ORIGINAL RESEARCH PAPER

General Medicine

A STUDY ON THYROID FUNCTION TESTS IN CIRRHOSIS OF THE LIVER AND THE IMPLICATION OF SERUM-FREE T3 AS A PROGNOSTIC INDICATOR

KEY WORDS:

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ABSTRACT

This study examined serum-free T3 as a predictive indicator and the thyroid function test in individuals with decompensated liver disease. This study looked at 50 individuals who had been identified as having liver cirrhosis using clinical, biochemical, ultrasonographic, histological, or endoscopic findings. To demonstrate the relevance of serum-free T3 as a prognostic predictor, thyroid function testing was performed on all patients, and the association between the results and the severity of liver disease was calculated. T3, FT3, and FT4 serum levels significantly inversely correlate with the degree of cirrhosis. When a person has liver cirrhosis, their level of FT3 can be used as a prognostic indicator because it is correlated with the severity of their liver disease. As a result, since hypothyroidism is linked to cirrhosis, all patients with the condition should have their thyroid function evaluated. These numbers can be used to gauge how severe cirrhosis is.

INTRODUCTION:

The liver is one of the most important organs in the body, and it is also the second-largest organ after the skin. The liver is responsible for maintaining metabolic homeostasis in the body, which includes the processing of dietary amino acids, carbohydrates, lipids, and vitamins, the removal of microbes and toxins from splanchnic blood en route to the systemic circulation, and endogenous waste product detoxification and excretion into bile. India is another location where improving prevention and control of liver cirrhosis risk factors is critical, with India accounting for nearly one-fifth (18.3%) of global liver cirrhosis mortality in 2010[1].

The relationship between the thyroid and the liver is intricate. The liver is a target organ for T3 and T4 action, manufactures thyroid hormone-binding proteins, stores a large amount of extrathyroidal thyroxine (T4) and triiodothyronine (T3), oversees the bulk of peripheral T4 and T3 transformation, and accounts for hormone degradation and excretion. 6 Triiodothyronine is produced as a result of the liver's selenium-dependent 5' deiodinase (T3). The phenolic ring of thyroxine (T4) is also deiodinated by a selenium-independent enzyme to produce the hormonally inactive reverse T3 (rT3). 7 Patients with the chronic liver illness have different levels of thyroid hormone and thyroid-binding proteins. In people with liver cirrhosis, low free T3 syndrome is characterized by high rT3, low T3, and a decreased T3:T4 ratio. Low T3 levels may be an adaptive thyroid response to lower hepatocyte's basal metabolic rate and protect liver function[2-4].

A wide variety of systemic disorders can affect both organs, and thyroid and liver diseases can both impair each other's functions. The most prevalent thyroid hormone profiles in people with cirrhosis are low total and free T3 and elevated rT3, reflecting decreased deiodinase type 1 activity, which results in less T4 to T3 conversion. The rT3 to T3 ratio increases as a result of the deiodinase type 3 system's improved ability to convert T4 to rT3. The plasma T3/rT3 ratio exhibits a negative connection with the severity of cirrhosis in non-alcoholic cirrhotics. Since T3 and rT3 bind to the same plasma proteins, the T3/rT3 ratio offers a measure of liver function that is unrelated to protein binding. The T3/rT3 ratio and free T3 levels in plasma both have predictive value and correlate with liver function in cirrhosis, but they are rarely used. Cirrhosis of the liver may affect several hormones, including thyroid hormone due to iodination defects, glucocorticoids and gonadal steroids due to conjugation issues, and insulin and glucagon due to deamination faults.

Long-term evidence of an association between chronic liver disorders and thyroid changes has been recorded, however, the results are mixed. Most studies have focused on cirrhosis caused by alcohol or primary biliary cirrhosis, and the incidence of thyroid changes in cirrhosis about the aetiology of liver disease has yet to be determined[5-6].

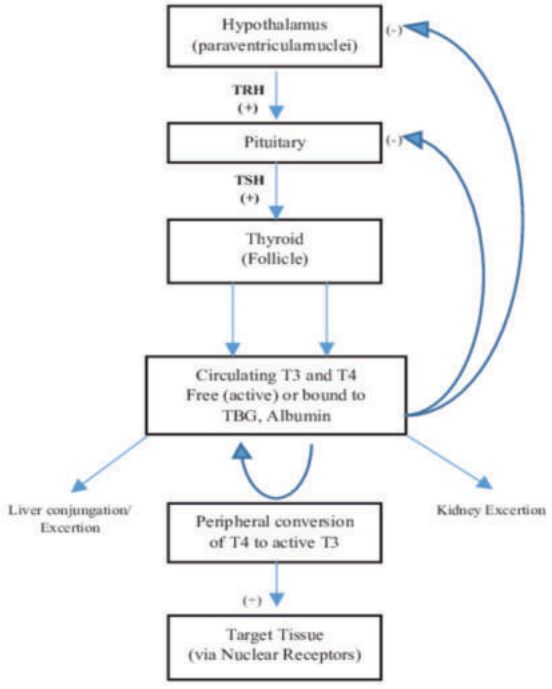

Figure 1 *Regulation Of Thyroid Hormones*

AIMS AND OBJECTIVES:

Aim:

The current study aims to analyze the thyroid function test in patients with decompensated liver disease, as well as the implications of serum-free T3 as a prognostic predictor.

Objectives:

To investigate thyroid function tests in patients with decompensated liver disease.

To see if serum-free t3 is useful as a prognostic biomarker in decompensated liver disease.

MATERIALS AND METHODS:

This is a descriptive, cross-sectional study. The Source of data is patients who got admitted to general medical and medical gastroenterology wards in the government general hospital, Kurnool. Simple randomization is done. The sample size is 50. The study is done for 18 months duration from December 2019 to June 2021.

Inclusion Criteria:

Patients who had been diagnosed with the decompensated chronic liver disease were based on clinical evidence of decompensation/varices, radiological evidence of nodularity of the liver, or collaterals in chronic liver disease, and biochemical and ultra-sonographic findings.

Exclusion Criteria:

Patients with cardiac failure, Patients with chronic kidney disease, Patients with pre-existing thyroid dysfunction (hypo/hyperthyroidism) and Patients who are terminally ill.

Procedure:

The hospital's Ethics Committee approved the study protocol, and informed consent was taken from all included patients. The current disease, previous illnesses, and personal history were all meticulously documented. A full physical exam, demographics, and systemic measurements were performed.

The thyroid hormones were correlated with the severity of liver disease by assessing hepatic encephalopathy, ascites, bleeding, total bilirubin, Albumin, INR, Child-Turcotte-Pugh (CTP) score and MELD score.

Standard laboratory tests including CBC, Liver and Renal function, and other biochemical tests were performed in all cases.

To test the mean difference between the two groups, Student's t-test was used. To test the correlation between the groups, Pearson's correlation test was used. To test the mean difference between three or more groups, the ANOVA test was used. ROC curve was used and to measure how well a parameter can distinguish between two diagnostic groups, the area under the ROC curve (AUC) was used. Statistical significance was defined as a P-value greater than 0.05. SPSS 23.0 was used for statistical analysis (IBM, Chicago, Illinois).

RESULTS:

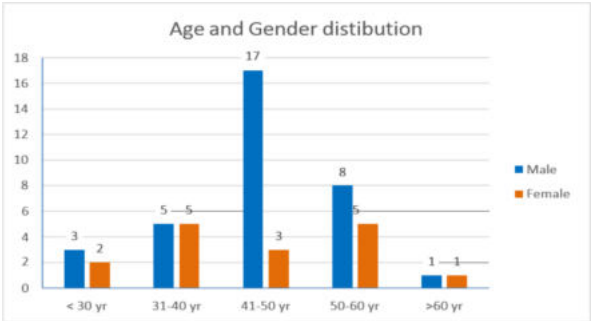

Figure 2 *Age Distribution*

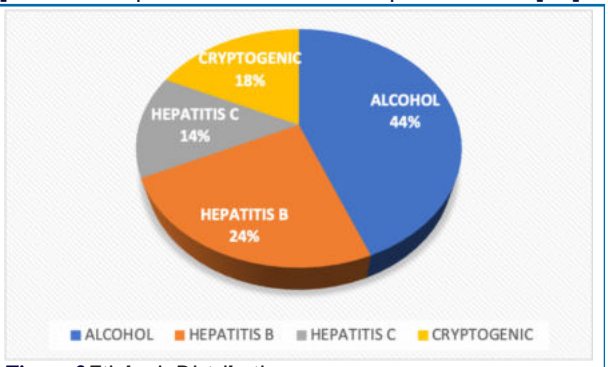

Figure 3 *Etiologic Distribution*

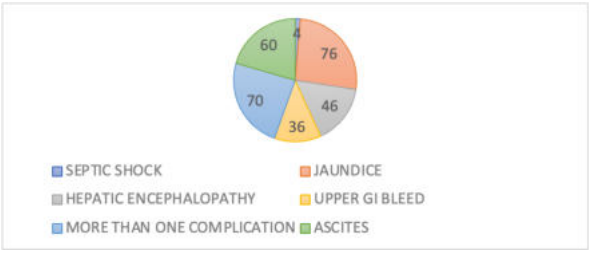

Figure 4 *Complications*

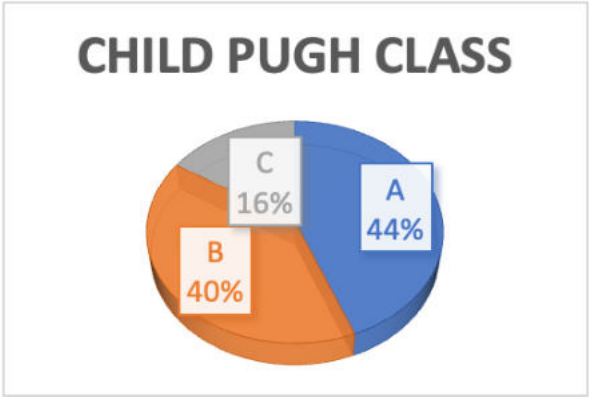

Figure 5 *Child-pugh Classification*

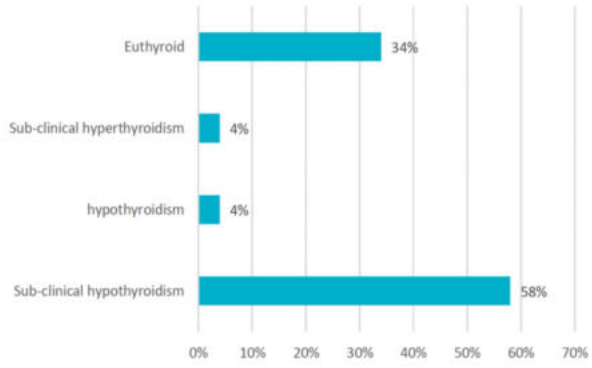

Figure 6 *Thyroid Status*

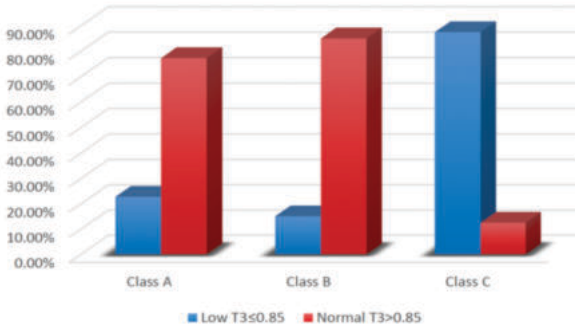

FIGURE 7 *Relation Between Child PUGH Class And T3*

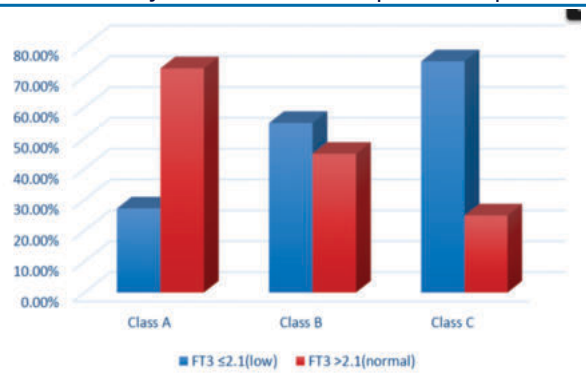

FIGURE 8 *Relation Between Child PUGH Class And fT3*

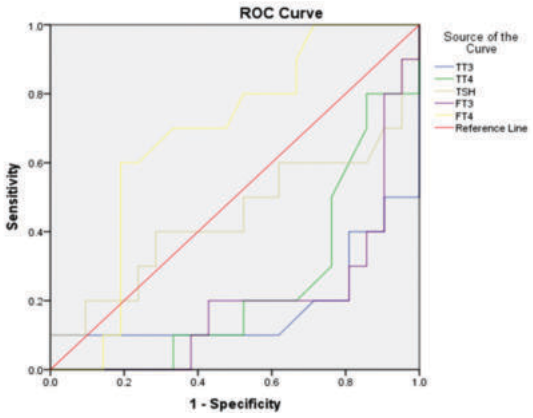

FIGURE 9 *Comparison of the Area Under ROC curves (AUC) of TT3, TT4, TSH, fT3 and fT4 of severe CTPS group for predicting the risk of mortality*

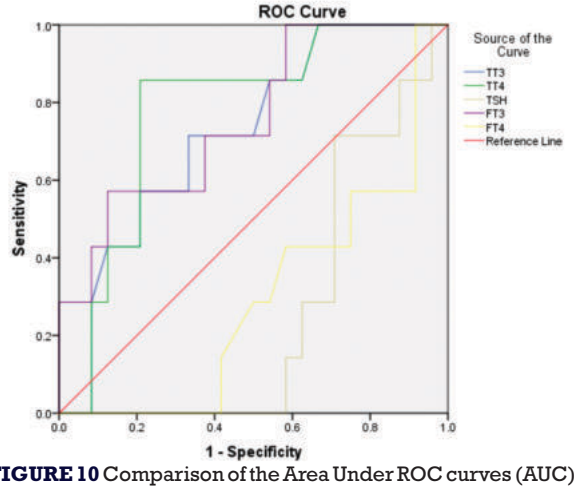

FIGURE 10 Comparison of the Area Under ROC curves (AUC) of TT3, TT4, TSH, fT3 and fT4 of severe CTPS group for predicting the risk of mortality

DISCUSSION:

In the current study, we examined the relationships among the thyroid profile, CTP class, ascites grades, encephalopathy grades, and several laboratory parameters in cirrhosis patients.

AGE: The age range in the present study is 28 to 61 years, with the mean age standard deviation of 31 patients being 46.36 9.395 years. The average age of women was the same as that of men (46.44178.6521 years), at 46.18711.1188. The age difference between girls and boys, however, is not statistically significant (P = 0.98, not significant). So it was observed that the thyroid hormone profile in women did not differ from men in patients with liver cirrhosis.

ETIOLOGY AND COMPLICATIONS:

In etiologies, most cirrhotic cases are due to alcohol in 22 cases, followed by Hepatitis B in 12 cases. Hepatitis C was found in 7 instances, while cryptogenic aetiology was found in 9 cases.

In this study, 18 (36%) patients had upper gastrointestinal bleeding, 30 (60%) patients had ascites, 23 (46%) patients had hepatic encephalopathy, and 38 patients had jaundice, respectively. There were no ascites in 40% of the patients, mild ascites in 32%, moderate ascites in 20%, and severe ascites in 8% of the patients. There was encephalopathy in 54% of patients, 20% of whom had grade 1 hepatic encephalopathy, 14% had grade 2 encephalopathies, 8% had grade 3 encephalopathies, and 4% had degree 4 encephalopathies.

CTPS GROUPS: In the present study, 22(44%) patients are Mild class (A), 20 (40%) patients are moderate class (B) and 8 (16%) patients are severe class (C) in the CTPS group. This indicates that most of the patients in our study were in various stages of decompensated liver cirrhosis. In the present study, the mean age of a severe group of the CTPS group is higher (58.37±3.42yr) than the moderate group (50±5.428967yr) and the mild group (38.68±6.785042yr).

Only two of the participants in our study reported clinical signs and symptoms of hypothyroidism. Subclinical hypothyroidism was found in 58% of cirrhosis patients, while hypothyroidism was found in 4% of cirrhosis patients. As a result, the thyroid profile is altered in patients with liver cirrhosis, but clinical euthyroidism is always maintained.

fT3 LEVELS: In the current study, the CTPS group had 22 (44 percent) mild, 20 (40 percent) intermediate, and 8 (16 percent) severe patients. For the CTPS group, the mean free T3 value is considerably lower in the severe group (1.52250.5116) compared to the moderate group (2.15250.83374) and the mild group (3.081.12) (P = 0.007, Significant). It is seen that as the CTPS group's severity level rises, the mean value of free T3 tends to fall. We discovered an inverse relationship between free T3 levels and the Child-Pugh class, and earlier research also pointed to outcomes that were similar[7-8].

Table 1 Comparision Of CTPS Groups With Other Studies

CTPS Group	Mild (Group A)	Moderate (Group B)	Severe (Group C)
El-Feki et al. (2016)	2.5 ± 0.6	1.9 ± 1.0	1.4 ± 1.0
Punekar et al. (2018)	1.9 ± 0.00	2.20 ± 0.55	1.80 ± 0.53
Present study	3.08± 1.12	2.1525± 0.83374	1.5225±0.5116

TT3 LEVELS:

In the present study, the mean value of the total T3 of the severe group is significantly lower (0.89±0.32) than the Moderate group (1.07±0.19) and the mild group (1.261±0.36) [P = 0.01, Significant] for the CTPS group. It is observed that the level of severity of the CTPS group is increasing then the mean value of TT3 is decreased. A study by Govindan NP et al[9] reported the Means of T3 in CPS A, CPS B and CPS C were 1.26 ± 0.26, 1.06 ± 0.27 and 0.87 ± 0.27 respectively and the difference in means was statistically significant with a p-value of 0.001.

Table 2 Comparision Of FT4 With Other Studies

CTPS Group	Mild (Group A)	Moderate (Group B)	Severe (Group C)
El-Feki et al. (2016)	1.1 ± 0.4	1.3 ± 0.9	0.7 ± 0.4
Patira et al. (2017)	28.89%	57.78%	13.33%
Punekar et al. (2018)	0.76 ± 0.00	1.44 ± 0.54	1.17 ± 0.51
Present study	1.42 ± 0.59	1.14 ± 0.327	0.97 ± 0.29

FT4 LEVELS:

In the current study, the severe group's mean fT4 value was greater (0.97 0.29) than those of the moderate (1.14 0.327) and mild (1.42 0.59) groups (P = 0.308, Not Significant) for the CTPS group. The mean value of fT4 is shown to grow when the severity level of the CTPS group increases.

TT4 LEVELS:

The mean total T4 value for the severe group in this study is substantially lower (6.68 1.10) than for the moderate group (7.70 1.66) and the mild group (8.76 2.15) for the CTPS group (P = 0.029, Significant). It is seen that when the severity level of the CTPS group rises the mean value of TT4 appears to be declining.

TSH LEVELS:

In this study, the mild group's mean TSH value is higher (4.29 1.29) than that of the severe (3.83 1.59) and moderate (3.98 0.489) groups. It demonstrates, however, that there is no statistically significant difference in the TSH group's means [P = 0.121, Not Significant].

Table 3 Comparision Of TSH For CTPS Groups With Other Studies

CTPS Group	Mild (Group A)	Moderate (Group B)	Severe (Group C)
El-Feki *et al.* (2016)	1.5 ± 1.2	3.3 ± 3.1	18.1 ± 14.3
Punekar *et al.* (2018)	4.41 ± 0.00	3.68 ± 1.64	4.34 ± 1.71
Present study	4.29 ± 1.29	3.98 ± 0.489	3.83 ± 1.59

Table 4 Correlation Of Thyroid Profile And CTPS With Other Studies

	Correlation value (r) [P Value]				
Thyroid profile	Tt3	TT4	fT3	fT4	TSH
Mansour-Ghanaei *et al.* (2012)[52]	-0.453 [<0.0001]	-0.172 [0.175]	-0.09 [0.481]	-0.06 [0.639]	0.294 [0.018]
Tas *et al.* (2012)	-	-	-0.669 [<0.001]	-0.376 [<0.001]	-0.01 [0.920]
Present study	-0.447 [0.012]	-0.398 [0.027]	0.470 [0.008]	0.203 [0.274]	0.146 [0.434]

Area Under Curve (ROC) Values Of Thyroid Profile For CTPS:

When ROC values for the mild CTPS group's TT3, TT4, fT3, and fT4 were compared in the current study, it was discovered that TT4 (AUC = 0.777, P = 0.028 [Sig.]) is substantially more accurate than fT3 (AUC = 0.756, P = 0.042 [Sig.]). However, TT3 (AUC = 0.746, P = 0.085 [Not Sig.]), TSH (AUC = 0.466, P = 0.749 [Not Sig.]), and FT4 (AUC = 0.376, P = 0.246 [Not Sig.]) are similarly having higher AUC values, but they do not demonstrate a meaningful outcome for determining the risk of death in the mild CTPS group.

MELD Score:

In the MELD group, 22 (44%) patients are in the MELD score ≤ 9 groups, 18 patients are in the MELD score 10-19, 8 patients are in the MELD score 20-29, and 2 patients are in the MELD score 30-35 group, respectively.

Table 5 Correlation Of Thyroid Profile For Meld In Other Studies

	Correlation value (r) [P Value]				
Thyroid profile	TT3	TT4	fT3	fT4	TSH
Mansour-Ghanaei *et al.* (2012)[52]	-0.305 [0.014]	-0.204 [0.106]	-0.058 [0.647]	-0.138 [0.279]	-0.016 [0.903]
Tas *et al.* (2012)	-	-	-0.594 [<0.001]	-0.256 [0.008]	0.046 [0.64]
Punekar *et al.* (2018)	-	-	-0.30 [0.003]	-0.23 [0.02]	0.39 [0.0001]
Present study	-0.539 [0.0020	-0.389 [0.03]	-0.535 [0.002]	0.035 [0.850]	0.072 [0.702]

With the exception of TSH [r value = 0.072, P value = 0.702 (Not Sig.),] there is a substantial negative association between TT3 [r value = - 0.539, P value = 0.002], TT4 [r value = -0.389, P value = 0.03], and fT3 [r value = - 0.535, P value = 0.002]. and fT4 in the MELD group [r value = 0.035, P value = 0.850 (Not Sig.)].

MELD AND FT3:

There was a substantial inverse relationship between MELD score and free T3 levels in our study (p=0.01), which was also supported by Tas A et al. when MELD 20 was used as a cutoff for separating the more severe disease from less severe disease. In our study, two groups were created based on the MELD scores, with group 1 comprising 62.7 per cent (n=64) of the patients and a MELD score of 20. In agreement with Dehghani SM et al., we also found a strong inverse connection between free T4 levels and MELD score (p=0.01). The most likely culprit is type 3 deiodinase, which converts free T4 to rT3 more frequently. In line with other research, we found no connection between TSH and MELD scores that were statistically significant.

FREE T3 IMPLICATIONS ON CIRRHOSIS:

According to the findings of the current study, ascites, hepatic encephalopathy, and bleeding varices are more common in patients with low fT3 levels. It was determined that there was a statistically significant connection between low fT3 and severe ascites (p=0.03) and hepatic encephalopathy (p=0.02). There was no discernible link between free T4 and TSH levels and the side effects of liver cirrhosis.

T3 AND ETIOLOGY:

In the current study, patients with hepatitis B-related cirrhosis had low free T3 levels in 58.33 percent (n=7/12) of cases, and those with hepatitis C-related cirrhosis in 42.85 percent (n=3/7) of cases, those with alcoholic cirrhosis in 31.88 percent (n=7/22) of cases, and those with cryptogenic cirrhosis in 66.67 percent (n=6/even though a higher percentage of individuals with cryptogenic cirrhosis had low free T3, this distinction was not statistically significant. TSH levels and free T4 levels did not differ in a statistically meaningful way.

IMPLICATION OF SERUM-FREE T3 AS A PROGNOSTIC INDICATOR:

Patients with low fT3 were more common in people with liver cirrhosis (p-value 0.001). The mean serum fT3 was lowest in decompensated patients (2.46181.0967), with a p-value of 0.001. The development of liver cirrhosis was observed to be independently correlated with low FT3, ascites, and encephalopathy (OR 95 percent CI: 1.1, 2.1 - 4.4). The degree of liver disease and the decline of liver function are significantly negatively correlated with FT3. FreeT3 concentration levels typically show a statistically significant link with the stage of chronic liver disease and can predict how far along the disease will develop.

CONCLUSION:

Men predominate over women. The mean value of TT3 decreases as the severity level of the CTPS group increases. The mean value of TT4 decreases as the severity level of the CTPS group increases. The mean value of fT3 decreases as the severity level of the CTPS group increases. The mean value of fT4 drops as the severity level of the CTPS group increases. For the severe CTPS group, TT4 has a much higher level of sensitivity, followed by fT3 and TT3. For the mild CTPS group, the level of sensitivity is noticeably higher in TT4 and fT3. With a statistical p-value of 0.008, fT3 demonstrated a significant correlation R-value of -0.470.

The progression of liver disease and the severity of liver disease are significantly negatively correlated with fT3. The MELD group's severity level is rising while TT3 and TT4's mean values are declining.

When compared to the mean value of fT3 and fT4, which decreased, the MELD group's severity level is growing. For the mild CTPS group, the level of sensitivity is noticeably higher in TT4 and fT3. With a statistical p-value of 0.008, fT3 demonstrated a significant correlation R-value of -0.470. The progression of liver disease and the severity of liver disease are significantly negatively correlated with fT3. The MELD group's severity level is rising while TT3 and TT4's mean values are declining. When compared to the mean value of fT3 and fT4, which decreased, the MELD group's severity level is growing. To evaluate the severity and prognosis of liver illnesses in all patients, thyroid function testing can be done. It was determined that lower free T3 levels were linked to more severe liver injury.

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