The patients were then classified according to the Child Turcotte Pugh score and further divided based on the level of serum free T3 (Low and Normal). Out of 102 cirrhotic patients, a total of 72.5% had low free T3 whereas 27.5% had normal free T3 levels. 2 cirrhotic patients with CTP A (50%),24 patients with CTP B (60%) and 48 patients with CTP C (82.76%) had low free T3 levels. 2 cirrhotic patients with CTP A (50%),16 patients with CTP B (40%) and 10 patients with CTP C (17.24 %) had normal free T3 levels. In this study free T3 levels were inversely correlated with the Child-Pugh class. Our study also displayed an inverse correlation between serum free T3 and Child Pugh score.

In a study by Patira et al[43], a total of 50 patients with cirrhosis of liver were selected, out of which, 13 (26%) patients had low serum free T3 levels (<3.10 pmol/L). Severity of cirrhosis of liver was determined by Child Pugh scoring system. 13 patients who were categorized in Child Pugh A had normal serum Free T3 levels. Out of 26 patients who were included in Child Pugh B, 2 had low serum free T3 level (<3.10 pmol/L). Remaining 11 patients who were categorized in Child Pugh C also had low serum free T3 level (< 3.10 pmol/L). Study showed that as the severity of cirrhosis increased from Child- Pugh A to C, serum Free T3 level decreased (p <0.001). In a study by Neeralagi *et al* [49], 6.3% patients were in Child Pugh class A, 37.3% in class B and 56.4 % in class C. In Child A class, mean Free T3 was 3.2 ± 0.4, in Child B class, 2.9 ± 0.7 and in Child C class, 2.3 ± 0.6. There was significant difference in Free T3 with respect to Child Pugh grade (p <0.001). In a study by Chaudhary et al[46], 56.36% were in Class C, 31.82 % were in Class B and 11.82% were in Class A. The majority of the patients belonged to CTP class C. The mean of serum free T3 in patients of CTP class A, B and C was 2.85±0.801 ,2.80 ± 0.994 and 2.31±0.642 (p=0.0048). Hence this study also showed a statistically significant difference in the mean serum free T3 among various classes of CTP score. In a study by Huang et al[45], 14.29% of CTP Class A, 51.02% of CTP class B and 34.69% of CTP class C had low free T3 levels (p<0.001). This study proposed that the low free T3 level correlated with poor prognosis. Takahashi et al[50] conducted a study on changes of thyroid hormones in various liver diseases, various thyroid parameters in liver disease where patients with acute hepatitis (AH), chronic persistent hepatitis (CPH) and chronic aggressive hepatitis (CAH) and Liver cirrhosis (LC) was compared with in normal controls (C). Serum T3 levels were elevated in CAH and reduced in liver cirrhosis (LC). Serum free T3 (FT3) levels reduced in CLD in order of CPH, CAH and LC. Serum free T3 levels also had a positive correlation with prothrombin time (PT) and serum albumin levels. Therefore serum FT3 level was considered as a sensitive index of liver damage. Agha et

al[9] measured thyroid hormones in 55 patients with liver cirrhosis where they found significantly decreased mean serum concentration of free T3 in patients with cirrhosis. T3/T4 ratio was also lower than the normal. This indicates an impaired liver conversion of T4 to T3 in peripheral tissues. There was an inverse correlation between with serum T3 and free T3 with serum bilirubin and a positive correlation with serum albumin. Free T3 and T3/T4 ratios were significantly low in patients who had ascites. This study confirms the presence of thyroid hormone abnormalities in cirrhosis of liver. Changes in serum T3 and free T3 levels correlate well with the severity of liver disease and may be useful in assessing the course and prognosis in cirrhotic patients. In a study by Joeimon *et al*[38], on thyroid dysfunction in patients with liver cirrhosis, hypothyroidism was seen in 24 out of 111 patients (21.6%). There was a decrease in serum free T3 in 12 patients out of 111 patients (10.8%). Of the 24 patients having hypothyroidism, 5 belonged to CTP A (17.8%), 11 belonged to CTP B (20.7%), and 8 belonged to CTP C (26.6%). In this study, as the severity of liver disease increased so did the CTP score. This study concluded that thyroid hormone abnormalities are associated with more advanced liver disease.

All of the above mentioned studies showed a significant negative correlation between serum free T3 with the CTP score. According to Takahashi *et al*, the abnormalities of serum levels of thyroid hormones are frequently found in liver diseases. The pattern of abnormalities may be observed according to the type of disease and its severity. Our study also showed statistical difference in the mean serum free T3 among various CTP classes and a statistically significant negative correlation between free T3 with the CTP score.

Our study was most consistent with that of El-Feki *et al*, Punekar *et al* and Kharb *et al*. There was no statistical significance in the mean serum free T3 between CTP class A and CTP class B in our study.

According to Mohamed Abdel-Fattah El-Feki *et al*, the lack of a statistically significant difference between CTP A and B was probably due to the fact that the patients were in the early stages of CTP A and CTP B. Hence, there was a significant correlation between free T3 with the severity of liver dysfunction as evidenced by the above findings.

Relationships of serum free T3 in males and females and also with various classes of Child Turcotte Pugh (CTP) based on gender:

In our study, the mean free T3 in male subjects was 2.76 ± 0.85 and in female subjects was 2.70 ± 0.71 (p=0.714). The results were not statistically significant after ANOVA test was done. The majority of male subjects were grouped under CTP class C (n=51) and the mean free T3 of male subjects under CTP class C , CTP class B and CTP class A was 2.23 ± 0.61, 3.33±0.63 and 3.59±0.62, respectively (p<0.01) . The result was statistically significant for males, following ANOVA test. Post-hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C(p<0.01), and also between CTP class B and CTP class C (p<0.01); but there was no statistical significance between CTP class A and CTP class B(p=0.23).The majority of female subjects were grouped under CTP class C (n=22) and the mean free T3 of female subjects under CTP class C , CTP class Band CTP class A was 2.50±0.56, 3.45±0.72 4.10, respectively (p=0.003) . The result was statistically significant for females, following ANOVA test. Post-hoc analysis also showed statistically significant difference in the mean serum free T3 levels between CTP class A and CTP class C(p=0.01) , and also between CTP class B and CTP class C (p<0.01); but there was no statistical

significance between CTP class A and CTP class B(p=0.47).

In a study by Chaudhary *et al*[46], the mean value of Free T3 was 2.53±0.78 pg/ml. The low level of free T3 was seen in 27 patients out of which 23 patients were male and 4 were female.

Relationship of serum free T3 with various etiologies of CLD and also with various classes of Child Turcotte Pugh Score (CTP) based on etiology:

In our study, the mean free T3 in subjects with alcohol related CLD was 2.72 ± 0.91, NAFLD related CLD was 2.89 ± 0.57, Chronic Hepatitis B related CLD was 2.59 ± 0.45, Chronic Hepatitis C related CLD was 1.90, Wilsons Disease related CLD was 2.90 ± 0.28 and Cryptogenic causes of CLD was 2.90 (p=0.823). However, the results were not statistically significant following the ANOVA test.

The mean free T3 in subjects with alcohol related CLD was 2.72 ± 0.91. In CTP class A of alcohol related CLD, the mean serum free T3 was 3.82 ± 0.59; CTP class B of alcohol related CLD, the mean serum free T3 was 3.44±0.74; CTP class C of alcohol related CLD, the mean serum free T3 was 2.24±0.63 (p<0.01). There was a statistically significant difference in the mean serum free T3 of patients with alcohol related CLD belonging to various CTP classes.

In a study by Neeralagi et al[49], which correlated the various thyroid hormones with Child Turcotte Pugh score in patients with liver cirrhosis due to alcohol, the mean free T3 in Child A group was 3.2 ± 0.4, in Child B group was 2.9 ± 0.7 and in Child C group was 2.3 ± 0.6. There was a significant difference in Free T3 with respect to Child Pugh grade.

In our study, the mean free T3 in subjects with NAFLD related CLD was 2.89 ± 0.57. In CTP class A of NAFLD related CLD, the mean serum free T3 was 3.3±0.46; CTP class B of NAFLD related CLD, the mean serum free T3 was 3.22±0.33; CTP class C of NAFLD related CLD, the mean serum free T3 was 2.52±0.54 (p=0.003). There was a statistically significant difference in the mean serum free T3 of patients with NAFLD related CLD belonging to various CTP classes.

In a study by Eshraghian et al[51], The mean Free T3 in those patients without NAFLD was 3.80 ± 0.73 and those with NAFLD was 4.09 ± 1.64 (p=0.06) There was no statistical significant difference between the participants with NAFLD and the participants without NAFLD.

In our study, the mean free T3 in subjects with Chronic Hepatitis B related CLD was 2.59±0.45. There were no cases of CTP class A Chronic Hepatitis B patients. There was only 1 case of Chronic Hepatits B CTP class B and the mean serum free T3 was 2.9; There were 6 cases of CTP class C Chronic Hepatitis B related CLD, and the mean serum free T3 was 2.53±0.46 (p=0.82). The results were not statistically significant after ANOVA test. The mean free T3 in subjects with Chronic Hepatitis C related CLD was 1.90, Wilsons Disease related CLD was 2.90 ± 0.28 and Cryptogenic causes of CLD was 2.90. El-Feki et al[42] observed that the lowest levels of serum free T3 were among the Child C group (1.4 ± 1.0), followed by the Child B group (1.9 ± 1.0), while the Child A group was within the normal range (2.5 ± 0.6). The results of this study showed that there was a statistically significant difference in the free T3 level between the groups (except between Child A and B) as follows: Child A, B, and C (P = 0.004); Child A and B (P = 0.078); Child A and C (P = 0.001); and Child B and C (P = 0.048).El-Sawy et al[40] found that the mean free T3 in patients with Hepatitis C related cirrhosis in CTP class A,B and C was 2.559 ± 0.687 , 2.334 ± 0.46 and 1.56 ± 0.35 (p value <0.0001) respectively. Hence the results were statistically significant.

Distribution and comparison of free T3 with complications of chronic liver disease

In our study, the majority of the subjects in the study group presented with grade 2 hepatic encephalopathy accounting for 18.3% of cases.12.5% of subjects had grade 1 hepatic encephalopathy and 5.83% of subjects had grade 3 hepatic encephalopathy. Only 2.5% of patients presented with grade 4 hepatic encephalopathy. 60.83% of subjects in the study group did not have hepatic encephalopathy (60.83%). The mean serum free T3 levels in grade 1 was 2.54 ±0.50; in grade 2 was 2.31 ±0.74; grade 3 was 1.76 ±0.40 and grade 4 was 1.83 ±0.31. The cases without hepatic encephalopathy had serum free T3 of 3.06 ± 0.77(p<0.01). The result was statistically significant for different grades of hepatic encephalopathy. Hence with an increase in the grade of hepatic encephalopathy there was a decrease in the mean serum free T3.

In a study by Verma et al[37], 52.94% had mild ascites, 17.65% had severe ascites and 29.41% patients had hepatic encephalopathy. Low free T3 was found with mild ascites (55.41%), severe ascites (22.97%), hepatic encephalopathy (36.49%). Patients with low free T3 levels were found to have a higher incidence of complications like ascites, hepatic encephalopathy. The correlation between low free T3 with severe ascites (p=0.022) and hepatic encephalopathy (p=0.011) was found to be statistically significant. The free T3 levels was significantly and negatively correlated with severe ascites. The low free T3 was also significantly related to hepatic encephalopathy. The findings in this study were in concordance with our study. In a case control study by Kayacetin et al[39], on low serum total thyroxine and free triiodothyronine in patients with hepatic encephalopathy due to non-alcoholic cirrhosis, 15 patients with hepatic encephalopathy (non-alcoholic cirrhosis) had a mean serum free T3 of 1.15±0.25. Compared to controls, patients with hepatic encephalopathy and decompensated cirrhotic patients (Child C group) showed a significant decrease in free T3 levels (2.76 ± 0.45pg/ml in control group vs 1.15 ± 0.25 and 1.61 ± 0.38 for free T3 respectively; p <0.05). Cirrhotic patients with hepatic encephalopathy had significantly reduced serum levels of free T3 compared to all cirrhotic patients (p <0.001). Punekar et al[36] found significantly low free T3 levels (P < 0.0001) in cirrhosis patients with hepatic encephalopathy compared to cirrhosis patients without HE. The levels of free T3 were significantly low in hepatic encephalopathy Grade 4 as compared to Grade 3, Grade 2, Grade 1, and cirrhotic patients without HE. Our study also showed similar findings with the above study where the serum free T3 levels decreased with an increase in the grade of hepatic encephalopathy. In a study by Huang et al [45], 47.27% patients presented with ascites out of which had mild ascites (5.97%) and severe ascites (41.3%). They also found low free T3 with mild ascites (5.10%), severe ascites (54.08%) and without ascites (52.73%).

Correlation of Free T3 with various parameters

In our study, there was a statistically significant negative correlation between serum free T3 with CTP score (r value: -0.69, p <0.01), total bilirubin (r value: -0.33, p=0.0002), PT (r value: -0.19, p=0.04), INR (r value: -0.46, p<0.01). There was a statistically significant positive correlation between serum free T3 only with serum albumin (r value: 0.29, p=0.001).

Vincken et al [47] found that free T3 had a statistically significant (positive) correlation with ALT (r value : 0.447 , p= 0.017) and albumin (r value : 0.403 , p =0.033) and a statistically significant (negative) correlation with Child–Pugh score(r value : −0.477, p= 0.010).Punekar et al[36] observed that serum free T3 was

negatively correlated with total leukocyte count s(TLC),total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), globulin, PT, blood urea, serum creatinine, and severity of liver cirrhosis (CTP and MELD score). El-Feki et al[42] found a statistically significant negative correlation between serum free T3 levels and ALT (r value: −0.3, p= 0.037) and also with serum total bilirubin (r value: −0.4, p value = 0.006). There was a statistically significant positive correlation between serum free T3 levels and Platelets (r value : −0.4, p= 0.005) , with albumin (r value : −0.5, p value = 0.001) and also with platelet count (r value: 0.5, p= 0.001).Neeralagi et al[49] observed negative correlation between Child Pugh score and Free T3 (r value: -0.516).In a study by Chaudhary et al [46], there was a statistically significant positive correlation between serum free T3 and AST , ALT and ALP (r value : 0.24 , 0.21, 0.22 respectively) and there was a statistically significant negative correlation between different Child Turcotte Pugh scores with the mean Free T3.Verma et al[37] found significant correlation between low free T3 levels and hyponatremia (p=0.004) and raised INR (p=0.038).

A few of the findings in the above studies were consistent with our study such as the statistically significant negative correlation of serum free T3 with Child Turcotte Pugh score, Serum total bilirubin and raised INR, and also statistically significant positive correlation between serum free T3 with serum albumin.

Limitations

1. Our study was an observational, cross-sectional study and hence, it could not show a causal relationship between serum free T3 and cirrhosis of liver.

2. Our study had taken into account only one prognostic score i. e, Child Turcotte Pugh score and not MELD score. As such, Child Pugh score does not take include many prognostic factors.

3. We did not take into account the mortality in our study.

4. Liver biopsy could not be done to confirm cirrhosis. We avoided liver biopsy as it is an invasive procedure.

5. The low free T3 state is regarded as an adaptive response to reduce the basal metabolic rate of the hepatocytes and hence preserve liver function.

As our study was an observational study, it could not determine whether these adaptive changes have a protective or a deleterious effect on the liver in patients with cirrhosis. Only prospective cohort studies with clinical outcomes can resolve this issue.

Conclusion

Our study showed that there was a statistically significant negative correlation between serum free T3 and the Child Turcotte Pugh (CTP) score. This feature of low free T3 in patients with chronic liver disease either may be a part of the “low T3 syndrome” or the “sick euthyroid syndrome” or may be regarded as an adaptive response to reduce the basal metabolic rate of the hepatocytes to preserve liver function. However, it is still a matter of discussion as to whether these adaptive changes have a protective or a deleterious effect on the liver in patients with cirrhosis. However, serum free T3 can be used as a marker of severity in patients with chronic liver disease, which should be evaluated as a part of the routine investigations.

References

1. Mansour-Ghanaei F, Mehrdad M, Mortazavi S, Joukar F, Khak M, Atrkar- Roush an Z. Decreased serum total T3 level in hepatitis B and C related cirrhosis by severity of liver damage. Ann Hepatol. 2012 Sep 1;11(5):667– 71.

2. Kamath PS, Shah VH. Overview of cirrhosis. In: Feldman M, Friedman LS, Brandt L. J., editors. Sleisenger amd Fordtran. 10th editi. Philadelphia : Saunders; 2002. p. 1254–60.

3. McCormick PA. Hepatic Cirrhosis. In: Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ, editors. Sherlock's Diseases of the Liver and Biliary System, 12th Edition. Wiley-Blackwell, A John Wiley and Sons, Ltd; 2011. p. 103–20.

4. Jameson J, Mandel S, Weetman A. Disorders of the Thyroid gland. In: Kasper D, Hauser S, Jameson J, Fauci A, Longo D, Loscalzo J, editors. Harrison's Principles of Internal Medicine Textbook. 19th editi. New York: McGraw-Hill Education; 2015. p. 2283–308.

5. Kelly GS. Peripheral metabolism of thyroid hormones: a review. Altern Med Rev. 2000 Aug;5(4):306–33.

6. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine seleno deiodinases. Endocr Rev. 2002;23(1):38–89.

7. Zafar MN, Rizvi SJ, Syed S. Thyroid hormone levels in hepatitis B. J Pak Med Assoc. 1992 Mar;42(3):56–7.

8. Gardner DF, Carithers RL, Utiger RD. Thyroid function tests in patients with acute and resolved hepatitis B virus infection. Ann Intern Med. 1982;96(4):450–2.

9. Agha F, Qureshi H, Khan RA. Serum thyroid hormone levels in liver cirrhosis. J Pak Med Assoc. 1989 Jul;39(7):179–83.

10. Green JRB, Snitcher EJ, Mowat NAG, Ekins RP, Rees LH, Dawson AM. Thyroid function and thyroid regulation in euthyroid men with chronic liver disease: evidence of multiple abnormalities. Clin Endocrinol (Oxf). 1977 Dec 1;7(6):453–61.

11. Yamanaka T, Ido K, Kimura K, Saito T. Serum levels of thyroid hormones in liver diseases. Clin Chim Acta. 1980 Feb 14;101(1):45–55.

12. Hepner GW, Chopra IJ. Serum thyroid hormone levels in patients with liver disease. Arch Intern Med. 1979 Oct;139(10):1117–20.

13. Guven K, Kelestimur F, Yucesoy M. Thyroid function tests in non-alcoholic cirrhotic patients with hepatic encephalopathy. Eur J Med. 1993 Feb 1;2(2):83–5.

14. Van Thiel DH, Udani M, Schade RR, Sanghvi A, Starzl TE. Prognostic value of thyroid hormone levels in patients evaluated for liver transplantation. Hepatology. 1985;5(5):862–6.

15. Hasselbalch HC, Bech K, Eskildsen PC. Serum Prolactin and Thyrotropin Responses to Thyrotropin-Releasing Hormone in Men with Alcoholic Cirrhosis. Acta Med Scand. 1981;209(1-6):37–40.

16. Garcia-Tsao G, Groszmann RJ, Fisher RL. Portal Pressure, Presence of Gastroesophageal Varices and Variceal Bleeding. Hepatology. 1985;5(3):419–24.

17. Eshraghian A, Taghavi SA. Systematic review: endocrine abnormalities in patients with liver cirrhosis. Arch Iran Med. 2014 Oct;17(10):713–21. a prospective population study. Hepatology. 1996 May;23(5):1025–9.

18. Stewart S, Day C. Alcohol and the liver. In: Dooley J, Lok A, Burroughs A, Heathcote E, editors. Sherlock's Diseases of the Liver and Biliary System. 12th ed. Oxford, UK: Wiley-Blackwell; 2011. p. 507–19.

19. Dawn M T, Stephen A H. Non-alcoholic fatty liver disease. In: Feldman M, Friedman LS BL, editor. Sleisenger and Fordtran's gastrointestinal and liver disease. 10th ed. Philadelphia: Elsevier; 2016. p. 1428–41.

20. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Can cado EL, et al. International

Autoimmune Hepatitis Group Report: Review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31(5):929–38.

21. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1):169–76.

22. Roberts EA. Wilson's Disease. In: Dooley J, Lok A, Burroughs A, Heathcote EJ, editors. Sherlock's diseases of the liver and biliary system. 12th ed. Oxford, UK: Wiley-Blackwell; 2011. p. 534–45.

23. Bruce Bacon, Robert Britton. Hemochromatosis. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 10th ed. Philadelphia: Elsevier; 2016. p. 1261–9.

24. Dahlan Y, Smith L, Simmonds D, Jewell LD, Wanless I, Heathcote EJ, et al. Pediatric-Onset Primary Biliary Cirrhosis. Gastroenterology. 2003;125(5):1476–9.

25. Kim WR, Lindor KD, Locke GR, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a U.S. community. Gastroenterology. 2000;119(6):1631–6.

26. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60 (8): 646 –9.

27. Ferenci P. Hepatic encephalopathy. Gastroenterol Rep. 2017 May 1;5(2):138–47.

28. Giorgio A, Amoroso P, Lettieri G, Fico P, de Stefano G, Finelli L, et al. Cirrhosis: Value of caudate to right lobe ratio in diagnosis with US. Radiology. 1986;161(2):443–5.

29. Sandford NL, Walsh P, Matis C, Baddeley H, Powell LW. Is ultrasonography useful in the assessment of diffuse parenchymal liver disease? Gastroenterology. 1985; 8 9(1):186–91.

30. Freeman MP, Vick CW, Taylor KJW, Carithers RL, Brewer WH. Regenerating nodules in cirrhosis: Sono graphic appearance with anatomic correlation. Am J Roentgenol. 1986;146(3):533–6.