ABSTRACT
This study aimed to develop a prediction model for the prognosis of patients with Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF). 122 patients were divided into survival group and death group according to 90-day prognosis after diagnosis. Risk factors affecting the prognosis were identified by the logistic regression analysis and then were used to establish an FT3-related prediction model. Age, proportion of liver cirrhosis, AST, TBil, INR, Cr, Na, WBC, and several scores (CTP, MELD, MELD-Na, CLIF-SOFA, CLIF-OF, and AARC scores) of the death group were significantly higher than that of the survival group on admission. FT3 and Na were protective factors for the prognosis of patients; Age, TBil, INR, HE grading, and Cr were risk factors. FT3 levels were (2.79 ± 0.34) (95%CI 2.73–2.87) pmol/L for the survival group and (2.20 ± 0.20) (95%CI 2.11–2.29) pmol/L for the death group. The level of FT3 in survival group was significantly higher than that of the death group in patients regardless of gender, initial liver disease, and liver failure stages (P < 0.05). The ROC curve for FT3-related prognostic model score was 0.923 (95%CI 0.809–0.947), significantly higher than that of the CTP, MELD, MELD-Na, CLIF-SOFA, CLIF-OF, and AARC scores (P < 0.001). The FT3-related prediction model has good predictive value for 90-day prognosis.

ARTICLE HISTORY
Received 10 February 2022
Revised 5 May 2022
Accepted 9 May 2022

KEYWORDS
Free triiodothyronine; hepatitis B; acute-on-chronic liver failure; FT3; prognosis

CONTACT
Zhongping Duan zhongpingd12@126.com duan@ccmu.edu.cn Department of Difficult & Complicated Liver Diseases and Artificial Liver Center, Beijing Youan Hospital, Capital Medical University, No. 8, You An Men Outer Street, Fengtai District, Beijing 100069, China

© 2022 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Highlights

- FT3 concentration was significantly decreased in death group, indicated that FT3 may be a protective predictor of the prognosis of HBV-ACLF.
- FT3 was significantly higher in survival group with different gender, different initial liver disease and different stages of liver failure, suggesting FT3 has good stability as a predictor.
- The FT3 level may facilitate prediction of prognosis of HBV-ACLF.

1 Introduction

Acute-on-chronic liver failure (ACLF) is recognized as a complex, clinical disease relating to the acute decline of liver function and even organ failure, which is associated with an elevated short-term mortality [1]. ACLF caused by HBV is the most predominant type of ACLF in China [2]. Early diagnosis and management is essential for ACLF patients’ prognosis there is no effective treatment apart from liver transplantation [3].

Most of the prognostic prediction models that were established have different evaluation effects, including the Child–Turcotte–Pugh (CTP) score, the model for end-stage liver disease (MELD) score, the MELD-Na score, the chronic liver failure–sequential organ failure assessment (CLIF-SOFA), the CLIF-consortium organ failure score (CLIF-C OF) and the APASL ACLF research consortium (AARC) score. CTP score is calculated using bilirubin, albumin, ascites, encephalopathy, and international normalized ratio [INR]. This score can be used to assess liver cirrhosis, but the accuracy has been questioned. MELD-Na score is calculated using lab tests such as total bilirubin (TBil), the international normalized ratio (INR), serum creatinine (Cr), serum sodium (Na), and etiology. However, it has some limitations regarding the accuracy of assessment and ease of clinical application [4]. CLIF-SOFA and CLIF-OF are calculated using TBil, HE, Cr, PT or PLT, mean arterial blood pressure, and SPO2. Research indicated that they have advantages in predicting short-term (28 days) mortality of ACLF, but their accuracy for long-term prognostic assessment remains to be verified [5,6]. These scores have been used for ACLF patients’ risk stratification to optimize the treatment strategy. However, the accuracy of predicting patient prognosis is often questioned.

Moreover, thyroid hormone is involved in many pathophysiological mechanisms. Liver is of great importance for thyroid hormones synthesis, metabolism, and excretion [7]. Therefore, damage to hepatocytes may affect thyroid hormone levels. Previous study [8] indicated that serum thyroid hormone levels could be used to predict the prognosis of patients with ACLF. This retrospective, observational cohort study was performed to explore the relationships between various risk factors and the predictive value in HBV-ACLF patients, especially for the clinical application of FT3 to assess a patient’s prognosis.

2 Methods

2.1 Subjects

We enrolled 122 consecutive HBV-ACLF patients in our hospital between September 2018 and February 2020. Inclusion criteria: (1) the diagnosis of chronic hepatitis B in accordance with the guidelines [9]; (2) meet the diagnostic criteria for acute-on-chronic (or subacute) liver failure in the Guidelines by the Chinese Medical Association [1]. The exclusion criteria were: (1) age ≤18 years old; (2) patients with another hepatitis virus infection before the diagnosis of ACLF; (3) patients with imaging and a pathological biopsy of liver and extrahepatic tumors; (4) pregnant patients; (5) patients with disseminated intravascular coagulation, heart, brain, kidney, respiratory failure, pituitary, and thyroid diseases before the diagnosis of ACLF; and (6) patients who had used thyroid hormones and glucocorticoid or propranolol and other drugs affecting thyroid function within the previous three months.

The etiology of ACLF in this study was all caused by HBV. Patients received standard medical support treatment and routine anti-HBV treatment. Patients who met the conditions of liver transplantation were included in the waiting queue for liver transplantation. AKI patients
required hemodialysis treatment when they reached the standard of renal replacement therapy. Patients were followed for at least three months. According to 90-day prognosis, patients were separated into the survival (n = 77) and the death groups (n = 45). The protocol was approved by our institutional review board and informed consent was obtained from all participants.

2.2 Methods

The following information was collected from patients on admission: age, gender, BMI, history of alcohol intake, anamnesis, mean arterial pressure (MAP), and other general information; laboratory parameters were measured at 6:00 a.m. the next day: FT3, alanine transaminase (ALT), aspartate transaminase (AST), TBil, albumin (ALB), Cr, platelet, hemoglobin, serum sodium, and white blood cell (WBC) count were recorded; and the prothrombin time was evaluated, and the INR and HBV viral load (DNA) were calculated.

2.2.1 Laboratory tests

Enzyme-linked immunosorbent assay was performed using an Abbott i2000SR fully automatic chemiluminescence analyzer to determine the patient’s serum FT3 level; a Sysmex XE-2100 fully automatic blood cell analyzer was used to determine the WBC; an Olympus AU 5400 automatic biochemical analyzer was used to test the following blood biochemical indexes; an ACL TOP 700 automatic coagulation analyzer was used to measure the prothrombin time and calculate the INR; HBV-DNA and HBeAg were detected by the kit produced by Roche company, and the detection limit of HBV DNA is 500 IU/ml.

2.2.2 Evaluation indexes

According to the results of laboratory examination and clinical manifestations of patients, Child and the Model for End-stage Liver Disease (MELD) score were calculated. According to the results of laboratory examination and clinical manifestations of patients, Child and the Model for End-stage Liver Disease (MELD) score were calculated. Each patient’s condition was evaluated by CTP score, MELD score, MELD-Na score, CLIF-SOFA score, CLIF-OF score (Chronic Liver Failure Organ Failure score), and AARC score.

2.3 Statistical analysis

All statistical analyses were conducted with SPSS 25.0 and MedCalc 19.0 software. The continuous data were expressed as mean ± standard deviation (x ± s); Comparisons between the two groups were made using a Mann–Whitney U test; a comparison check of the count data of the two groups was performed using an X² test; The logistic regression analysis was used to identify the independent factors affecting the prognosis. We also assessed the discrimination of the prediction model by using receiver-operating characteristic (ROC) curves. The ROC curve was constructed to compare the difference between the prediction model and the other scores in predicting prognostic value, and the Kaplan-Meier test was used between groups. A two-tailed P-value < 0.05 was used to indicate the statistical significance.

3 Results

For all 122 patients, survival group had higher value of FT3 and Na, and death group had higher values of AST, TBil, INR, Cr, Na, WBC, BMI, MAP, hemoglobin level, and various prognostic scores. Further work showed that FT3 was significantly higher in the survival group independent on gender, initial liver disease, and liver failure stages. With the decrease of FT3 level, the mortality of patients increased. The area under the ROC curves of FT3-related prognostic model-1 score was significantly higher than that of other risk scores.

3.1 Patients characteristics and prognosis

Among the 122 patients, 77 cases (63.1%) in the survival group, including 65 males (84.4%) and 12 females (15.6%), aged (43.66 ± 9.94) years; 45 cases (36.9%) in the death group, including 35 males (77.8%) and 10 females (22.2%), aged (48.86 ± 8.91) years. The direct death cause of
death group was liver failure. Death group showed significant higher values of AST, TBil, INR, Cr, Na, WBC, BMI, MAP, hemoglobin level, and various prognostic scores than survival group on admission (Table 1). After a 90-day follow-up, there were 77 surviving patients (63.11%) and 45 deaths (36.89%) (Figure 1).

### 3.2 Variable screening of prognostic influences

As shown in Table 2, multiple variables were included in the logistic regression model. The OR value was 0.152 (0.088–0.336) for FT3 (P < 0.001); 1.055 (1.012–1.089) for age (P = 0.018); 1.100 (1.022–1.184) for INR (P = 0.018); 1.119 (1.074–1.166) for TBil (P < 0.001);
4.850 (2.082–7.296) for Cr (mg/dl) (P < 0.001); 0.883 (0.818–0.952) for sodium (P = 0.034); Grade of hepatic encephalopathy (HE) was used as categorical variable (P < 0.05). The results indicated that FT3 and Na were protective factors affecting the prognosis of patients (P < 0.05); age, TBil, INR, HE grading, and Cr were risk factors (P < 0.05). The patients’ prognosis was used as a dependent variable, and factors were used as independent variables to establish the logistic proportional hazards model (Table 3). FT3-related prognostic model 1 was constructed as follows

\[ Y = 3.13 + 1.76 \text{Cr} - 1.56 \text{FT3} + 1.15 \text{HE grading} + 0.11 \text{TBil} + 0.08\text{INR} - 0.06 \text{Na} + 0.06 \text{age}. \]

### 3.3 The comparison of serum FT3 levels between two groups

FT3 levels were (2.79 ± 0.34) (95% CI 2.73–2.87) pmol/L and (2.20 ± 0.20) (95% CI 2.11–2.29) pmol/L in survival and death group, P < 0.001. The FT3 levels of the two groups are compared in Figure 2a.

### 3.3.1 Comparison of FT3 levels between different genders

Male: survival group was (2.80 ± 0.37) (95% CI 2.72–2.88) pmol/L, death group was (2.00 ± 0.20) (95% CI 2.11–2.29) pmol/L, P < 0.001 (Figure 2b). Female: survival group was (2.76 ± 0.18) (95% CI 2.60–2.93) pmol/L, death group was (2.21 ± 0.33) (95% CI 1.68–2.74) pmol/L, P = 0.007 (Figure 2c).

### 3.3.2 Comparison of FT3 levels in different initial liver disease

Chronic hepatitis B: survival group was (2.79 ± 0.34) (95% CI 2.73–2.87) pmol/L, death group was (2.33 ± 0.22) (95% CI 2.15–2.51) pmol/L, P = 0.0001 (Figure 2d). Cirrhosis: survival group was (2.85 ± 0.35) (95% CI 2.75–2.95) pmol/L, death group was (2.15 ± 0.19) (95% CI 2.2, 05–2.25) pmol/L, P < 0.001 (Figure 2e).

### 3.3.3 Comparison of FT3 levels stratified by liver failure stages

Early stage of liver failure: survival group was (2.87 ± 0.38) (95% CI 2.77–2.98) pmol/L, death group was (2.08 ± 0.11) (95% CI 1.95–2.21) pmol/L, P < 0.001 (Figure 2f). Middle stage of liver failure: survival group was (2.79 ± 0.27) (95% CI 2.68–2.92) pmol/L, death group was (2.24 ± 0.28) (95% CI 2.04–2.43) pmol/L, P < 0.001 (Figure 2g). Late stage of liver failure: survival group was (2.52 ± 0.29) (95% CI 2.34–2.70) pmol/L, death group was (2.26 ± 0.20) (95% CI 2.12–2.39) pmol/L, P = 0.018 (Figure 2h).

The above results showed that the survival group had a significantly higher FT3 level than the death group regardless of gender, initial liver disease (chronic hepatitis B or cirrhosis) and stages of liver failure.
3.4 Relationship between FT3 level and mortality

The FT3 level of all patients ranged from 1.13 to 4.17 pmol/L. We were divided into four zones from high to low according FT3 level: Q1 area (11 cases) was 3.44–4.27 pmol/L; Q2 area (38 cases) was 2.61–3.43 pmol/L; Q3 area (59 cases) was 1.78–2.60 pmol/L; Q4 area (14 cases) was 0.95–1.77 pmol/L. The mortality of patients in Q1, Q2, Q3, and Q4 were 9.1%, 26.3%, 32.2%, and 50%, respectively. It is suggested that with the decrease of FT3 level, the mortality of patients increases gradually (Figure 3).

3.5 Analysis of FT3 ROC curve and survival curve

The accuracy of FT3 level in predicting patients’ 90-day prognosis was analyzed by the ROC curve (Figure 4a). The results showed that AUROC was 0.780, 95% CI (0.731–0.829) (P < 0.001), Youden index was 0.461 (95% CI 0.343–0.529), sensitivity was 86.14%, specificity was 59.92%. The optimum critical value was 2.77 pmol/L. The ROC curves of baseline FT3 level and other competing scores were plotted for predicting the 90-day prognosis (Figure 4b). The results showed that for HBV-ACLF patients, the baseline FT3 level could be

Figure 2. Comparison of FT3 levels between survival group and death group. (a): all patients; (b) and (c): different genders; (d) and (e): different initial liver disease; (f), (g), (h): different stages of liver failure.
useful for predicting their 90-day prognosis. However, the prediction effect of baseline FT3 level was not significantly better than other four competing scores.

### 3.6 The discrimination and calibration of FT3-related formula scores

Each item value of patients was substituted into the regression equation, ROC curve of prediction probability value was drawn to get the FT3-related prognostic model-1 score (Figure 5), AUROC was 0.923 (95%CI 0.809–0.947), Youden index was 0.659 (95% CI 0.560–0.709), sensitivity was 91.09% (95%CI 83.8%-95.8%), specificity was 81.78% (95%CI 76.4%-86.4%). In this study, the calibration degree of FT3-related prognostic model-1 was validated by the calibration plot and goodness-of-fit test. The results showed that $R^2 = 0.615$, Brier score = 0.103 (Figure 6). The result indicated that there was no difference between the predicted value and the actual observation value of the model.

### 3.7 The comparison of FT3-related formula scores with main prognostic scores

The ROC curves of FT3-related prognostic model-1 score and other competing scores on the 90 day prognosis of patients were plotted (Table 4). The results showed that FT3-related prognostic model-1 score was significantly higher than any of other scores in predicting the 90-day death of HBV-ACLF patients, $P < 0.001$ (Figure 7).

|                      | AUROC (95%CI) | P-value |
|----------------------|---------------|---------|
| FT3-related          | 0.923 (0.809–0.947) | <0.001  |
| prognostic          |               |         |
| model-1 score       |               |         |
| CTP score           | 0.707 (0.656–0.754) | <0.001  |
| MELD score          | 0.837 (0.793–0.880) | <0.001  |
| MELD-Na score       | 0.861 (0.821–0.901) | <0.001  |
| CLIF-SOFA score     | 0.792 (0.740–0.845) | <0.001  |
| CLIF-OF score       | 0.784 (0.732–0.836) | <0.001  |
| AARC score          | 0.859 (0.821–0.898) | <0.001  |

$P < 0.05$ was considered to be statistically significant.

---

**Figure 3.** Relationship between FT3 level and mortality.

**Figure 4.** (a) ROC curve of the FT3 level; (b) ROC curves of baseline FT3 level, CTP score, MELD score, CLIF-SOFA score, and AARC score.
ACLF is a condition of hepatic decompensation with multiple organ failure caused by a systemic inflammation [10]. Considering the life-threatening risk of HBV-ACLF in short term, scientists pay more attention to the early determination of prognosis. There was a lot of research showed the predictors of ACLF prognosis, including liver predictive factor (TB), kidney predictive factors (creatinine), brain predictive factor (HE), coagulation predictive factor (INR), circulation predictive factors (mean arterial pressure and vasopressor use) and thyroid hormone predictive factors (T3, T4, FT3, and TSH concentrations) [11–13].

In our study, there was a higher level of various risk index values in the death group were compared with the survival group whereas serum FT3 concentration was significantly decreased in death group. FT3 may be a protective factor for the development of HBV-ACLF, which is similar to the previous findings in this field. The reason for the decrease of FT3 may be that HBV-ACLF patients occur the euthyroid sick syndrome [14,15]. In addition, the thyroid binding globulin (TBG) and ALB are mainly synthesized in the liver [16], liver failure may decreased the synthesis of TBG, the accelerated breakdown of TBG could lead to thyroid hormone-binding capacity decrease, then serum TT3 and TT4 levels were decrease, and FT3 would also decrease subsequently [9,17].

Previous studies have identified different predictors for the ACLF patients’ prognosis. However, few researches evaluated the prognostic value of FT3 for

4 Discussion

ACLF is a condition of hepatic decompensation with multiple organ failure caused by a systemic inflammation [10]. Considering the life-threatening risk of HBV-ACLF in short term, scientists pay more attention to the early determination of prognosis. There was a lot of research showed the predictors of ACLF prognosis, including liver predictive factor (TB), kidney predictive factors (creatinine), brain predictive factor (HE), coagulation predictive factor (INR), circulation predictive factors (mean arterial pressure and vasopressor use) and thyroid hormone predictive factors (T3, T4, FT3, and TSH concentrations) [11–13].

In our study, there was a higher level of various risk index values in the death group were compared with the survival group whereas serum FT3 concentration was significantly decreased in death group. FT3 may be a protective factor for the development of HBV-ACLF, which is similar to the previous findings in this field. The reason for the decrease of FT3 may be that HBV-ACLF patients occur the euthyroid sick syndrome [14,15]. In addition, the thyroid binding globulin (TBG) and ALB are mainly synthesized in the liver [16], liver failure may decreased the synthesis of TBG, the accelerated breakdown of TBG could lead to thyroid hormone-binding capacity decrease, then serum TT3 and TT4 levels were decrease, and FT3 would also decrease subsequently [9,17].

Previous studies have identified different predictors for the ACLF patients’ prognosis. However, few researches evaluated the prognostic value of FT3 for
HBV-ACLF. We studied the level of FT3 in different gender, different initial liver disease and different stages of liver failure. The results indicated that the death group had a significantly lower FT3 value than survival group, suggesting FT3 has good stability as a predictor. Its predictive ability is not affected by population, basic liver diseases and severity of liver failure.

This study integrated with predictor factors analyses, we developed FT3-related prognostic model-1 score, which could predict the prognosis of patients with HBV-ACLF. We also assessed the performance of several risk scores in prediction of HBV-ACLF patients’ prognosis. The results indicated that these prognostic scores have a better ability to predict the HBV-ACLF patients’ prognosis, which is supported by previous researches confirming the efficiency of the scores [18,19]. At the same time, we compared the prediction ability of FT3-related prognostic model-1 score with other scores. The specificity and sensitivity of FT3-related prognostic model-1 score was superior to other prediction scores. The reason for its high prediction effectiveness may be that massive hepatocyte death stimulates immune-mediated liver pathological injury in the pathophysiological process of ACLF. Then, it can result liver failure, activate the inflammatory response, trigger the systemic inflammatory response syndrome, and eventually lead to multiple organ failure [20]. It plays an inhibitory role in cellular uptake of T3 and T4 and intracellular T4 conversion of T3 and T3 secretion [21].

5 Limitation
This study had several limitations. As it was a retrospective observational study, there were only a relatively small number of observation cases. And the study is lacking external validation, so the findings probably reflect overly optimistic model performance. In the future, a prospective study with an expanded sample size and a multicenter approach could explore the association between FT3 and the severity of HBV-ACLF patients.

6 Conclusion
The FT3-related prognostic model-1 score has better prognostic value than the CLIF-OF, CLIFSOFa, MELD, MELD Na, and AARC scores. The FT3 level may facilitate the risk-stratification and clinical decision-making of HBV-ACLF.

Acknowledgements
No funding or sponsorship was received for this study or publication of this article.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Consent for publication
The manuscript is not submitted for publication or consideration elsewhere.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
This research did not receive any funding support.

Ethics approval and consent to participate
This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Beijing Youan Hospital, Capital Medical
University (Jing You ke Lun [2020] 40, LL-2020-178-K). Written informed consent was obtained from all participants.

**Author contributions**

(I) Conception and design: Zhang J  
(II) Administrative support: Chen Y and Duan ZP  
(III) Provision of study materials or patients: Zhang J and Duan ZP  
(IV) Collection and assembly of data: Chen Y and Duan ZP  
(V) Data analysis and interpretation: Zhang J Chen Y and Duan ZP  
(VI) Manuscript writing: All authors  
(VII) Final approval of manuscript: All authors

**References**

[1] Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association, Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. Guideline for diagnosis and treatment of liver failure (2018). J Clin Exp Hepatol. 2019;39(1):38–44.

[2] Liu CR, Li YP, Luo S, et al. Influencing factors for the short-term prognosis of patients with HBV-related acute-on-chronic liver failure. J Clin Hepatol. 2021;37(1):56–62.

[3] Li J, Liang X, You S, et al. Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure. J Hepatol. 2021;75(5):1104–1115.

[4] Acharya G, Kaushik RM, Gupta R, et al. Child-Turcotte-Pugh Score, MELD score and MELD-Na score as predictors of short-term mortality among patients with end-stage liver disease in Northern India. Inflamm Intest Dis. 2020;5(1):1–10.

[5] Li N, Huang C, Yu KK, et al. Validation of prognostic scores to predict short-term mortality in patients with HBV-related acute-on-chronic liver failure: the CLIF-C OF is superior to MELD, CLIF SOFA, and CLIF-C ACLF. Medicine (Baltimore). 2017;96(17):e6802.

[6] Richard M, Rajiv J, Pere G, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–1437.

[7] Piantanida E, Impolito S, Gallo D, et al. The interplay between thyroid and liver: implications for clinical practice. J Endocrinol Invest. 2020;43(7):885–899.

[8] Zhao WM, Dong PL, Fan CL, et al. The clinical value of thyroid function in patients with acute-on-chronic liver failure. Beijing Med J. 2020;42(6):554–556.

[9] Chinese Society of Infectious Diseases, Chinese Medical Association, Chinese Society of Hepatology, Chinese Medical Association. Guidelines for the prevention and treatment of chronic hepatitis B (version 2019). J Clin Hepatol. 2019;35(12):2648–2669.

[10] Stål P, Oksanen A. Acute-on-chronic liver failure (ACLF) is a separate clinical entity. Lakartidningen. 2016;113. DLUL.

[11] Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut. 2018;67(12):2181–2191.

[12] Kamath PS, Kim WR, Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797–805.

[13] Choudhury A, Jindal A, Maiwall R, et al. Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. Hepatol Int. 2017;11(5):461–471.

[14] Wu D, Sun Z, Liu X, et al. HINT: a novel prognostic model for patients with hepatitis B virus-related acute-on-chronic liver failure. Aliment Pharmacol Ther. 2018;48(7):750–760.

[15] Carulli L, Ballestri S, Lonardo A, et al. Is nonalcoholic steatohepatitis associated with a high-though-normal thyroid stimulating hormone level and lower cholesterol levels? Intern Emerg Med. 2013;8(4):297–305.

[16] Sun L, Alan PF. Euthyroid sick syndrome. Compr Physiol. 2016;6(2):1071–1080.

[17] Punekar P, Sharma AK, Jain A. A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian J Endocrinol Metab. 2018;22(5):645–650.

[18] Peng Y, Qi X, Guo X. Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Medicine (Baltimore). 2016;95(8):e2877.

[19] Wu FL, Shi KQ, Chen YP, et al. Scoring systems predict the prognosis of acute-on-chronic hepatitis B liver failure: an evidence-based review. Expert Rev Gastroenterol Hepatol. 2014;8(6):623–632.

[20] Li Q, Wang J, Lu MJ, et al. Acute-on-chronic liver failure from chronic hepatitis B, who is the behind scenes. Front Microbiol. 2020;11:583423.

[21] Luca R DE, Davis PJ, Lin HY, et al. Thyroid hormones interaction with immune response, inflammation and non-thyroidal illness syndrome. Front Cell Dev Biol. 2021;8:641030.