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Review Article

# Mechanisms and Prognostic Assessment Value of Thyroid Hormone in Liver Failure

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## Abstract

Early and accurate prognostic assessment is crucial to avoid serious disease progression in patients with liver failure. Thyroid hormone is an important metabolic regulator involved in hepatic function. This review examines in detail the pathophysiological regulation of the hypothalamic-pituitary-thyroid axis in patients with liver failure and emphasizes the importance of thyroid profiling (thyroid-stimulating hormone, T3, and T4) in prognostic assessment and risk stratification. T3 can enhance liver regeneration. The clinical application of thyroid hormone replacement therapy in patients with acute-on-chronic liver failure complicated by non-thyroidal illness syndrome is controversial. This review aims to inform clinical practice regarding the relevance of TH level assessment in liver failure and to provide novel insights into the prognostic evaluation and comprehensive care of liver failure complicated by thyroid dysfunction.

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## Introduction

In recent years, global consensus on liver disease has increasingly emphasized the critical role of systemic multi-organ interactions in disease progression.[1] The thyroid hormones (THs), mainly thyroxine (T4) and the more biologically active triiodothyronine (T3), control the body's metabolic rate and energy homeostasis, affecting almost all organ systems of the body.[2] Among these organs, the liver occupies a uniquely central position, with hepatic function and TH status sharing a complex bidirectional relationship that is mediated by the hypothalamic-pituitary-thyroid (HPT) axis.[3] The liver is the main site of the metabolism and biological transformation of TH, playing an important role in its activation, inactivation, transport, and excretion (Fig. 1). In this context, the conversion of T4 into T3 through the activity of type 1 deiodinase (DIO1), as well as the production of thyroxine-binding globulin, the main serum carrier protein of TH, are some of the important processes that occur in the liver.[4] Additionally, the expression of several hepatic genes involved in important physiological processes, such as liver glucose metabolism, lipid metabolism, detoxification, and protein synthesis, is regulated by the interaction of TH with TH receptors (TR) (Fig. 2).[5] Consequently, severe hepatic dysfunction inevitably disrupts these physiological pathways, thereby corroborating the direct mechanistic link between liver failure and TH dysregulation.

States of severe liver dysfunction, such as acute liver failure, chronic liver failure, or acute-on-chronic liver failure (ACLF), are accompanied by significant impairment of the metabolism and transport of TH and metabolic activities.[6,7] Clinical data show that liver failure is often accompanied by non-thyroidal illness syndrome (NTIS), which is characterized by abnormal TH levels caused by serious systemic diseases (such as liver failure, critical infection, heart failure, trauma, and malignant tumors) or physiological stress, without inherent thyroid dysfunction. The occurrence of this syndrome is closely related to the severity of liver failure and has been confirmed as a key biomarker for patients with poor prognosis.[8]

This review systematically examines the mechanism underlying TH dysfunction in the progression of liver failure, the clinical significance of TH analysis in prognostic assessment, and the latest therapeutic strategies for ACLF patients with NTIS. Ultimately, we seek to reexamine secondary thyroid dysfunction associated with liver failure as an important pathological link and intervention target, thus gaining new insights into clinical prognostic evaluation and customized treatment.

## Pathophysiological mechanisms of the HPT axis in liver failure

The HPT axis closely controls the production and secretion of TH through a cascade of negative feedback mechanisms involving thyrotropin-releasing hormone and thyroid-stimulating hormone (TSH), and the liver is closely involved in the metabolism, transport, and regulation of TH. Hormonal changes occurring in pathological states such as hypothyroidism (decreased T3 and T4 with elevated TSH), hyperthyroidism (elevated T3 and T4 with decreased TSH), and liver failure can adversely affect the anatomic structure and physiological function of the liver.

**Keywords:** Liver failure; Thyroid hormone; Non-thyroidal illness syndrome; Triiodothyronine; Acute-on-chronic liver failure; Prognosis.

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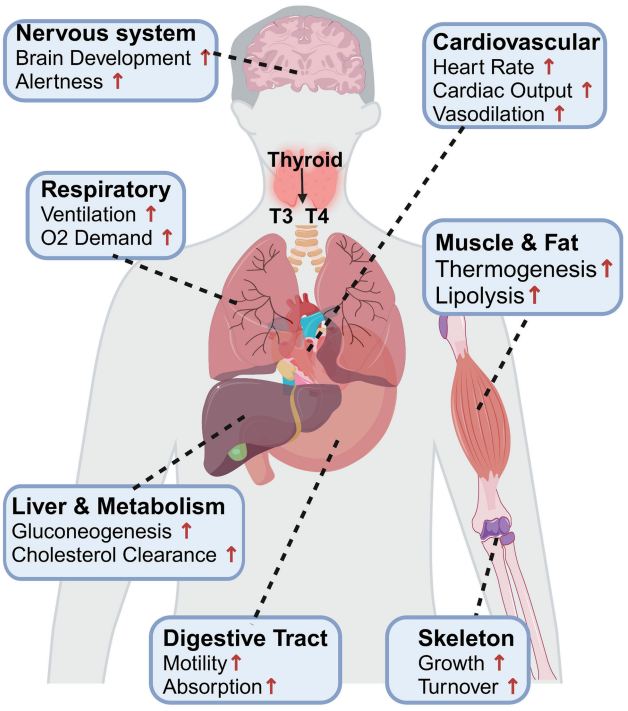


**Fig. 1. Systemic actions of thyroid hormones.** The schematic summarizes the systemic actions of T3 and T4. Key effects include the stimulation of neurological development and alertness, upregulation of cardiorespiratory functions (ventilation, heart rate, cardiac output), enhancement of gastrointestinal motility, promotion of skeletal growth, and regulation of hepatic and peripheral metabolism (gluconeogenesis, lipolysis, thermogenesis). The solid black arrow indicates the secretion of T3 and T4 from the thyroid gland, while the black dashed lines represent their systemic effects on various target organs. The red upward arrows (↑) denote the stimulation or upregulation of these specific physiological processes. O2, oxygen; T3, triiodothyronine; T4, thyroxine.

## Impact of hypothyroidism and hyperthyroidism on hepatic function

In hypothyroidism, T3 regulates lipid metabolism by activating TRβ to increase the expression of low-density lipoprotein receptors, stimulating the activity of sterol regulatory element-binding proteins, and enhancing the signaling of the peroxisome proliferator-activated receptor alpha pathway.[3,9] Therefore, decreased T3 levels lead to increased hepatic accumulation of lipids and, consequently, fatty degeneration and steatohepatitis. The resultant increase in TSH levels causes a direct increase in the hepatic expression of TR, stimulates the cAMP cascade signaling, and promotes hepatic gluconeogenesis. These effects together hinder the production of bile acid and eventually aggravate hyperlipidemia.[10] In addition, hypothyroidism not only promotes the progression of liver fibrosis directly,[11,12] but also aggravates oxidative damage to liver cells by increasing the formation of reactive oxygen species (ROS).[13] Thus, in the presence of hypothyroidism, liver lipid metabolism in liver failure is further dysregulated, resulting in hepatocyte damage and aggravation of fibrosis (Fig. 3).

Hyperthyroidism has both direct and indirect effects on the liver, although the specific mechanisms underlying these effects remain elusive. The main features include elevated TH levels and hepatic manifestations such as congestive liver disease and hepatotoxicity caused by autoimmune-mediated liver damage.[14] The indirect effects, on the other hand, are closely associated with liver damage caused by antithyroid drugs (ATDs).[15] Therefore, current guidelines advocate a consistent assessment of liver function throughout the course of ATD therapy; if liver damage occurs, transition to safe and effective radioactive iodine ($^{131}I$) treatment is recommended.[16] However, the effectiveness of ATDs in patients with hyperthyroidism aggravated by severe liver disease (such as liver failure) still remains uncertain.[17] In short, in severe liver disease complicated by hyperthyroidism, liver dysfunction may be caused by primary liver disease, thyrotoxicosis, or the synergistic effect of both (Fig. 4).

## Abnormal THs in liver failure

Although both hypo- and hyperthyroidism can cause serious liver damage, the current understanding is that TH abnormalities in liver failure are mainly related to NTIS.[8] NTIS is primarily characterized by a significant reduction in serum free triiodothyronine (FT3) levels, despite relatively normal TSH and free thyroxine (FT4) levels.[18] This reduction in FT3 levels is directly driven by the impaired activity of hepatic DIO1, which hinders the peripheral conversion of T4 to its biologically active form, T3. Another factor that contributes partly to this drop in free hormone concentrations and the marked decrease in total TH levels is the reduced synthesis of transport proteins such as thyroxine-binding globulin, transthyretin, and albumin.[19] Furthermore, although the HPT axis negative feedback loop should theoretically increase thyrotropin-releasing hormone and TSH secretion in response to low T3 levels, TSH levels often do not show this elevation due to reduced pituitary reactivity and impaired clearance in liver failure. This results in the characteristic biochemical profile of NTIS: low T3 levels coexisting with normal or only slightly elevated TSH and T4 levels.[20] In other words, NTIS is a common endocrine disorder in patients with end-stage liver disease, and its development is mainly related to abnormal TH metabolism and HPT axis dysfunction caused by the disease.

## Research advances in TH profiles for prognosis assessment in liver failure

China's Guidelines for the Diagnosis and Treatment of Acute-on-Chronic Liver Failure (2025 Edition) define ACLF as acute liver failure occurring against a background of chronic liver disease . It is characterized by rapid disease progression and increased short-term mortality, resulting in adverse outcomes in patients with chronic liver disease.[21,22] Given the critical regulatory role of the HPT axis in key hepatic metabolic pathways, the dynamic changes in its hormone profile can serve as important predictors for the progression of liver failure and short-term prognosis.

## Diagnostic value of TSH in patients with liver failure

As a sensitive indicator of the HPT axis, TSH level has been consistently identified as a robust predictor of outcomes in liver failure. Evidence from large-scale multicenter cohorts confirms the prognostic value of TSH level (Table 1).[22–25] Chen *et al*. analyzed a large cohort of 1,862 patients and found that low TSH levels are independently associated with increased short-term mortality.[23] Building on these findings, novel prognostic models integrating TSH with other parameters have been developed: the HINT prognostic score (HINT score = 1.48 × HE + 3.92 × ln(INR) + 0.73 × ln(neutrophils) − 0.46 × ln(TSH) − 5.78) and modified Chronic Liver Failure Consortium organ failure score. These scoring systems have been validated in both single-center and multicenter

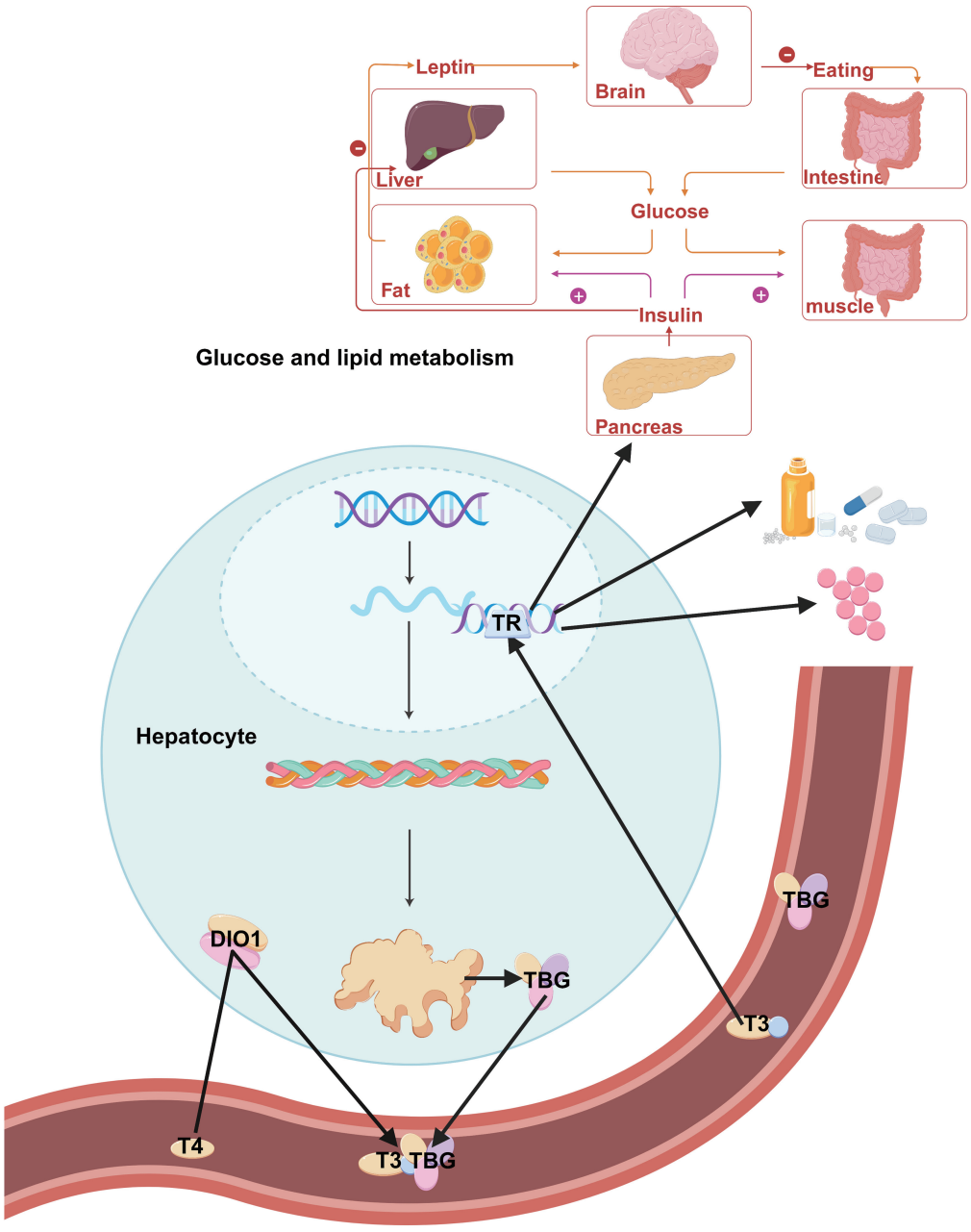


**Fig. 2. Mechanisms of hepatic thyroid hormone signaling and regulation of systemic metabolism.** The schematic illustrates the intracellular action of thyroid hormones in hepatocytes and their downstream metabolic effects. (Bottom) Circulating T3 and T4, transported by TBG, enter the hepatocyte. Intracellularly, DIO1 converts T4 to T3. T3 enters the nucleus and binds to TR to regulate gene transcription, including the synthesis of TBG. (Top) Hepatic thyroid signaling orchestrates systemic glucose and lipid metabolism through inter-organ crosstalk. This network involves insulin regulation from the pancreas and leptin signaling, which provides feedback to the brain to inhibit appetite ("Eating"). DIO1, iodothyronine deiodinase 1; T3, triiodothyronine; T4, thyroxine; TBG, thyroxine-binding globulin; TR, thyroid hormone receptor.

settings.[24] Composite scores have consistently outperformed traditional systems (e.g., Model for End-stage Liver Disease [MELD], MELD-Sodium) in risk stratification, suggesting that TSH provides unique prognostic information related to the systemic metabolic response to liver injury.[25,26]

In summary, TSH holds considerable clinical importance in the assessment of liver injury, specifically disease severity and prognosis, in patients with ACLF. Future research should focus on the dynamic monitoring of the TH profile and its integration with other biomarkers to enhance the comprehensiveness and accuracy of prognostic evaluation in this population.

## Function of T3 in prognostic assessment and risk stratification for patients with ACLF

Several basic and clinical studies have shown that T3 promotes liver regeneration and can serve as a prognostic marker in ACLF patients.[27] T3 enhances the expression of E2F transcription factor and cell cycle proteins (such as Cyclin

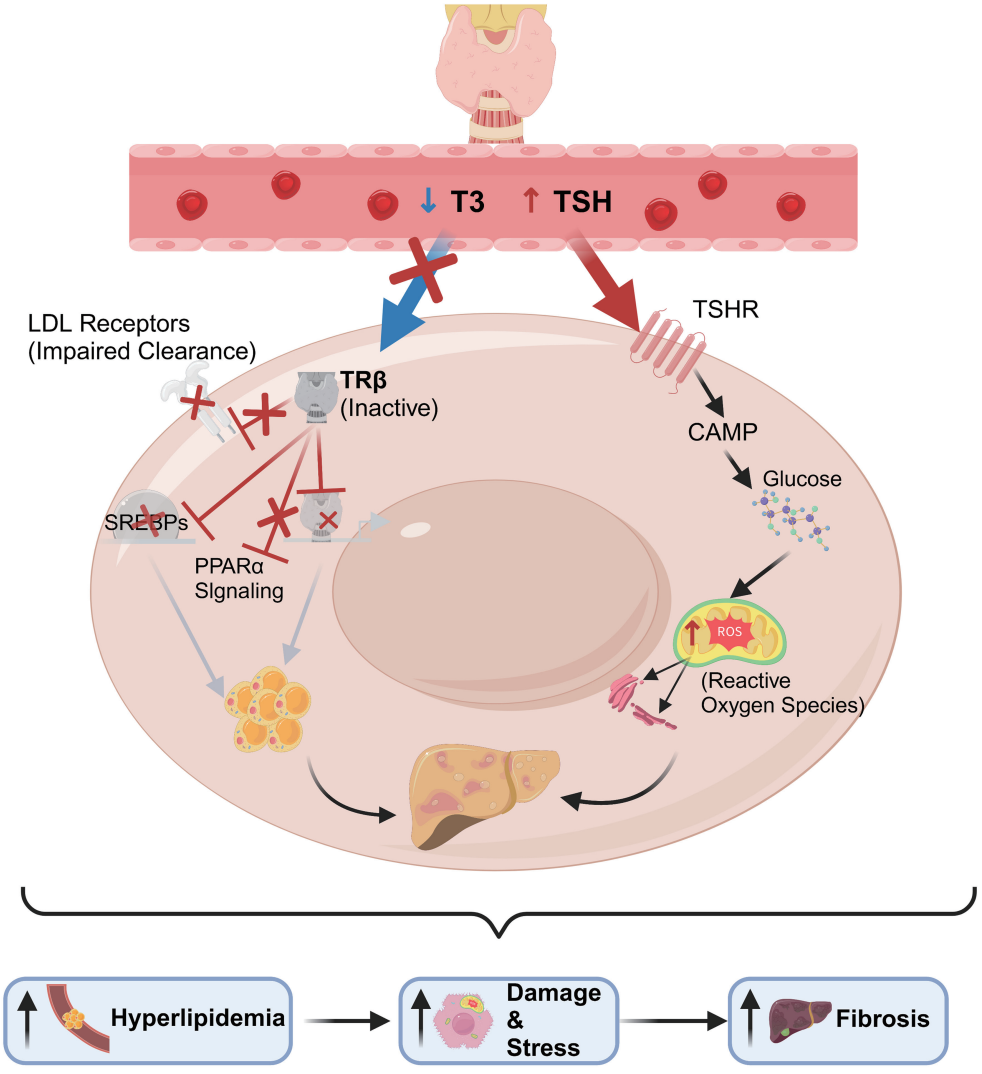


**Fig. 3. Pathogenic mechanisms linking hypothyroidism to hepatic steatosis and fibrosis progression.** The schematic illustrates the dual impact of hypothyroidism, characterized by low T3 and elevated TSH levels, on hepatocyte function. (Left Pathway) Reduced T3 availability results in the inactivity of TRβ. This leads to the suppression of PPARα signaling and impaired LDL receptor-mediated clearance, alongside dysregulation of SREBPs, collectively promoting hepatic lipid accumulation. Red crosses indicate blocked physiological pathways. (Right Pathway) Concurrently, elevated circulating TSH binds to the TSHR on hepatocytes, activating the cAMP signaling cascade. This stimulates glucose metabolism but leads to mitochondrial dysfunction and increased ROS production. (Outcome) The convergence of these pathways results in hyperlipidemia, cellular damage, and oxidative stress, ultimately driving the progression to hepatic fibrosis. The upward arrows (↑) denote an increase, elevation, or progression of the respective biomarkers and pathological conditions, while the downward arrow (↓) denotes a decrease. T3, triiodothyronine; TSH, thyroid-stimulating hormone; TRβ, thyroid hormone receptor beta; PPARα, peroxisome proliferator-activated receptor alpha; LDL, low-density lipoprotein; SREBPs, sterol regulatory element-binding proteins; TSHR, thyroid-stimulating hormone receptor; cAMP, cyclic adenosine monophosphate; ROS, reactive oxygen species.

D1), activates Ras-Raf-MEK-ERK and Wnt/β-catenin signaling pathways,[28] inhibits the activity of CDK inhibitors (p16, p27) and tumor suppressor proteins (p53, p73); these activities, in turn, counteract the inhibitory effects of TGF-β/SMAD signaling, reduce mitochondrial oxidative damage and cell apoptosis, and accelerate mitochondrial regeneration, thereby promoting liver regeneration. Furthermore, T3 combines with TR to promote *KLF9* gene expression, which promotes liver stem cell differentiation.[29] These activities together accelerate the growth and regeneration of liver cells.[30,31] During liver failure, the level of circulatory T3 decreases significantly, which not only aggravates hepatocyte damage but also further inhibits the liver's inherent regenerative ability. Therefore, circulating T3 levels may reflect the liver regeneration ability of patients with liver failure (Fig. 5).

Clinical evidence strongly suggests that, besides being a marker of thyroid function, FT3 is a critical indicator of the liver's regenerative capacity and metabolic reserve. Table 2 summarizes the findings of key studies that show that low T3 syndrome is an independent risk factor for mortality.[7,17,32–36] A recurring theme across these studies is the link between FT3 suppression, systemic inflammation (e.g., IL-6 levels), and clinical frailty, thus highlighting the role of the immune-metabolic axis in disease progression.[8,32–39]

Researchers have increasingly moved from using single biomarkers to scoring systems that integrate thyroid parameters for improved predictive accuracy. Models such as the FT3-MELD and MELD-FT3/FT4 have demonstrated greater discriminatory power than MELD alone. Furthermore, recent data emphasize the importance of dynamic

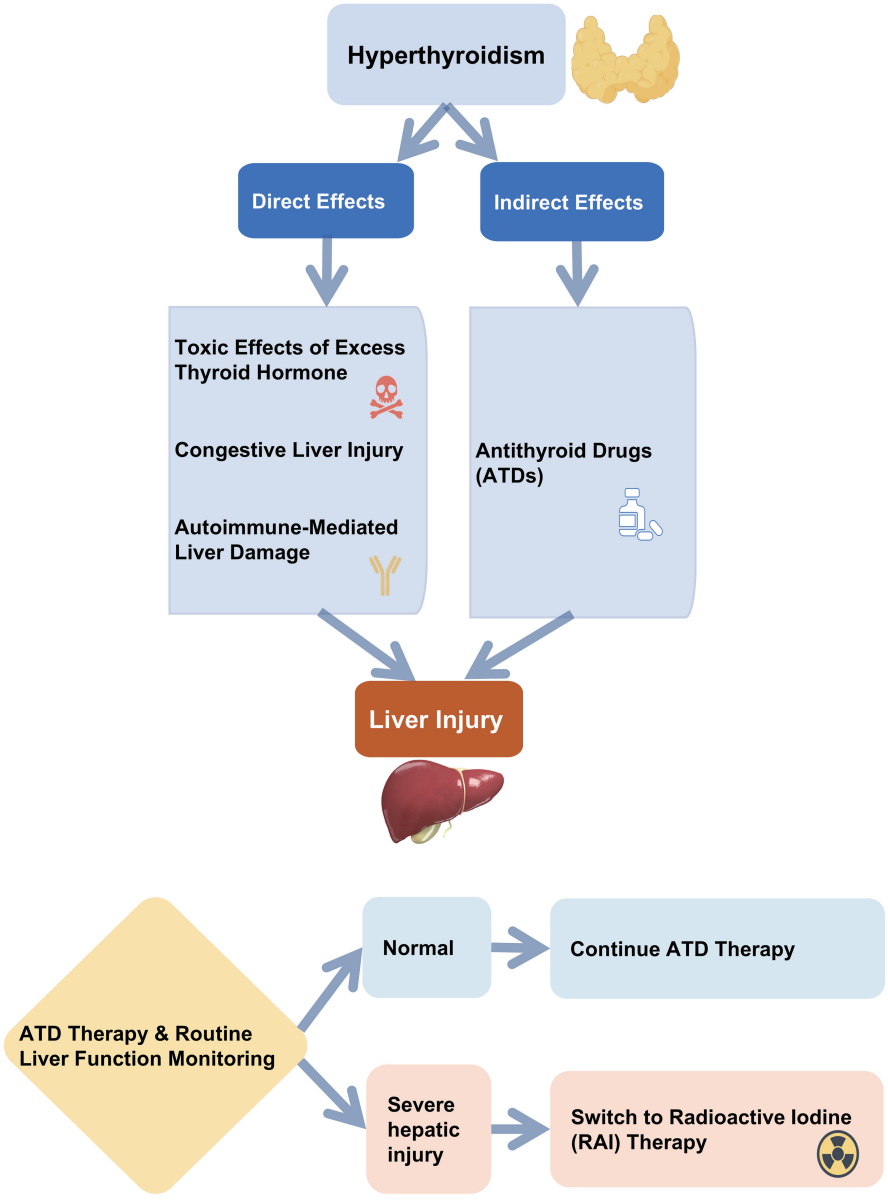


**Fig. 4. Pathogenic pathways of hyperthyroidism-associated liver injury and the clinical management algorithm for ATD therapy.** The left panel illustrates the pathogenic triad contributing to hepatic dysfunction: toxic effects of excess thyroid hormone, congestive liver injury, and autoimmune-mediated damage. The right panel outlines the safety monitoring protocol during ATD therapy. Patients maintaining normal liver function should continue treatment, whereas those developing severe hepatic injury require discontinuation of ATDs and a transition to RAI. ATD, antithyroid drug; RAI, radioactive iodine.

monitoring; a progressive decline in FT3 levels during hospitalization effectively identifies patients with deteriorating trajectories who may require urgent intervention, such as liver transplantation.[40]

Fundamentally, T3 acts as a critical regulator of liver regeneration. Consequently, a decline in T3 levels marks the onset of NTIS, serving as a critical indicator of metabolic dysfunction and an independent predictor of mortality risk in ACLF.

## Treatment advances for patients with ACLF complicated by NTIS

Currently, the use of TH replacement therapy (THRT) for ACLF patients with NTIS is not recommended by any of the major international societies. The lack of clarity regarding the pathophysiological basis of NTIS makes the routine application of THRT in this population highly controversial.[41] NTIS is widely considered to be an adaptive metabolic defense mechanism aimed at conserving energy during critical illness; thus, indiscriminate hormonal intervention at this juncture could potentially disrupt this protective response and induce catabolic stress, causing more harm than good.[42] Recent observational studies indicate that fluctuations in TH levels in ACLF patients correlate significantly with survival outcomes and the necessity for liver transplantation.[43] Consequently, FT3 and FT4 levels serve as valuable tools for optimal risk stratification and clinical decision-making, par-

**Table 1. Summary of studies evaluating the prognostic value of TSH in patients with liver failure**

| Author (Year) [Ref] | Study design | Population (Sample Size)/Center | Key parameter | Main findings / Prognostic value |
|---|---|---|---|---|
| Chen *et al*. (2022)[22] | Retrospective study | HBV-ACLF (*n* = 1,862) Multicenter | TSH | Largest cohort. Confirmed a robust positive correlation between TSH and survival. Lower TSH was an independent predictor of mortality |
| Wu *et al*. (2018)[23] | Retrospective study | HBV-ACLF (*n* = 635) Single-center | TSH | Pioneer study. Developed the HINT score (incorporating TSH), which outperformed MELD and MELD-Na in predicting mortality |
| Tu *et al*. (2024)[25] | Retrospective study | HBV-ACLF (*n* = 346) Multicenter/Validation | WeightedTSH | Model Evolution. Integrated weighted TSH into CLIF-OFs. The modified mCLIF-OFs model showed superior accuracy (AUC = 0.865) |
| Belu *et al*. (2024)[24] | Observational study | Cirrhosis (*n* = 419) Single-center | TSH | Validation. TSH levels significantly decreased with worsening liver function (Child-Pugh C) and showed inverse correlation with MELD |

AUC, area under the curve; CLIF-OFs, Chronic Liver Failure Consortium organ failure score; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; HINT, hepatic injury and thyroid function; mCLIF-OFs, modified Chronic Liver Failure Consortium organ failure score; MELD, Model for End-stage Liver Disease

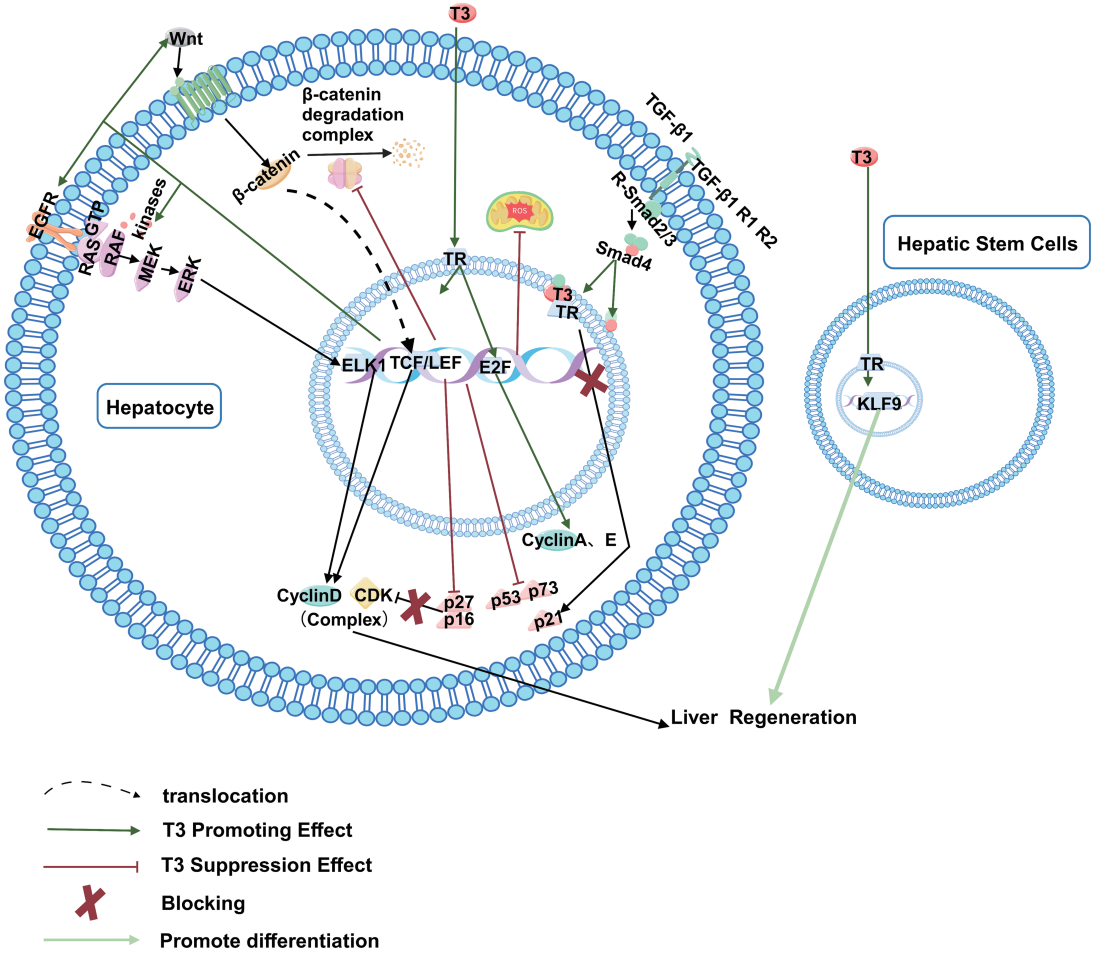


**Fig. 5. Proposed mechanisms of T3 in promoting liver regeneration.** Upon entering the hepatocyte, T3 binds to its nuclear TR. The activated TR complex orchestrates hepatocyte proliferation through multiple pathways: (1) It activates the Wnt/β-catenin signaling pathway, leading to β-catenin stabilization, nuclear translocation, and subsequent transcription of proliferative genes like *CCND1* (cyclin D1). (2) It stimulates the Ras-Raf-MEK-ERK cascade, upregulating transcription factors. (3) It promotes cell cycle progression by upregulating E2F transcription factors and cyclin-CDK complexes, while simultaneously suppressing cell cycle inhibitors (p16, p27) and tumor suppressors (p53, p73), thereby relieving inhibition on CDKs. (4) T3 exerts anti-apoptotic effects by enhancing mitochondrial integrity and reducing ROS production. (5) It antagonizes the TGF-β/SMAD pathway, delaying the termination phase of regeneration. The concerted action of these mechanisms drives the G1 to S phase transition, resulting in robust hepatocyte proliferation and liver regeneration. T3, triiodothyronine; TR, thyroid hormone receptor; EGFR, epidermal growth factor receptor; GTP, guanosine triphosphate; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; TCF, T-cell factor; LEF, lymphoid enhancer-binding factor; CDK, cyclin-dependent kinase; ROS, reactive oxygen species; TGF-β1, transforming growth factor beta 1; KLF9, Krüppel-like factor 9.

**Table 2. Summary of studies evaluating FT3 and other thyroid parameters in liver failure**

| Author (Year) [Ref] | Study design | Population (Sample Size)/Center | Key parameter | Main findings / Prognostic value |
|---|---|---|---|---|
| Xiong *et al*. (2022)[33] | Retrospective study | HBV-ACLF (*n* = 193) Single-center | FT3 | Baseline Risk. Low T3 syndrome was identified as a robust independent risk factor for 28-day mortality |
| Hartl *et al*. (2024)[32] | Cohort study | Cirrhosis (*n* = 297) Single-center | FT3 | Inflammation Link. Lower FT3 independently predicted ACLF development and mortality, reflecting systemic inflammation |
| Langer *et al*. (2023)[17] | Prospective study | AD / ACLF (*n* = 207) Single-center | FT3, rT3 | Severity Link. Low FT3 and high rT3 levels correlated with IL-6 and disease severity (CLIF-C ACLF score) |
| Li *et al*. (2022)[34] | Retrospective study | Cirrhosis (*n* = 214) Single-center | FT3 | Clinical Phenotype. Low FT3 levels were significantly associated with a frail phenotype, aiding in early risk stratification |
| Feng *et al*. (2020)[7] | Retrospective study | Liver Failure (*n* = 569) Single-center | FT3 | Model Development. Developed FT3-MELD score. FT3 improved the prognostic ability of MELD for 90-day mortality |
| Nardin *et al*. (2024)[36] | Prospective study | AD (*n* = 119) Single-center | FT3/FT4 ratio | Model Refinement. Developed MELD-Thyro (using FT3/FT4 ratio). Achieved superior accuracy for 90-day mortality.(AUC = 0.899) |
| Zhang *et al*. (2024)[35] | Retrospective study | HBV-ACLF (*n* = 106) Single-center | FT3 Dynamics | Real-time Monitoring. Continuous decline in FT3 levels was associated with higher mortality ($P < 0.001$). Dynamic monitoring improved prediction |

AUC, area under the curve; ACLD, advanced chronic liver disease; AD, acute decompensation; CLIF-C, Chronic Liver Failure Consortium; FT3, free triiodothyronine; FT4, free thyroxine; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; IL-6, interleukin-6; MELD, Model for End-stage Liver Disease; OR, odds ratio; rT3, reverse triiodothyronine.

ticularly for transplant candidates, rather than as a direct guide for hormone replacement. Notably, successful liver transplantation typically increases TH levels to the normal range, confirming that the hormonal dysregulation is secondary to hepatic dysfunction.[44] Recently, thyroid TR agonists have shown potential for promoting liver regeneration in preclinical animal models.[45] However, these findings are currently limited to experimental settings and are not substantiated by prospective clinical data validating the safety and efficacy of TR agonists in humans. Consequently, the translation of these promising experimental findings into clinical practice necessitates rigorous validation through future clinical trials.

In summary, while liver transplantation remains a viable life-saving treatment for ACLF, with short-term survival rates exceeding 70%,[46] the general clinical consensus currently advocates for active management of the underlying liver disease and supportive care rather than hormonal manipulation. The spontaneous recovery of TH levels often mirrors the resolution of liver failure, serving as a marker of recovery rather than a therapeutic target. Given the lack of evidence from large-scale randomized controlled trials, THRT and TR agonists cannot be routinely recommended in current clinical practice; well-designed prospective studies are warranted to verify their therapeutic potential and establish standardized protocols.

## Discussion

The integration of TH parameters into the prognostic evaluation of liver failure offers distinct clinical advantages. Unlike traditional scoring systems (e.g., MELD, Chronic Liver Failure Consortium), which primarily focus on renal function and coagulation, the assessment of THs, particularly FT3, provides a unique metabolic perspective, reflecting the systemic exhaustion and regenerative capacity of the liver. Furthermore, thyroid function tests are widely available, cost-effective, and standardized in most clinical laboratories, making them an easily accessible tool for routine risk stratification.

However, there are several limitations to the widespread application of these markers in clinical practice. First, current evidence mostly stems from retrospective single-center studies, which are susceptible to selection bias and lack the rigorous control of prospective randomized trials. Second, there is significant heterogeneity regarding the optimal cut-off values for FT3 and TSH across different studies, which impedes the establishment of a uniform diagnostic consensus. Third, it is still unclear whether TH suppression is a maladaptive driver of liver failure or merely an adaptive "bystander" of critical illness. Consequently, while thyroid parameters significantly enhance prognostic precision when used along with established models (e.g., FT3-MELD), they can currently serve as complementary biomarkers to further refine clinical decision-making rather than as standalone criteria for transplant prioritization or therapeutic intervention.

## Prospective research avenue

Future research in this field must be directed at overcoming some key challenges. Large-scale multicenter prospective studies are needed to verify whether THRT can actually improve the prognosis of ACLF patients with NTIS, including survival rate and organ function recovery. If the treatment results are favorable, further investigation is necessary to guide drug selection (T3, T4, or combined treatment) and optimal dosage and duration of treatment. Furthermore, further clarity is required regarding the differences in the pharmacokinetic and pharmacodynamic behavior of the drugs in ACLF caused by different pathologic conditions and at different stages of disease. Third, safety tests are required for the use of THRT in patients with unstable cardiovascular function, especially those with the risk of arrhythmia. Treatment

decisions must be individualized. In addition, the role of T3 in hepatogenesis needs to be elucidated, along with its potential role in promoting hepatocyte proliferation and enhancing liver function recovery; this would help identify new treatment strategies for ACLF patients with impaired liver regeneration.

In short, THs are no longer considered "bystander" biomarkers, but rather active participants and potential treatment targets in ACLF. Despite considerable obstacles at present, advances in this field are expected to enhance the precise prognostic assessment and treatment of ACLF and help identify important therapeutic significance for critically ill patients with NTIS.

## Conclusions

In ACLF patients, abnormal TH levels are usually manifested as NTIS, with T3 levels having prognostic significance by virtue of their close relationship with the severity, progression, and short-term prognosis of the disease. However, the existing treatment regimen for liver failure affords limited success, and prognostic assessment mainly relies on traditional scoring systems. Future research should prioritize improving the accuracy and thoroughness of prognostic evaluation in liver failure. To this end, the main goal would be to combine the TH profile (e.g., TSH, FT3, FT4) with a recognized scoring system (e.g., Chronic Liver Failure Consortium – Organ Failure, MELD) and thereby create an innovative and comprehensive scoring system. Such a system would identify high-risk patients in time and provide reliable evidence for clinical action.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Review concept and design (HZ, HW), literature search and synthesis of the evidence (HZ, SHS), and critical revision of the manuscript for important intellectual content (HW, SHT). All authors were involved in the writing and revision of the manuscript. All authors have read and approved the final manuscript.

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