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# The Relationship of Thyroid Hormones Levels with the Liver Cirrhosis Prognosis Criteria and Complications: A Cross-Sectional Study

**Fateme Ziamanesh[1], Mohammad Sadeghi[2], Foroogh Alborzi Avanaki[3]*, Mohammad Taher[3,4], Hesam Aldin Varpaei[5], Soghra Rabizadeh[6], Hediyeh Imannejad[7], Najme Aletaha[3] and Arash Mirolyaee[3]**

[1]*School of Medicine, Tehran University of Medical Sciences, Iran*

[2]*Department of Internal Medicine, School of Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Iran*

[3]*Division of gastroenterology & Hepatology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Iran*

[4]*Liver Transplantation Research Center, Tehran University of Medical Sciences, Iran*

[5]*College of Nursing, Michigan State University, USA.*

[6]*Endocrinology and metabolism research center, Vali-Asr Hospital, Tehran University of Medical Sciences, Iran*

[7]*Tehran University of Medical Sciences, Iran*

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***Corresponding author:** Foroogh Alborzi Avanaki, Division of gastroenterology & Hepatology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran, Email: falborzi@sina.tums.ac.ir

## Abstract

**Background:** Impact of thyroid function on the prognosis and complications of liver cirrhosis remains unclear. Therefore, the aim of this study was to determine the relationship of thyroid hormones with cirrhosis prognosis and complications.

**Methods:** This cross-sectional study was conducted from March 2021 to March 2022 at the Imam Khomeini Hospital in Iran. A total of 100 cirrhotic patients, aged 18 to 80, were recruited. The questionnaire designed for collecting data included patients' demographics, laboratory data, and criteria for cirrhosis progression.

**Results:** The study revealed a significant correlation between MELD and FT3 (p=0.019). For each unit increase in FT3, the MELD score is expected to decrease by approximately 2.268 units. In males, there was a correlation between MELD and FT3 (p=0.033). Additionally, in females, there was a correlation between MELD and FT4 (p=0.03). MELD had a significant correlation with ascites and hepatic encephalopathy. Furthermore, a significant relationship was found between FT3 and ascites and esophageal varices. Results of analysis of the relationship between FT3 and MELD components revealed a significant correlation between FT3 and bilirubin (p=0.001). Moreover, an inverse relationship was between TSH and INR (p=0.03). High FT3 levels were found to be 15 times more frequent in Child-Pugh A and B patients compared to Child-Pugh C patients.

**Conclusion:** FT3 is correlated with the MELD score and the complications of cirrhosis. The value of FT3 can serve as a prognostic criterion. It is recommended to monitor thyroid levels in patients with cirrhosis and provide treatment if any disorder is detected.

**Keywords:** Cirrhosis; Thyroid; MELD; Child-Pugh score; Thyroid hormones; Prognosis

**Abbreviations:** NAFLD: Nonalcoholic Fatty Liver Disease; MELD: Model for End-Stage Liver Disease; TBG: Thyroid-Binding Globulin; PSC: Primary Sclerosing Cholangitis; UC: Ulcerative Colitis; NASH: Nonalcoholic Steatohepatitis; AIH: Autoimmune Hepatitis plasia 2B

## Introduction

Chronic liver damage can lead to a condition known as cirrhosis, which is characterized by regenerative nodules and diffuse liver fibrosis [1,2]. Cirrhosis is the end stage of chronic liver disease [3]. It is often the result of various diseases such as alcohol consumption, nonalcoholic fatty liver disease (NAFLD), hepatitis viruses, and autoimmune diseases [4]. Progression of cirrhosis includes asymptomatic stages such as compensated cirrhosis, or decompensated stages, which could cause several complications including ascites, gastroesophageal variceal hemorrhage, and hepatic encephalopathy [5,6]. Child-Pugh and model for end-stage

liver disease (MELD) scores are commonly used to evaluate the outcome of cirrhosis [7,8]. In severe cases, cirrhosis can lead to liver failure and death, which is a significant burden on global public health due to the high mortality and morbidity rates [9,10].

There is an important relationship between the liver and the thyroid gland. So, disorders of these two organs interact with each other [11,12]. Thyroid hormones are crucial for cell growth, differentiation, and metabolism in the body, especially in the liver, and they have effects on liver fat homeostasis and bilirubin metabolism. Hypothyroidism increases the risk of diseases such as NAFLD. A low level of free triiodothyronine (FT3) is considered an independent criterion for mortality in diseases like myocardial infarction, renal disease, and NAFLD [13,14]. On the other hand, the liver has a vital impact on the metabolism of thyroid hormones like synthesis, excretion, peripheral deiodination, and thyroid-binding globulin (TBG) production [15]. A cirrhotic liver reduces the conversion of thyroxine (T4) to triiodothyronine (T3), due to the decrease in the activity of the deiodinase enzyme in the liver [16].

Until now, many studies have investigated the relationship between chronic liver disease and thyroid hormone levels. However, limited data on cirrhotic patients are available, especially on the prognosis of cirrhosis and complications such as esophageal varices, hepatic encephalopathy, and ascites [17]. Therefore, we assess the relationship of FT3 with MELD, Child-Pugh score, hepatic encephalopathy, ascites, and esophageal varices. If there was an association with MELD score, we would conduct further analysis to specify which component of MELD score has an association with FT3.

## Methods

### Study design

This was a cross-sectional study conducted March 2021 to 2022 in Imam Khomeini Hospital Complex, Gastroenterology and liver disease clinic, Tehran, Iran.

### Data collection

A researcher designed a questionnaire to collect data for this study. The questionnaire includes patients' demographics as well as laboratory data such as thyroid hormone levels, liver enzymes, and criteria for liver disease progression.

### Cirrhosis diagnosis

Cirrhosis was verified by two gastroenterologists by CBC, liver function test and radiologic testing like ultrasound. In the case of incomplete information in the patients' medical records, we contacted the patient by phone. This approved institutional review board (IRB) of Tehran University of Medical science (IR.TUMS.IKHC.REC.1400.165).

### Participants

All cirrhotic patients aged 18 to 80 were eligible to be recruited for this study. Patients were excluded from the study if they were younger than 18 years old or older than 80 years old, had a history of thyroid malignancy, had taken thyroid hormone medications in the last three months, had taken anti-thyroid medications in the last three months, or had a history of simultaneous severe disease in other organs.

### Statistical analysis

Data was analyzed using IBM SPSS version 26 software, which qualitative data analyzed using the chi-square test and quantitative data analyzed using the t-test. The Pearson correlation test used to measure the strength and direction of the linear relationship between MELD score and TSH, T3, T4, FT3, and FT4.Multilinear regression is a statistical modeling technique used to understand the relationship between MELD score and TSH, T3, T4, FT3, and FT4.

## Results

100 subjects were included in the study; 63 were men and 37 were women. The mean age of the patients was 48 years. The age, MELD score, and laboratory data details are described in table 1.

26 subjects had Child-Pugh A, 46 Child-Pugh B, and 28 Child-Pugh C. Thirty-five participants had no history of ascites, 27 had a history of mild ascites, and 38 had a history of moderate to severe ascites leading to paracentesis. 39 patients had no history of varices, 18 had grade F1 varices, and 43 had grade F2 to F3 varices leading to band ligation. Sixty-six patients had no history of encephalopathy, 22 had a history of grade 1 and 2 of encephalopathy, and 12 had a history of grade 3 and 4 of encephalopathy.

The etiology of cirrhosis in patients varied: 37 individuals had cryptogenic cirrhosis, 17 had cirrhosis due to primary sclerosing cholangitis (PSC) and ulcerative colitis (UC), 13 had cirrhosis due to HBV and HCV, 11 had cirrhosis due to nonalcoholic steatohepatitis (NASH), 10 had cirrhosis due to autoimmune hepatitis (AIH), and 2 had cirrhosis due to Wilson disease.

The study showed a significant correlation between MELD and FT3 (p=.019), whereas the correlation between MELD and FT4, total T3, total T4, and TSH was not significant. Based on gender classification, there was a significant correlation between MELD and FT3 in males, with (p=.0330). In female subjects, there was a correlation between MELD and FT4 (p=.03). Other hormones had no significant correlation with MELD in males and females (Table 2). Subjects were divided into two groups based on the MELD score: those over 16 who are candidates for liver transplantation and those under 16, and among thyroid hormones, there was a significant correlation only between FT3 and MELD (P=.03).

Among the components of MELD, a strong correlation was found between FT3 and bilirubin (p=.001). There was also an inverse relationship between TSH and INR (p=.03) (Table 3). MELD score and FT3, showing a statistically significant small negative correlation (r = -0.292, p = 0.019). This means that as the MELD score increases, there is a tendency for FT3 levels to decrease, albeit


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to a modest degree. There was a significant relationship between FT3 and ascites and varices, but no significant relationship with encephalopathy (Table 4).

In the study, MELD was significantly correlated with ascites and hepatic encephalopathy, but there was no significant association with varicose veins (Table 5).

**Table 1:** Demographics, laboratory data, and MELD score in patients.

| Variables | Mean ± Standard Deviation |
|---|---|
| Age | 48.05±13.284 |
| MELD | 14.26±5.080 |
| TSH (mIU/L) | 2.78742±1.739656 |
| T3 (nmol/L) | 1.3130±0.56467 |
| T4 (µg/dL) | 7.9349±2.35014 |
| FT3 (pg/mL) | 2.5978±0.61616 |
| FT4 (ng/dL) | 1.0932±0.25799 |
| Bilirubin (mg/dL) | 2.9000±2.55887 |
| INR | 1.4074±0.37615 |
| Albumin (g/dl) | 3.6321±0.62981 |
| Creatinine (mg/dl) | 1.1509±1.29087 |
| Na (meq/dl) | 138.742±3.2861 |

**Table 2:** Association between thyroid hormones and MELD in the total population, male, and female.

| Thyroid Hormones | P Value | | |
|---|---|---|---|
| | All (n=100) | Male (n=63) | Female (n=37) |
| FT3 | 0.019 | 0.033 | 0.301 |
| FT4 | 0.14 | 0.68 | 0.03 |
| T4 | 0.246 | 0.824 | 0.06 |
| T3 | 0.99 | 0.093 | 0.069 |
| TSH | 0.658 | 0.593 | 0.863 |

P value<0.0 5 was considered statistically significant.

**Table 3:** Relationship of thyroid hormones with components of MELD.

| | Bilirubin | INR | Albumin | Creatinine | MELD |
|---|---|---|---|---|---|
| FT3 | 0.001 | 0.615 | 0.088 | 0.387 | 0.019 |
| TSH | 0.423 | 0.03 | 0.572 | 0.647 | 0.658 |
| T3 | 0.089 | 0.917 | 0.492 | 0.379 | 0.99 |
| T4 | 0.2 | 0.651 | 0.26 | 0.11 | 0.246 |
| FT4 | 0.851 | 0.951 | 0.972 | 0.48 | 0.14 |

P value<0.0 5 was considered statistically significant.

**Table 4:** Association of FT3 with cirrhosis complications.

| Cirrhosis Complications | P Value |
|---|---|
| Ascites | 0.033 |
| Varicose veins | 0.046 |
| encephalopathy | 0.248 |

P value<0.0 5 was considered statistically significant.



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**Table 5:** Association between MELD and cirrhosis complications.

| P Value | Subgroups* | Cirrhosis Complications |
|---|---|---|
| 0.003 | None and moderate to severe | Ascites |
| 0.17 | None and F2 to F3 | Varicose veins |
| 0.002 | None and grades 3 to 4 | Hepatic encephalopathy |

P value<0.0 5 was considered statistically significant. *Subgroups which their means were compared and their association with MELD analyzed.

There was no significant association between thyroid hormones and Child-Pugh. For more assessment of the association between FT3 and Child-Pugh, FT3 was first divided into four categories. In Child A, the group with a low FT3 was the lowest, and in Child C, the group with a high FT3 was the lowest. When the association between Child-Pugh and FT3 was assessed on the basis of age and sex adjustment, high FT3 was 15 times more common in Child-Pugh A and B than in Child C.

The multilinear regression analysis table 6 suggests that there is a statistically significant negative relationship between FT3 and the MELD score. Specifically, for each unit increase in FT3, the MELD score is expected to decrease by approximately 2.268 units after controlling for the other independent variables in the model. On the other hand, the p-values for the other independent variables (TSH, T3, T4, and FT4) were greater than 0.05. This indicates that there was insufficient evidence to suggest a significant relationship between these variables and the MELD score in this analysis (Figure 1).

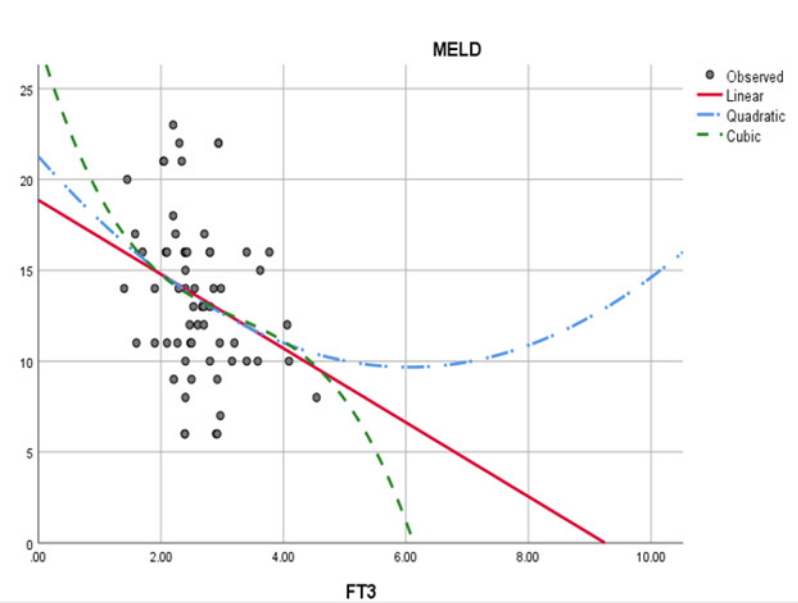


**Figure 1:** Linear relationship between MELD scores and FT3, then MELD scores = 18.86 – 2.04 (FT3) level, R2=.085, p=.019.

**Table 6:** Multiple linear regression to predict MELD score.

| | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. | 95.0% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| Overall model | 18.187 | 4.19 | | 4.341 | 0 | 9.772 | 26.603 |
| TSH | -0.204 | 0.384 | -0.072 | -0.531 | 0.598 | -0.976 | 0.568 |
| T3 | 0.804 | 1.465 | 0.088 | 0.549 | 0.586 | -2.138 | 3.746 |
| T4 | -0.361 | 0.321 | -0.155 | -1.125 | 0.266 | -1.007 | 0.284 |
| FT3 | -2.268 | 1.078 | -0.33 | -2.104 | 0.04 | -4.433 | -0.103 |
| FT4 | 3.404 | 2.751 | 0.169 | 1.238 | 0.222 | -2.121 | 8.93 |


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## Discussion

Thyroid hormone levels are associated with chronic disease, which both overproduction and underproduction contribute to the development of chronic diseases. They have effects on several metabolic pathways in the body, including insulin resistance, lipid metabolism, and inflammation. While the exact mechanism by which thyroid hormones affect chronic diseases has still been studied [18,19].

Previous studies have shown that thyroid dysfunction is associated with liver disease, lung and kidney malignancies, severe systemic diseases, fasting, malnutrition, trauma, and acute infections [20]. Individuals with hypothyroidism and hyperthyroidism are at higher risk for developing cardiovascular disease. Subclinical hypothyroidism, particularly in individuals with TSH > 10 mIU/L, is associated with an increased risk of coronary heart disease and mortality [21]. The regulation of glucose metabolism is a crucial function of the thyroid hormone, and its imbalances contribute to the development of metabolic disorders such as type 2 diabetes [22]. During pregnancy, thyroid dysfunction and autoantibodies can predict pregnancy complications and maternal morbidity in later life [23]. Additionally, both hyperthyroidism and hypothyroidism have been associated with an increased risk of fractures, particularly in the hip and spine [24]. Dysregulation of the thyroid-brain axis may also contribute to mood disorders in individuals with thyroid disorders [25]. Hypothyroidism can lead to neuropsychiatric symptoms, such as depression, anxiety, and cognitive impairment. However, appropriate treatment can reverse these symptoms [26].

Patients suffering from chronic liver disease commonly experience thyroid dysfunction, which poses a higher risk of morbidity and mortality [15,27]. Additionally, subclinical hypothyroidism raises the risk of NAFLD, while higher levels of thyroid-stimulating hormone lower the risk of NAFLD. Hence, conducting thyroid function tests can help identify individuals who are at risk of developing NAFLD [28]. Moreover, Borzio et al. [29] evaluated thyroid function tests in chronic liver disease. In this study, the severity of liver dysfunction was correlated with T3.

Cirrhosis is the end stage of chronic liver disease, and cirrhotic portal hypertension results in the progression of decompensation complications like ascites, varicose bleeding, and hepatic encephalopathy [30]. According to pieces of evidence, thyroid disorders are related to chronic liver disorders, including cirrhosis [27]. Because of the impact of thyroid hormones on the liver and vice versa, this study was performed in cirrhotic patients to evaluate the relationship between FT3 and cirrhosis prognosis.

In this study, there was an inverse correlation between MELD and FT3 hormone levels. Considering that the MELD scoring system is one of the scoring systems designed to predict mortality in cirrhosis patients, FT3 can be used as a prognostic factor. Bilirubin was determined as the reason for the relationship between FT3 and MELD which there was a strong inverse relationship between FT3 and bilirubin. The lowest number of patients with low FT3 in Child-Pugh class A and the lowest number of patients with high FT3 in Child-Pugh class C were present.

In our study, there was an inverse relationship between FT3 and complications of portal hypertension, including ascites and esophageal varices, but there was no significant relationship with hepatic encephalopathy. While Bajaj et al. [31] showed that at the time of admission to the hospital, if there are low levels of thyroxine and certain metabolites linked to the gut microbiota, it can indicate the possibility of developing advanced hepatic encephalopathy in the future, regardless of other clinical biomarkers. Thus, it could be used as a prognosis index. The study performed by Huang et al. in 2020 showed that a low FT3 level was related to the poor prognosis of cirrhotic portal hypertension, which is in accordance with our results [13].

Rink et al. [32] in 1991 demonstrated that a low T3 level is a sensitive factor for predicting cirrhosis prognosis. According to Walfish's study in 1979, there is a relationship between the severity of liver dysfunction in alcoholic liver disease and low admission serum T3 and FT3 levels when accompanied by normal serum T4, FT4, and TSH levels. In addition, these factors are associated with increased mortality risk [33]. Results of the study done in 1989 by F Agha et al. [17] demonstrated that changes in T3 and FT3 are related to cirrhosis progression and can be used as a prognostic value. Sikarwar et al. found a significant relationship between the Child-Pugh score and levels of T3, T4, and TSH. Among these hormones, total T3 is believed to be the most accurate predictor of the severity of cirrhosis [34]. Punekar et al. [35] claimed that there was a negative correlation between FT3 and FT4 levels, but a positive correlation between TSH levels and several markers such as leukocyte counts, bilirubin levels, liver enzymes, globulin levels, blood clotting time, urea levels, creatinine levels, Child–Turcotte–Pugh score, and MELD score in cirrhosis. The most common abnormality observed in these patients was low T3 (low FT3) syndrome, which occurred in 41% of cases overall, 50% of cases with HE in cirrhosis, and 32% of non-survivors.

Several studies have found that cirrhotic patients commonly exhibit abnormal levels of serum thyroid hormones, specifically low levels of serum T3, high levels of rT3, and normal levels of TSH. Multiple factors could contribute to these abnormalities, including changes in the plasma levels of thyroid-binding proteins, alterations in the binding of T4 and T3 to their carrier proteins, impaired clearance of reverse T3 (rT3) by the liver, and reduced conversion of T4 to T3 outside the thyroid gland. In cirrhotic patients, extensive inflammation and fibrosis in the liver inhibit Type 1 (D1) deiodinase enzymes, leading to decreased conversion of T4 to T3. As a result, most of the remaining T4 is converted into rT3, resulting in increased rT3 levels while Type 2 (D2) deiodinase enzymes remain active [36].


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This is the first time this issue has been analyzed at a referral hospital. Although the subjects were from one center, this may be indicative of the Iranian population because it is a referral center. Further studies are recommended to compare thyroid hormone tests between cirrhotic patients and patients with acute complications of cirrhosis. In addition, further studies are recommended to evaluate the score improvement of these prognostic systems when thyroid abnormalities are corrected. Classification of cirrhosis into categories based on etiology to analyze the relationship between thyroid function and cirrhosis prognosis is suggested.

## Conclusion

This study has shown the association of FT3 with MELD score and the complications of cirrhosis. FT3 can be used as a prognostic criterion. It is recommended to check thyroid levels in patients with cirrhosis; if there is a disorder, treatment must be given.

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