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Emerging Problems in Infectious Diseases

PNI, NLR and PLR combined detection prognosis of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM

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Abstract

Introduction: The prognostic nutrition index (PNI), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been studied widely in the context of cancer; however, their correlation with chronic hepatitis C-associated cirrhosis complicated by type 2 diabetes mellitus (T2DM) is unknown.

Aim: To investigate the correlation of the PNI, NLR, and PLR with chronic hepatitis C-associated cirrhosis complicated by T2DM.

Methodology: We investigated 226 patients, comprising 56 patients with chronic hepatitis C-associated cirrhosis complicated by T2DM mellitus (group A), 85 patients with chronic hepatitis C-associated cirrhosis (group B), and 85 patients with T2DM (group C). The baseline data of all patients were analyzed.

Results: A comparison of baseline data among the three groups showed significant differences in age ($p = 0.008$). The levels of PNI were different among the three groups ($p < 0.01$). The NLR, PNI, and PLR were significantly different between the good and poor prognosis groups ($p < 0.05$). The AUC for the combined determination of PNI, NLR, and PLR, showed excellent diagnostic performance (AUC = 0.911, 95% CI 0.741—0.985, sensitivity = 80.00 %, and specificity = 88.89%).

Conclusions: The PNI, NLR, and PLR were closely related to the prognosis of chronic hepatitis C-associated cirrhosis complicated by T2DM, and their combined detection had the highest specificity and sensitivity for the early prediction of the poor prognosis of chronic hepatitis C-associated cirrhosis complicated by T2DM, which has important clinical value.

Key words: Prognostic nutrition index; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; chronic hepatitis C-associated cirrhosis; T2DM.

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Introduction

Chronic hepatitis C (CHC) is an inflammatory liver disease caused by the hepatitis C virus (HCV), which is a major public health issue and a leading cause of chronic liver disease worldwide. With its characteristic high degree of chronicity, HCV infection often causes chronic inflammatory necrosis of the liver, which can lead to liver cirrhosis and even hepatocellular carcinoma (HCC) [1]. Although acute HCV infection is usually not life-threatening, complications such as ascites, upper gastrointestinal bleeding secondary to varix, and portal hypertensive gastropathy, which are associated with chronic hepatitis, are associated with a decreased quality of life and a poor prognosis [2]. Moreover, extrahepatic manifestations, such as autoimmune disorders, mixed cryoglobulinemia, Sjogren's syndrome, and endocrinological diseases (e.g. autoimmune thyroid disorders and type 2 diabetes [T2DM]) [3]. HCV infection has been shown to be a significant risk factor for developing T2DM. CHC, cirrhosis, and decompensated cirrhosis contribute to an increasingly greater risk of T2DM in individuals with HCV, but HCV clearance, either spontaneously or through clinical treatment may immediately reduce the risk of the onset and development of T2DM [4]. At present, it is clinically infected with HCV virus, and the prevalence of T2DM is generally higher than that of the normal population. Furthermore, studies on the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), which are two important indicators of systemic inflammation, have been conducted in patients with liver cancer and have been

shown to be prognostic parameters in various cancer treatments [5-7]. The PNI, which is calculated based on the serum albumin and circulating peripheral blood lymphocyte count, has been used to assess the immune nutritional status of patients with cancer, also has been verified as a useful prognostic biomarker in various cancers, including esophageal carcinoma and osteosarcoma [8-9]. In patients with CHC, albumin is also regarded as an important factor for liver function.

Although increasing evidence shows that the PNI, NLR and PLR, which represent the inflammation and nutritional statuses, can accurately predict the prognosis of patients with cancer,the relationship between the PNI, NLR, and PLR, and clinical prognosis in patients with chronic hepatitis C-associated cirrhosis complicated by T2DM remains unclear. The main purpose of this study was to evaluate the prognostic value of the PNI, NLR, and PLR in patients with chronic hepatitis C-associated cirrhosis complicated by T2DM.

Methodology

Study subjects

Following the application of inclusion and exclusion criteria, 56 patients with chronic hepatitis C-associated cirrhosis complicated by T2DM (group A), 85 patients with chronic hepatitis C-associated cirrhosis (group B), and 85 patients with T2DM (group C) from the Fuyang Second People's Hospital were included in the study from January 2018 to December 2021. Hepatitis C-associated cirrhosis was diagnosed by laboratory parameters and liver histopathology tests according to clinic standards. The patients were divided into a poor prognosis group (23 cases) and a good prognosis group (33 cases) according to the prognosis of chronic hepatitis C-associated cirrhosis complicated by T2DM after 6 months of treatment. Permission to conduct the study was provided by the Ethics Committee of Fu Yang Second People's Hospital, and informed written consent was obtained from each patient.

Clinical laboratory data

Blood biochemistry parameters, including serum albumin (ALB), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using a HITACHI 7600-020 automated biochemistry analyzer. The platelet count, lymphocyte count, mononuclear count, and neutrophil count were analyzed by an XE-2100 hematology analyzer (Sysmex, Kobe, Japan). The NLR, PNI, and PLR were calculated as follows: NLR = neutrophil count/lymphocyte count; PNI = ALB (g/L) + 5 × total lymphocyte count (10^9/L); PLR = platelet count/lymphocyte count. For all patients, data from their first laboratory test on admissions were used. All operations were performed by specially assigned personnel and in strict accordance with the instructions regarding the use of the reagents.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 22.0 software. Summary statistics of the study population were expressed as the mean ± standard deviation (mean ± SD) or median value with the interquartile range (IQR), as appropriate. The Kolmogorov-Smirnov test was performed to evaluate the variable distribution. Comparisons of demographic and clinical parameters of the two groups were performed using the Chi-square test, Student's t-test (independent samples t-test), or Mann-Whitney U-test, as appropriate, while the Kruskal-Wallis-test was used for the comparison of more than two groups. A

Table 1. Baseline characteristics of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM.

Variable	group A (n = 56)	group B (n = 85)	group C (n = 85)	χ^2 value	*p* value
Sex					
Male	26 (46.42)	37 (43.53)	45 (52.94)	1.564	0.458
Female	30 (53.58)	48 (56.47)	40 (47.06)		
Age (years)					
< 40	4 (7.14)	7 (8.24)	5 (5.89)		
40~50	1 (1.79)	25 (29.41)	26 (30.59)	9.711	0.008
50~60	16 (28.57) *	28 (32.94) *	19 (22.35) *		
> 60	35 (62.50) *	25 (29.41) *	35 (41.17) *		
Region					
Urban	25 (44.64) #	35 (41.18) #	59 (69.41)	15.580	< 0.01
Rural	31 (55.36) #	50 (58.82) #	26 (30.59)		
Alcohol consumption					
No	24 (42.86) #	37 (43.53) #	66 (77.65)	25.477	< 0.01
Yes	32 (57.14) #	48 (56.47) #	19 (22.35)		

Date were number (%); Compared to those under 40 years old,* was statistically significant (*p* value < 0.05). Compared to group C,# was statistically significant (*p* value < 0.05).

Table 2. Clinical laboratory data between groups.

Variable	group A	group B	group C	*F/H* value	*p* value
ALT (U/L)	46.00 (21.00,68.00) #	49.00 (19.00, 69.00) #	15.00 (14.00, 30.00)	17.549	0.037
AST (U/L)	28.00 (26.00,55.00) #	67.00 (27.00, 93.00) #	11.00 (15.00, 30.00)	43.76	0.041
NLR	1.94 ± 1.42#*	1.24 ± 0.40#	3.51 ± 4.78	3.901	0.024
PNI	46.35 (42.66, 54.54) #*	48.85 (43.00, 50.99)	50.65 (47.20, 53.73)	10.263	0.006
PLR	111.45 ± 80.05#	91.86 ± 41.62#	147.51 ± 101.50	4.148	0.019

Data are mean ± SD and median (P25, P75); Compared with the group B, *was statistically significant (p value < 0.05); Compared with the group C, #was statistically significant (p value < 0.05).

receiver operating characteristic (ROC) curve was used to evaluate the predictors and to determine their sensitivities and specificities. A two-sided p value < 0.05 was considered significant. The results of the analysis were obtained using SPSS for Windows.

Results

Baseline data

The study involved 226 patients. Information on the sex, age, region, and alcohol consumption characteristics of patients are summarized in Table 1. Among the included patients, 56 had chronic hepatitis C-associated cirrhosis complicated by T2DM (group A), 85 had chronic hepatitis C-associated cirrhosis (group B), and 85 had T2DM (group C). The three groups of patients showed no significant differences in sex ($p > 0.05$), but did show significant differences in age, region, and alcohol consumption among ($p < 0.05$).

Clinical laboratory data

The clinical laboratory data of the patients are shown in Table 2. The ALT, AST, NLR, and PLR were significantly different among the three groups ($p < 0.05$), as was the PNI ($p < 0.01$). The levels of ALT and AST in group A [median (P25, P75): 46.00 (21.00, 68.00) U/L and 28.00 (26.00, 55.00) U/L; 0.17 (0.14, 0.26), respectively] were significantly higher than those in group C [median (P25, P75): 15.00 (14.00, 30.00) U/L; 11.00 (15.00, 30.00) U/L; 0.12 (0.08, 0.15)]. The level of ALT and AST in group B [median (P25, P75): 49.00 (19.00, 69.00) U/L; 67.00 (27.00, 93.00) U/L; 0.19 (0.15, 0.24)] were significantly higher than those in group C. The levels of ALT and AST in group A were not significant compared with group B. The NLR in group A (mean ± SD: 1.94 ± 1.42) was significantly lower than that in group C (mean ± SD: 3.51 ± 4.78). The NLR in group B (mean ± SD: 1.24 ± 0.40) was significantly lower than in groups C and group A. The PNI in group A [median (P25, P75): 46.35 (42.66, 54.54)] was significantly lower than that in group C [median (P25, P75): 50.65 (47.20, 53.73)]. The PNI in group A was significantly lower than that in group B [median (P25, P75): 48.85 (43.00, 50.99)]. The PNI in group B was not significantly different compared to that in group C. The PLR in group A [median (P25, P75): 111.45 ± 80.05] was significantly lower than that in group C [median (P25, P75): 147.51 ± 101.50]. The PLR in group B [median (P25, P75): 91.86 ± 41.62] was significantly higher than that in group C, while that in group A was not significantly different compared to group B.

Prognostic significance

The prognostic significance of the laboratory indicators of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM (group A) are shown in Table 3. Group A was divided into a good prognosis group (n = 23) and poor prognosis group (n = 33). The NLR, PNI and PLR were significantly different between the good and poor prognosis groups ($p < 0.05$). The NLR in the poor prognosis group (mean ± SD: 2.49 ± 0.71) was higher significantly than that in the good prognosis group (mean ± SD: 1.14 ± 1.99) ($t = 1.914$, $p = 0.022$). The PNI in the poor prognosis group [median (P25, P75): 42.65 (37.66, 49.54)] was significantly lower than that in the good prognosis group [median (P25, P75): 49.35 (42.66, 54.54)] ($z = -4.322$, $p < 0.001$). The PLR in the poor prognosis group (mean ± SD: 94.57 ± 35.27) was significantly lower than that in the good prognosis group (mean ± SD: 142.45 ± 69.22) ($t = 2.409$, $p = 0.023$). The level of ALT and AST in the good prognosis group were not

Table 3. Prognostic significance of laboratory indicators.

Variables	good prognosis group	poor prognosis group	t/z value	*p* value
ALT (U/L)	26.00 (15.00, 81.00)	42.00 (22.00, 77.00)	-1.128	0.259
AST (U/L)	34.00 (27.00, 41.00)	43.00 (26.00, 53.00)	-1.043	0.307
NLR	1.14 ± 1.99	2.49 ± 0.71	1.914	0.022*
PNI	49.35 (42.66, 54.54)	42.65 (37.66, 49.54)	-4.322	< 0.001*
PLR	142.45 ± 69.22	94.57 ± 35.27	2.409	0.023*

Data were mean ± SD and median (P25, P75); *was statistically significant (p value < 0.05).

significantly different to those in the poor prognosis group (z = -1.128, p = 0.259; z = -1.043, p = 0.307; z = -0.729, p = 0.472).

ROC curve analysis

The ROC curve was used to analyze the prognosis of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM. ROC curve analysis illustrated that the AUCs of PNI, NLR, and PLR for the evaluation of the prognosis of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM mellitus were 0.872 (95% CI: 0.692 to 0.967), 0.739 (95% CI: 0.539 to 0.885), and 0.717 (0.516 to 0.869) respectively. When the PNI and NLR were combined, the AUC was 0.906 (95% CI: 0.734 to 0.983), when the PNI and PLR were combined, the AUC was 0.906 (95% CI: 0.734 to 0.983), when NLR and PLR were combined, the AUC was 0.739 (95% CI: 0.539 to 0.885). We calculated AUC for the combined determination of the PNI, NLR, and PLR, and it showed excellent diagnostic performance (AUC = 0.911, 95% CI: 0.741-0.985, Sensitivity = 80.00 %, and Specificity = 88.89%) (Table 4 and Figure 1).

Discussion

HCV is a risk factor for cirrhosis. Cirrhosis takes an average of 30 years to develop after the HCV infection, although the average period varies considerably between people. Cirrhosis is the cause of 4% annual deaths worldwide [10]. The pathogenesis of chronic hepatitis C-associated cirrhosis complicated by T2DM is relatively complex, characterized by acute and chronic hyperglycemia. The resulting proinflammatory state, can promote the synthesis and secretion of various inflammatory factors Secretion, which can increase liver oxidative stress response and increase liver inflammation and subsequent fibrosis progression.

Liver cirrhosis is the terminal stage of most chronic liver conditions, with a high risk of mortality. Careful evaluation of the prognosis of patients with cirrhotic, as well as precise management are crucial to reduce the risk of mortality [11].

Figure 1. Receiver operator characteristic curves comparing the potential of different variables to predict the prognostic value of combined detection in patients with chronic hepatitis C-associated cirrhosis complicated by T2DM.

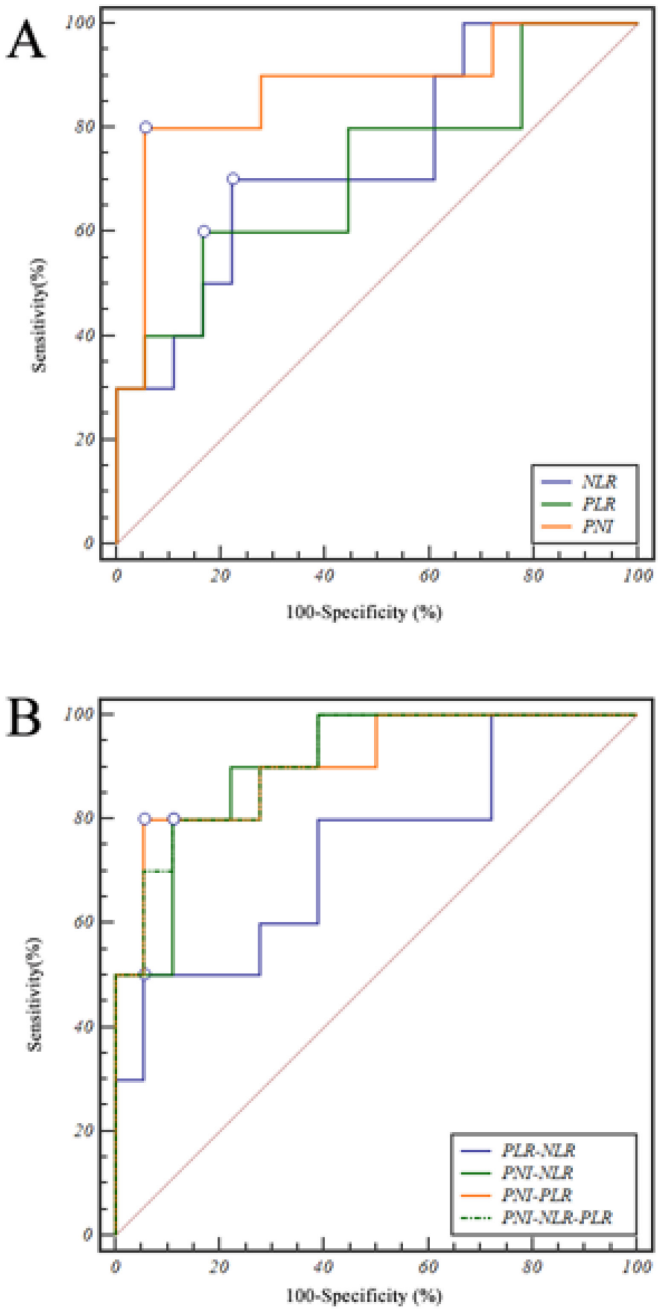

Table 4. ROC curve analysis of clinical laboratory indicators.

Variables	Sensitivity (%)	Specificity (%)	AUC	95% CI	*p* value
PNI	80.00	94.44	0.872	0.692 - 0.967	<0.0001
NLR	70.00	77.78	0.739	0.539 - 0.885	0.0196
PLR	60.00	83.33	0.717	0.516 - 0.869	0.0498
PNI-NLR	80.00	88.89	0.906	0.734 - 0.983	<0.0001
PNI-PLR	80.00	94.44	0.906	0.734 - 0.983	< 0.0001
NLR-PLR	50.00	94.44	0.739	0.539 - 0.885	0.0227
PNI-NLR-PLR	80.00	88.89	0.911	0.741 - 0.985	< 0.0001

AUC: area under the curve; CI: confidence interval.

In recent years, continuous efforts have been made to investigate the prognostic value of body fluid biomarkers for patients with cirrhosis, and promising results have been reported. As the collection of fluid specimens is easy, noninvasive, and repeatable, fluid biomarkers represent ideal indicators to predict the prognosis of cirrhosis [11]. In the present study, we evaluated and compared the performances of the PNI, PLR and NLR in patients with chronic hepatitis C-associated cirrhosis complicated by T2DM.

The proportion of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM was higher in rural areas and the proportion of alcohol consumption was also higher compared to patients with T2DM without chronic hepatitis C-associated cirrhosis. Similarly, a higher proportion of alcohol consumption was found in patients with chronic hepatitis C-associated cirrhosis without T2DM. Compared to patients with T2DM with or without chronic hepatitis C-associated cirrhosis, the prevalence of patients with chronic hepatitis C-associated cirrhosis in rural areas was higher than that in urban areas, and the prevalence of alcohol consumption was more than that of no alcohol consumption. These findings suggest that attention should be paid to the prevention and treatment of hepatitis C in patients who live in rural areas and drink alcohol. The results also demonstrated that the proportion of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM more than 60 years old and 50-60 years old was significantly increased compared to those in the age group < 40 years old ($p < 0.05$), indicating that the older the patients with chronic hepatitis C-associated cirrhosis were, the more likely they were to be complicated with T2DM. Moreover, the number of patients with chronic hepatitis C-associated cirrhosis and T2DM aged more than 60 years old and between 50 and 60 years old was significantly higher than that in the age group < 40 years old, ($p < 0.05$). Nguyen *et al.* [12] also confirmed this view through a meta-analysis. Older age was positively correlated with the prevalence of T2DM, indicating that the incidence of T2DM gradually increases with increasing age, suggesting that age is a risk factor for T2DM, and that older people need to pay more attention to the management of blood sugar.

Ali *et al.* [13] showed that serum levels of liver enzymes (AST, ALT) in both HCV and HCV/DM groups were significantly higher than those in the control group, but without any discrimination among the two HCV-diseased groups. HCV infection occurs in the human liver cells and replicate in large numbers, resulting in the release of enzymes in the cytoplasm into the bloodstream, so that the activity of these enzymes in the serum increased, causing liver damage, and liver function abnormalities [14]. Our results showed that the values of ALT and AST in patients with chronic hepatitis C-associated cirrhosis were significantly higher than those in patients with T2DM without chronic hepatitis C-associated cirrhosis ($p < 0.05$). Therefore, the liver function of patients with chronic hepatitis C-associated cirrhosis was worse than that of patients with T2DM patients without chronic hepatitis C-associated cirrhosis, and attention should be paid to the protection of the liver in chronic hepatitis C-associated cirrhosis to prevent further deterioration and induce a series of extrahepatic manifestations.

Proposed inflammatory scores, such as the NLR and PLR, are have been considered useful indicators for predicting the prognosis and survival of patients with cancers, however, due to variance in study designs and sample sizes, these studies have reported inconsistent results [15]. Our results showed that the values of NLR and PLR in patients with chronic hepatitis C-associated cirrhosis were significantly lower than those in patients with T2DM without chronic hepatitis C-associated cirrhosis ($p < 0.05$). Moreover, the NLR and PLR were significantly different between the good and poor prognosis groups ($p < 0.05$). A previous study by Li *et al.* showed that the PLR was elevated in patients with cirrhosis compared to that in liver disease, which is consistent with our findings [16]. From the pathogenetic analysis, hypersplenism and bone marrow suppression caused by hepatitis virus infection in patients with cirrhosis lead to decreased platelet count and decreased lymphocytes. In this study, compared to patients with chronic hepatitis C-associated cirrhosis without T2DM, the decline in platelets in patients with chronic hepatitis C-associated cirrhosis with T2DM was more significant than that of lymphocytes. Regarding the prognosis of patients with hepatitis C cirrhosis complicated with T2DM, the degree of platelet decline in patients with poor prognosis was more significant than that of lymphocytes. The NLR indicates the balance of the inflammatory and immune systems, making it a useful index that reflects systemic inflammation responses [17]. The NLR has attractive prognostic value for patients with hepatopathy. Our results showed that the NLR values in the good prognosis group were significantly lower than those in the poor prognosis group ($p < 0.05$). ROC curve analysis illustrated that the AUCs of the NLR and PLR for the evaluation of the prognosis of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM mellitus were 0.739 (95% CI: 0.539 to 0.885)

and 0.717 (0.516 to 0.869), respectively. However, the AUCs of the NLR and PLR were below 0.750, thus leading to poor predictive value.

The concept of the PNI was first proposed by Buzby *et al.* [18] to evaluate the risk of gastrointestinal surgery. Later, it was also used in prognostic studies of various diseases. The relationship between the PNI and clinical prognosis in patients with chronic hepatitis C-associated cirrhosis complicated by T2DM remains unclear. Our results showed that the PNI in patients with chronic hepatitis C-associated cirrhosis complicated by T2DM patients was significantly lower than in the chronic hepatitis C-associated cirrhosis patients. The level of PNI in the chronic hepatitis C-associated cirrhosis without T2DM was significantly lower than that in patients with T2DM. The PNI in the patients with chronic hepatitis C-associated cirrhosis with T2DM was not significantly different compared to those with chronic hepatitis C-associated cirrhosis without T2DM. The PNI in the poor prognosis group was significantly lower than that in the good prognosis group. The liver is the main site for the metabolism of sugars, when sugars metabolize work when it was damaged, other functions of the liver were often affected. The PNI, which was calculated based on serum albumin and circulating peripheral blood lymphocyte count, has been used to assess the immune nutritional status of patients with cancer. Many patients with T2DM have an overactive immune system, resulting in chronic inflammation in their bodies, which chould lead to impaired liver function. The PNI can be used to evaluate the nutritional status and prognosis of patients. ROC curve analysis illustrated that the AUC of the PNI for evaluating the prognosis of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM mellitus was 0.872 (95% CI: 0.692 to 0.967); as the AUC of the PNI was more than 0.750, the predictive value was considered good. However, the AUC for the combined use of the PNI, NLR, and PLR showed excellent diagnostic performance (AUC = 0.911, 95% CI: 0.741–0.985, sensitivity = 80.00%, and specificity = 88.89%), confirming the high prediction efficiency.

This study has several limitations. The sample size was relatively small. Since this study was a retrospective study, not all patients were continuously monitored for all indicators in the blood including PNI.

Conclusions

Our findings suggest that PNI, NLR, and PLR levels can be used to estimate the prognosis of patients with chronic hepatitis C-associated cirrhosis complicated by T2DM.

Authors' Contributions

Data curation: Xiaowu Wang, Yunyun Ding, Yan Liu, Tuantuan Li, Yi lang Zhu; Formal analysis: Dong Wu, Xiaowu Wang, Yi lang Zhu, Yong Gao, Xiaojuan Wang; Methodology: Dong Wu, Xiaowu Wang; Project administration: Yong Gao, Xiaojuan Wang; Writing – original draft: Dong Wu, Xiaowu Wang, Yong Gao, Xiaojuan Wang; Writing – review & editing: Dong Wu, Xiaowu Wang, Yi lang Zhu, Yong Gao, Xiaojuan Wang.

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