Clin. Lab. 2026;72:XXX-XXX
©Copyright

ORIGINAL ARTICLE

The Clinical Value of D-D, AT-III, NLR, PLT and ALB Measurement in Liver Diseases

Chenhao Xia, Zihe Xing, Jie Li, Caixin Liu, Kun Lv, Xiaoning Li

Department of Laboratory Medicine, The First Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, China

ABSTRACT

Background: **The aim is to investigate the clinical value of individual and combined assessment of plasma D-dimer (D-D), antithrombin III (AT-III), the neutrophil-to-lymphocyte ratio (NLR) and platelet count (PLT) in whole blood, as well as serum albumin (ALB) in the auxiliary diagnosis and clinical evaluation of liver diseases.**
Methods: **A total of 184 patients with hepatitis, cirrhosis, or hepatocellular carcinoma (HCC) admitted to our hospital between December 2024 and May 2025 were enrolled, together with 100 healthy individuals as controls. The levels of plasma D-D, AT-III, whole blood NLR, PLT, and serum ALB were measured. HCC patients were classified according to the China Liver Cancer (CNLC) staging system. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic performance of individual and combined markers.**
Results: **Compared with healthy controls, patients with liver diseases showed significant differences in D-D, AT-III, PLT, NLR, and ALB levels. The benign liver disease group (hepatitis and cirrhosis) had lower AT-III, PLT, and ALB levels than the HCC (malignant) group, while patients with stage II HCC exhibited lower AT-III and NLR levels than those with stage III/IV HCC. ROC analysis revealed that D-D (AUC = 0.826) and reciprocal of ALB (1/ALB, AUC = 0.822) had diagnostic value in differentiating hepatitis from cirrhosis. The combined detection of these two markers exhibited superior diagnostic performance for differentiating patients with hepatitis and cirrhosis compared to either individual indicator, achieving a further increased AUC of 0.886.**
Conclusions: **The levels of D-D, AT-III, NLR, PLT, and ALB can serve as indicators reflecting the progression of various liver diseases. These parameters can provide valuable reference information for the auxiliary clinical diagnosis, monitoring of therapeutic efficacy, and prognosis assessment of liver diseases. Among these, AT-III and NLR are associated with the staging of HCC. Notably, the combined detection of D-D and ALB can enhance the predictive value for the diagnosis of hepatitis and liver cirrhosis.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.251014)

Correspondence:
Xiaoning Li
Kun Lv
Department of Laboratory Medicine
The First Affiliated Hospital of Wannan Medical College
No. 2, Zheshan West Road
Wuhu City, 241001
Anhui Province
China
Phone: + 86 13705531365
Email: lixiaoning19702006@126.com

Manuscript accepted November 20, 2025

KEYWORDS

D-dimer, antithrombin III, hepatitis, cirrhosis, hepatocellular carcinoma, neutrophil-to-lymphocyte ratio, albumin

INTRODUCTION

Liver diseases are common conditions that pose a serious threat to human health worldwide, among which chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) representing the major types. These three conditions often follow a continuum of progression in clinical practice. Most cases of cirrhosis and

HCC develop from chronic viral hepatitis due to delayed diagnosis or inadequate treatment [1-3]. According to analyses of national cause-of-death surveillance data, including studies spanning 2013 - 2020, show that the age-standardized mortality rate of liver cancer in China has gradually declined, however, the disease burden remains substantial [4,5]. Owing to the liver's significant functional reserve capacity and the subtle and nonspecific nature of early manifestations, liver diseases are often overlooked in their initial stages. Once decompensation occurs, patients typically develop marked hepatic dysfunction accompanied by structural alterations, posing significant threats to life [6,7]. Consequently, identifying sensitive and reliable biomarkers for both diagnosis and prognosis is critically important for the early detection and timely management of liver diseases.

At present, several hematological and biochemical indicators are widely applied in clinical diagnosis and prognostic assessment, highlighting their potential value in liver diseases. D-dimer (D-D), a degradation product of cross-linked fibrin, reflects a hypercoagulable state and fibrinolytic activity, and its negative result is commonly used to exclude pulmonary embolism or deep vein thrombosis [8,9]. Antithrombin III (AT-III), synthesized by the liver and vascular endothelial cells, is the major endogenous anticoagulant that effectively inhibits coagulation and maintains hemostatic balance, playing an important role in assessing the risk of bleeding and thrombosis in patients with liver diseases [10,11]. Platelet count (PLT) is frequently used to evaluate hepatic injury and portal hypertension-related complications, and its level is often significantly reduced during the progression of liver fibrosis and portal hypertension [12-14]. In addition, the neutrophil-to-lymphocyte ratio (NLR) comprehensively reflects both inflammatory responses and immune status. It is closely associated with non-alcoholic fatty liver disease and the degree of hepatic fibrosis, and has also been linked to adverse prognosis in various chronic diseases and malignancies [15, 16]. Albumin (ALB), a classical indicator of nutritional status and liver function, also plays an essential role in risk stratification and prognostic evaluation of liver diseases [17,18].

Although these indicators have been widely applied in the diagnosis and prognostic evaluation of various diseases, their specific value in liver diseases remains unclear. In particular, different indicators may exhibit variations across pathological stages such as chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma, and it has not been fully established which indicators possess independent diagnostic significance or whether combining them might enhance classification and diagnostic efficiency.

Therefore, this study measured and compared the levels of D-D, AT-III, PLT, NLR, and ALB among patients with chronic hepatitis, cirrhosis, hepatocellular carcinoma, and healthy controls, to identify clinically relevant indicators and further evaluate the diagnostic and disease staging value of their combined detection. These findings are expected to provide a reference for the early auxiliary diagnosis, disease assessment, and prognostic evaluation of liver diseases.

MATERIALS AND METHODS

Study population

From December 2024 to May 2025, a total of 184 patients with liver diseases were recruited from the outpatient and inpatient departments of The First Affiliated Hospital of Wannan Medical College. The patient cohort comprised 30 cases of chronic hepatitis, 50 cases of liver cirrhosis, and 104 patients with HCC. Concurrently, 100 healthy individuals undergoing physical examination were enrolled as the control group. All healthy controls were without a history of acute or chronic inflammation, malnutrition, cardiopulmonary or renal diseases, immune system disorders, or malignant tumors. The inclusion criteria for the study group were as follows: patients meeting the diagnostic criteria for chronic hepatitis B [19], liver cirrhosis [20], and hepatocellular carcinoma [21], possessing normal cognitive and communication abilities, and having complete clinical data. Exclusion criteria comprised severe heart, lung, or kidney diseases; immune system abnormalities, psychiatric disorders, or infectious diseases; the presence of other primary or metastatic malignancies; and incomplete clinical data. Based on the China Liver Cancer Clinical Staging (CNLC) system, 67 HCC patients with complete data were further categorized: 33 cases in stage I, 18 in stage II, and 16 in stages III - IV.

Ethical considerations

This study was approved by the Ethics Committee of The First Affiliated Hospital of Wannan Medical College (Approval No.: (2022) Ethics Research No. 34, approved on November 22, 2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood sampling and laboratory assays

All participants were required to fast overnight before blood collection. Morning venous blood samples were collected into three types of tubes: a 1.8 mL sodium citrate anticoagulant tube (9:1 blood-to-citrate ratio), a 2 mL EDTA-K_2 tube, and a 2 mL serum separation tube. After thorough mixing, the samples were centrifuged at 3,500 rpm for 10 minutes at 4°C, and the supernatant was aliquoted.

D-D levels were measured with an immunoturbidimetric assay using the CN-6000 automated coagulation analyzer. AT-III was measured with a chromogenic substrate method. ALB was assessed by the bromocresol purple method on the Beckman AU-5800 automatic biochemical analyzer. PLT and NLR were measured using the Mindray BC-7500 automated hematology analyzer. All assays were performed strictly according to the manufacturers' instructions, with both internal

quality control and external quality assessment performed to ensure reliability.

Clinical parameters assessed

To compare the levels of plasma D-D, AT-III, whole blood PLT, NLR, and serum ALB among patients with different liver diseases (chronic hepatitis, liver cirrhosis, and HCC) and among HCC patients at different CNLC stages, respectively. ROC curves were used to evaluate the diagnostic value of each biomarker alone and in combination with others.

Statistical analysis

Data analysis was conducted using SPSS version 27.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA). Normally distributed variables were presented as mean ± standard (SD) deviation and compared using the independent-samples *t*-test or one-way ANOVA. Non-normally distributed data were presented as median (Q1, Q3) and analyzed with the Mann-Whitney U test or Kruskal-Wallis test, with Dunn-Bonferroni post hoc comparisons when appropriate. Categorical variables were compared using the chi-squared test. ROC curves constructed to determine the area under the curve (AUC), sensitivity, and specificity. Since lower ALB levels are associated with more severe liver disease, the reciprocal of ALB (1/ALB) was used in the ROC analysis to ensure that higher values correspond to worse disease status, consistent with the direction of other markers like D-D. Binary logistic regression analysis was performed to assess the diagnostic value of combined markers. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of D-D, AT-III, NLR, PLT, and ALB levels between different liver disease groups and control group

In this study, we first compared the control group with patients across three progressive stages liver disease (hepatitis, cirrhosis, and hepatocellular carcinoma) regarding D-D, AT-III, PLT, ALB, and NLR (Table 1). The results shown that compared with healthy controls, patients with liver disease presented significantly elevated D-D and NLR levels, whereas AT-III, PLT, and ALB levels were decreased to varying degrees. These findings indicate that enhanced activation of coagulation and fibrinolysis, weakened anticoagulant capacity, and impaired hepatic functional reserve occur in liver disease, with these alterations evident early in its progression.

Comparison of D-D, AT-III, PLT, and ALB levels in different liver disease groups

The levels of D-D, AT-III, PLT, ALB, and NLR were compared among the three patient groups (hepatitis, cirrhosis, and hepatocellular carcinoma groups). As shown in Table 2, significant differences were observed in D-D, AT-III, PLT, and ALB levels among the three groups ($p < 0.001$), except for NLR ($p > 0.05$). Therefore, post-hoc pairwise comparisons were performed for these four significantly different parameters (D-D, AT-III, PLT, and ALB). The results revealed stage-specific differences in these biomarkers among the groups (Table 2, Figure 1). Firstly, regarding D-D, levels in the hepatitis group were significantly lower than those in the cirrhosis group ($Z = -5.115$, $p < 0.001$) and the HCC group ($Z = -3.691$, $p = 0.001$), while the cirrhosis group had higher levels than the HCC group ($Z = 2.420$, $p = 0.047$). This pattern suggested that D-D increased markedly from the inflammatory to the cirrhotic stage but decreased to some extent in the malignant stage, exhibiting a nonlinear dynamic trend.

Meanwhile, AT-III levels were higher in the hepatitis group than in the cirrhosis group ($Z = 4.732$, $p < 0.001$), whereas the cirrhosis group had significantly lower levels than the HCC group ($Z = -4.203$, $p < 0.001$). No significant difference was observed between hepatitis and HCC ($p = 0.224$). These findings implied that AT-III was significantly reduced during cirrhosis but partially restored in HCC.

Concerning PLT levels, the hepatitis group exhibited higher levels than the cirrhosis group ($Z = 5.026$, $p < 0.001$), the cirrhosis group had lower levels than the HCC group ($Z = -4.457$, $p < 0.001$), while no significant difference was observed between hepatitis and HCC ($p = 0.172$). This observation indicated that PLT levels reached their lowest point in cirrhosis but shown partial recovery in HCC.

Notably, ALB levels were significantly higher in the hepatitis group than in the cirrhosis group ($T = 6.342$, $p < 0.001$), whereas cirrhosis patients had lower levels compared with HCC patients ($T = -4.801$, $p < 0.001$). No significant difference was found between hepatitis and HCC ($p = 0.127$). These results suggested that hepatic functional reserve is most severely impaired during cirrhosis, while in HCC, ALB levels might be influenced by both tumor burden and compensatory mechanisms, leading to a partial rebound.

It is noteworthy that although the median levels of AT-III and PLT (AT-III: $Z = 1.783$, PLT: $Z = 1.900$) and the mean difference of ALB ($T = 1.541$) in the hepatitis group were greater than those in the liver cancer group, the statistical analyses did not reach significance ($p > 0.05$). It is speculated that the limited number of cases in the hepatitis group and the imbalanced sample sizes may have contributed to insufficient statistical power to detect a difference.

Comparison of benign (hepatitis and cirrhosis) and malignant (HCC) groups

To further investigate the changes in coagulation, platelet, and synthetic functions across different stages of liver disease, the hepatitis group and cirrhosis group were combined as the benign group, while the HCC group was defined as the malignant group. As shown in

Table 1. Comparison of D-D, AT-III, PLT, NLR, and ALB among liver disease groups and healthy controls.

Groups	Cases (n)	D-D (mg/L, [Q1, Q3])	AT-III (g/L, [Q1, Q3])	PLT (10^9/L, [Q1, Q3])	NLR [Q1, Q3]	ALB (g/L, (mean ± SD))
Control	100	0.19 [0.19, 0.37]	104.2 [97.0, 115.4]	202.4 [170.2, 243.1]	1.70 [1.39, 2.17]	47.06 ± 2.24
Hepatitis	30	0.40 [0.25, 1.65]	93.4 [67.5, 108.5]	172.9 [113.0, 242.5]	2.13 [1.50, 4.75]	38.34 ± 4.51
Cirrhosis	50	3.74 [1.27, 7.50]	54.5 [47.8, 68.3]	68.3 [48.5, 113.5]	3.37 [1.82, 5.80]	32.00 ± 4.94
HCC	104	1.76 [0.58, 4.95]	75.3 [60.3, 87.2]	134.6 [94.5, 167.0]	2.71 [1.88, 5.08]	36.80 ± 4.91
H/*F*		160.256	140.050	107.167	51.262	182.513
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Values are expressed as median [Q1, Q3] or mean ± SD as appropriate. Overall group differences were tested by one-way ANOVA (for ALB) or Kruskal-Wallis test (for D-D, AT-III, PLT, and NLR). p < 0.05 was considered statistically significant.

Table 2. Intergroup comparison of D-D, AT-III, PLT, and ALB in patients with hepatitis, cirrhosis, and HCC.

Indicator	Test statistic (*H*/*F*)	p (overall)	Pairwise comparison	Z/MD	p-value (adjusted)
D-D	26.193	< 0.001	hepatitis vs. HCC	-3.691	0.001
			hepatitis vs. cirrhosis	-5.115	< 0.001
			cirrhosis vs. HCC	2.420	0.047
AT-III	26.835	< 0.001	hepatitis vs. HCC	1.783	0.224
			hepatitis vs. cirrhosis	4.732	< 0.001
			cirrhosis vs. HCC	-4.203	< 0.001
PLT	30.241	< 0.001	hepatitis vs. HCC	1.900	0.127
			hepatitis vs. cirrhosis	5.026	< 0.001
			cirrhosis vs. HCC	-4.457	< 0.001
ALB	21.634 (*F*)	< 0.001	hepatitis vs. HCC	1.541 (MD)	0.127
			hepatitis vs. cirrhosis	6.342 (MD)	< 0.001
			cirrhosis vs. HCC	-4.801 (MD)	< 0.001
NLR	2.886	0.236			

Overall group differences were tested using the Kruskal-Wallis test for nonparametric data or one-way ANOVA for parametric data. Post hoc pairwise comparisons were performed using the Dunn-Bonferroni test (nonparametric, results expressed as *Z*-values) or LSD test (parametric, results expressed as mean differences [MD]). p < 0.05 was considered statistically significant.

Figure 2 and Table 3, AT-III, PLT, and ALB were significantly lower in the benign group compared with the malignant group (AT-III: Z = -2.108, p = 0.035; PLT: Z = -2.231, p = 0.026; ALB: T = -3.102, p = 0.002). In contrast, no significant differences were observed for D-dimer (Z = -0.179, p = 0.858) and NLR (Z = -0.357, p = 0.721) between the two groups.

These findings suggested that in the benign stage, particularly in cirrhosis, patients already exhibited impaired anticoagulation capacity, reduced PLT, and decreased hepatic synthetic function. However, upon progression to HCC, specific indicators showed partial re-elevation, indicating potential attribution to compensatory mechanisms associated with tumor progression, regenerative nodule formation, or complex inflammatory pathways.

Differences in AT-III and NLR among HCC patients at different CNLC stages

In the preceding results, we observed significant alterations in coagulation function and inflammatory responses during the progression of liver diseases from

Table 3. Comparison of coagulation and liver function parameters between benign and malignant liver disease groups.

Indicator	Pairwise comparison	*Z/T*	p-value
AT-III	benign group vs. malignant group	-2.108	< 0.05
PLT	benign group vs. malignant group	-2.231	< 0.05
ALB	benign group vs. malignant group	-3.102 (*T*)	< 0.05
D-D	benign group vs. malignant group	-0.179	0.858
NLR	benign group vs. malignant group	-0.357	0.721

Data are compared between the benign group (hepatitis and cirrhosis) and the malignant group (HCC). For non-normally distributed variables, the Mann-Whitney U test was used (results expressed as *Z* values); for normally distributed variables, the independent samples *t*-test was used (results expressed as *T*-values). p < 0.05 was considered statistically significant.

Table 4. Comparison of AT-III and NLR among HCC patients with different CNLC stages.

Indicator	Test statistic (*H*)	p-value (overall)	Pairwise comparison	*Z*	p-value (adjusted)
AT-III	6.001	0.050	Stage I vs. II	1.549	0.364
			Stage I vs. III/IV	-1.259	0.624
			Stage II vs. III/IV	-2.437	0.044
NLR	7.865	0.020	Stage I vs. II	0.680	1.000
			Stage I vs. III/IV	-2.328	0.060
			Stage II vs. III/IV	-2.644	0.025

Overall group differences were tested using the Kruskal-Wallis test (H). Post-hoc pairwise comparisons were performed using the Dunn-Bonferroni test, and Z-values are reported. p < 0.05 was considered statistically significant.

Table 5. Binary logistic regression analysis of D-D, AT-III, PLT, and ALB for differentiating hepatitis and cirrhosis.

Indicator	B	SE	p-value	OR (95% CI)
D-D	0.258	0.131	0.048	1.295 (1.002 - 1.673)
AT-III	0.004	0.015	0.777	1.004 (0.975 - 1.033)
PLT	-0.008	0.004	0.083	0.992 (0.985 - 1.000)
ALB	-0.224	0.087	0.010	0.799 (0.674 - 0.948)

Logistic regression was performed to evaluate the diagnostic value of each parameter in differentiating hepatitis and cirrhosis. OR: odds ratio, CI: confidence interval. p < 0.05 was considered statistically significant.

Table 6. Diagnostic performance of D-D, ALB (reciprocal), and their combination in differentiating hepatitis and cirrhosis.

Indicator	AUC	95% CI	p-value	Sensitivity (%)	Specificity (%)
D-D	0.826	0.732 - 0.919	< 0.001	88	70
ALB (reciprocal)	0.822	0.729 - 0.941	< 0.001	82	70
D-D + ALB (reciprocal)	0.886	0.815 - 0.957	< 0.001	82	80

ROC curve analysis was performed to evaluate the diagnostic performance of D-D, ALB (reciprocal), and their combination for differentiating hepatitis and cirrhosis. AUC: area under the ROC curve, CI: confidence interval. p-values indicate the statistical significance of AUC compared with the null hypothesis of 0.5. p < 0.05 was considered statistically significant.

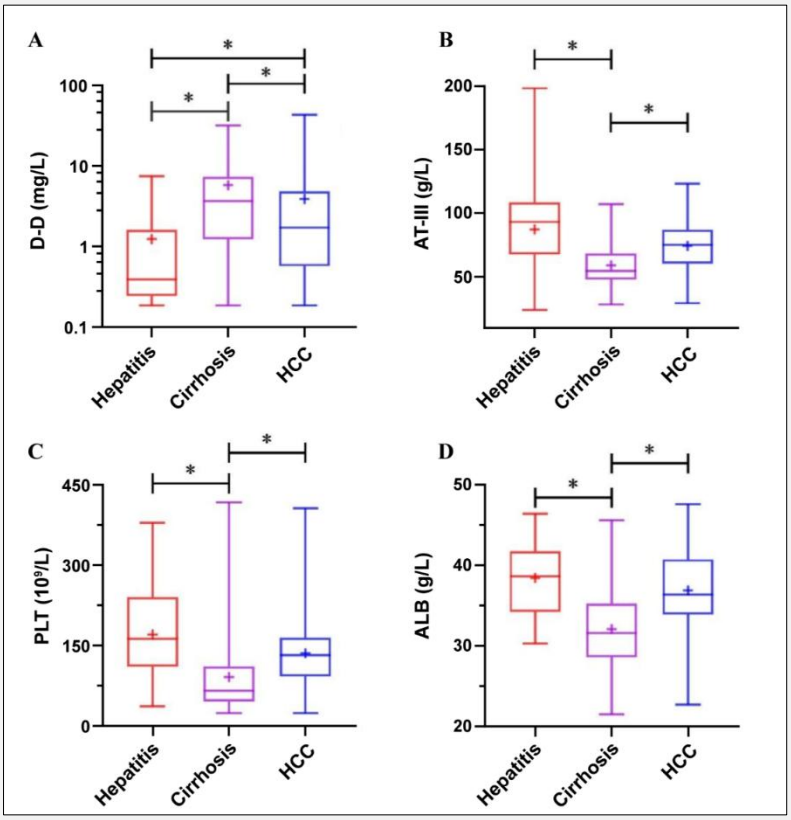


Figure 1. Comparison of biomarkers among patients with different liver diseases.

A: Plasma D-D levels, B: Plasma AT-III levels, C: Whole blood PLT counts, D: Serum ALB levels. Significant differences were observed among the three groups (* $p < 0.05$).

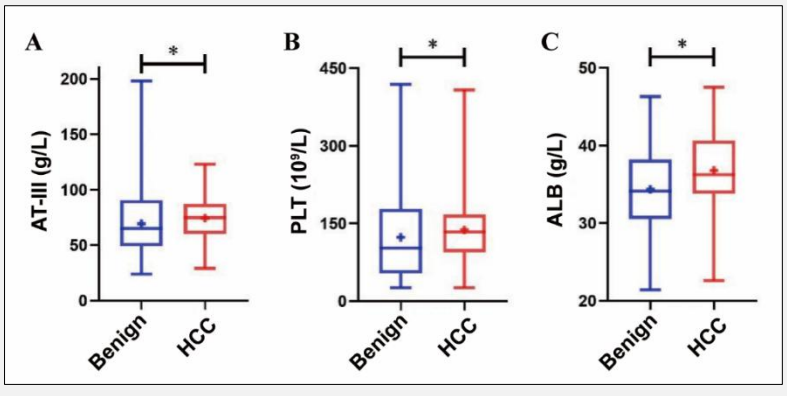


Figure 2. Comparison of biomarkers between benign and malignant liver disease groups.

A: Plasma AT-III levels, B: Whole blood PLT counts, C: Serum ALB levels. Significant differences were observed between the benign group (hepatitis + cirrhosis) and the HCC group (* $p < 0.05$).

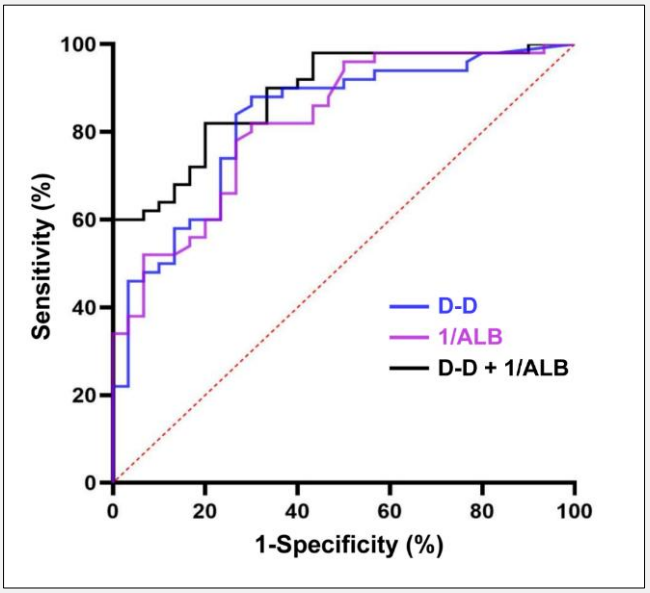


Figure 3. ROC curves of D-D, 1/ALB, and their combination for the diagnosis of hepatitis and cirrhosis.

the inflammatory stage to the malignant stage. However, intragroup heterogeneity persists among HCC patients, as different stages of tumor burden and liver function status may further influence the balance between coagulation and anticoagulation as well as systemic inflammation. Since D-D, PLT, and ALB demonstrated no statistically significant differences among patients stratified by the CNLC staging system, we subsequently performed post hoc pairwise comparisons focusing on the significantly different parameters: AT-III and NLR (Table 4).

The results showed that AT-III levels exhibited a borderline overall difference among the CNLC stages (H = 6.001, p = 0.050). Pairwise comparisons indicated that AT-III levels in stage II patients were significantly lower than those in stage III/IV (Z = -2.437, p = 0.044), while no significant differences were observed between stage I and stage II or between stage I and stage III/IV. These findings suggest that the decline in AT-III may primarily occur at stage II, with a possible partial rebound at advanced stages.

In contrast, NLR demonstrated a statistically significant difference among stages (H = 7.865, p = 0.020). Further pairwise analysis revealed that NLR levels in stage II patients were significantly lower than those in stage III/IV (Z = -2.644, p = 0.025), whereas differences between stage I and stage II or between stage I and stage III/IV were not significant. This indicates that NLR is related to tumor progression and tends to increase, particularly at stage III/IV. Overall, these results suggested that AT-III and NLR may be associated with tumor stage. Collectively, dynamic monitoring of these indicators may provide useful guidance for assessing disease severity in patients with liver disorders.

The diagnostic and predictive value of D-D and ALB in hepatitis and cirrhosis

Given that only the comparison between hepatitis and cirrhosis in the post-hoc pairwise comparisons showed significant differences in the D-D, AT-III, PLT, and ALB levels ($p < 0.001$) (Table 2), we therefore performed a binary logistic regression analysis to determine which of these indicators had independent diagnostic value for differentiating hepatitis from cirrhosis. The results shown that D-D (p = 0.048) and ALB (p = 0.010) reached statistical significance in the model, whereas AT-III and PLT did not (Table 5). These results suggested that both D-D and ALB were of high value in the diagnosis of hepatitis and cirrhosis.

Based on this, ROC curve analysis was further conducted to verify the diagnostic performance of these indicators identified by logistic regression (Table 6, Figure 3). Since lower ALB levels are associated with more severe liver disease, the 1/ALB was used in the ROC analysis to ensure that higher values correspond to worse disease status, consistent with the direction of D-D marker. The results demonstrated that both D-D (AUC = 0.826) and the 1/ALB (AUC = 0.822) alone had good diagnostic value, with sensitivities of 88% and 82% and specificities of 70%, respectively. More importantly, their com-

bination achieved an AUC of 0.886, with sensitivity maintained at 82% and specificity increased to 80%, which was superior to either indicator alone.
In summary, these results indicated that D-D and ALB not only have independent diagnostic significance, but have also shown higher diagnostic efficacy when combined, providing important reference value for early classification and clinical intervention of liver disease.

DISCUSSION

The liver is the primary site for the synthesis of most plasma proteins, including coagulation factors, anticoagulants, and fibrinolytic components, with the exception of γ-globulin and von Willebrand factor [22,23]. Once hepatic function is impaired, disease progression toward cirrhosis and even HCC is often inevitable if timely intervention is not achieved, typically manifesting as coagulation disorders, reduced ALB synthesis, and impaired PLT production [24,25]. Although liver biopsy remains the diagnostic gold standard, its invasiveness and bleeding risk limit its routine use [26]. Therefore, identifying non-invasive hematological indicators with the potential for dynamic monitoring and clinical guidance is of great importance.
Coagulation and fibrinolysis exhibited distinct stage-specific patterns. In our study, it was found that D-D levels peaked during cirrhosis but declined in HCC, indicating that peak hyperfibrinolysis corresponds to severe portal hypertension and endothelial injury rather than malignant transformation. Previous studies have consistently reported marked elevations of D-D in cirrhosis, a finding that is in line with our findings [27].
In our study, AT-III and PLT exhibited a stage-specific trajectory, which decreased significantly during cirrhosis compared with the other two groups of liver disease patients and healthy controls, but shown a modest rebound upon HCC developed. Rather than reflecting true recovery of hepatic function, this apparent improvement is more plausibly explained by residual synthetic activity, the metabolic demands of regenerative nodules, and the influence of therapeutic interventions. In clinical settings, such changes may also be influenced by antiviral therapy or interventional procedures, particularly as PLT levels can partially recover following improvement of splenic function or treatment-related modulation. Collectively, these findings underscore the intricate and compensatory nature of coagulation regulation in advanced liver disease, where the shifts observed in HCC are better interpreted as adaptive responses than as genuine restoration.
Regarding synthetic function, ALB levels were markedly reduced during cirrhosis and reached a nadir at this stage, but demonstrated a modest rebound in HCC. This rebound does not represent genuine recovery of hepatic synthetic capacity; rather, it may reflect tumor-associated metabolic reprogramming or the effects of supportive treatment. Specifically, HCC cells can reprogram glucose and lipid metabolism to maintain partial protein synthesis, which may mask the true extent of impaired hepatic function [28,29]. Clinically, this indicates that ALB alone is not a reliable marker for disease evaluation and should be interpreted in conjunction with other parameters to enhance diagnostic accuracy.
The NLR demonstrated a progressive increase across disease stages, with significantly elevated levels in stage III/IV HCC compared to stage II. This trend reflects the coexistence of amplified inflammatory signaling and profound immunosuppression, which is a hallmark of the tumor microenvironment in advanced liver disease. Our findings align with the tumor microenvironment characteristics, where pro-inflammatory cytokine upregulation coexists with lymphocyte depletion, further supporting the potential of NLR as a marker for tumor staging and prognosis [30,31]. Additionally, the overexpression of procoagulant factors by tumor cells may exacerbate the hypercoagulable state while simultaneously promoting tumor progression and metastasis, revealing a bidirectional interaction between coagulation disorders and malignant transformation.
More importantly, our combined analysis demonstrated that the pairing of D-D and ALB offered superior discriminatory ability for identifying early-stage disease (hepatitis and cirrhosis) compared with either marker alone. This finding indicated that single parameters often capture only a limited facet of hepatic pathology, whereas a composite approach can more effectively reflect the dynamic progression of liver disease. Unlike previous studies which primarily focused on individual markers, our work validates the clinical utility of a multi-marker strategy, providing preliminary evidence to support the development of risk stratification and predictive models based on multidimensional hematological parameters. In beyond risk stratification, this combined strategy also holds promise for early screening and longitudinal monitoring in clinical practice.
Nevertheless, several limitations must be acknowledged. The relatively small sample size and uneven distribution across groups may have compromised the robustness of the findings. In addition, the single-center design limits external validation, and the reliance on peripheral blood indices without integration of pathological or molecular evidence constrains mechanistic inference. Future multicenter, large-scale prospective studies, incorporating longitudinal follow-up and mechanistic investigations, will be necessary to further elucidate the dynamic interplay of coagulation, synthetic function, and immune-inflammatory markers across different stages of liver disease.

CONCLUSION

In conclusion, this study indicates that there are significant differences in the levels of plasma D-D, AT-III, whole blood PLT, NLR, and serum ALB between liver disease patients and healthy controls. Moreover, D-D,

AT-III, PLT, and ALB could distinguish hepatitis, cirrhosis, and HCC, while NLR mainly reflected HCC staging. Importantly, ROC analysis showed that although D-D (AUC = 0.826) and the 1/ALB (AUC = 0.822) alone had diagnostic value, their combination achieved the highest performance (AUC = 0.886). These findings suggest that D-D and ALB, especially when used in combination, demonstrate superior clinical diagnostic and predictive value in hepatitis and liver cirrhosis, and may serve as valuable indicators for liver disease assessment.

Ethical Approval:
All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of The First Affiliated Hospital of Wannan Medical College (Approval No.: (2022) Ethics Research No. 34, approved on November 22, 2024), written informed consent was obtained.

Consent for Publication:
Informed consent was obtained from all individual participants included in the study.

Consent to Participate Declaration:
Written informed consent was obtained from all individual participants included in the study.

Data Availability:
The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Declaration of Generative AI in Scientific Writing:
All authors confirm that they did not use AI tools to write the manuscript.

Source of Funds:
This study was received by China Higher Education Institution Industry-University-Research Innovation Fund - Jiuqiang Clinical Laboratory Special Project (Grant No. 2023JQ027), and Wuhu City 'Hua Tuo Plan' Tiered Talent Training - Municipal Level Special Funds for Renowned Physicians

Declaration of Interest:
The authors declare that there are no conflicts of interest regarding the publication of this paper.

References:

1. Yang K, Huang Z, Wang S, et al. The Hepatic Nerves Regulated Inflammatory Effect in the Process of Liver Injury: Is Nerve the Key Treating Target for Liver Inflammation? Inflammation 2023; 46(5):1602-11. (PMID: 37490221)
2. Kalantari L, Ghotbabadi ZR, Gholipour A, et al. A state-of-the-art review on the NRF2 in Hepatitis virus-associated liver cancer. Cell Commun Signal 2023;21(1):318. (PMID: 37946175)
3. Roulot D, Brichler S, Layese R, et al. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. J Hepatol 2020;73(5):1046-62. (PMID: 32634548)
4. Qin Y, Tang C, Li J, Gong J. Liver cancer in China: the analysis of mortality and burden of disease trends from 2008 to 2021. BMC Cancer 2024;24(1):594. (PMID: 38750424)
5. Gan T, Liu Y, Bambrick H, Zhou M, Hu W. Liver Cancer Mortality Disparities at a Fine Scale Among Subpopulations in China: Nationwide Analysis of Spatial and Temporal Trends. JMIR Public Health Surveill 2024;10:e54967. (PMID: 39118559)
6. Silvestre OM, Bacal F, de Souza Ramos D, et al. Impact of the severity of end-stage liver disease in cardiac structure and function. Ann Hepatol 2013;12(1):85-91. (PMID: 23293198)
7. Wallace K, Burt AD, Wright MC. Liver fibrosis. Biochem J 2008;411(1):1-18. (PMID: 18333835)
8. Stals MAM, Takada T, Kraaijpoel N, et al. Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Clinically Relevant Patient Subgroups : A Systematic Review and Individual-Patient Data Meta-analysis. Ann Intern Med 2022; 175(2):244-55. PMID: 34904857)
9. Huisman MV, Tromeur C, Le Gal G, Le Roux PY, Righini M. Diagnostic management of acute pulmonary embolism. Presse Med 2024;53(3):104241. (PMID: 39181236)
10. Sinegre T, Abergel A, Lecompte T, Lebreton A. Prothrombin conversion and thrombin decay in patients with cirrhosis-role of prothrombin and antithrombin deficiencies. J Thromb Haemost 2024;22(5):1347-57. (PMID: 38309434)
11. Quinn T, Cholette JM, Pinto MG, et al. Antithrombin activity and central venous catheter-associated thrombosis in critically ill children at high risk of bleeding. J Thromb Haemost 2024;22(1):213-24. (PMID: 37797693)
12. Adinolfi LE, Giordano MG, Andreana A, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Br J Haematol 2001;113(3): 590-5. (PMID: 11380442)
13. Chen SH, Tsai SC, Lu HC. Platelets as a Gauge of Liver Disease Kinetics? Int J Mol Sci 2022;23(19):11460. (PMID: 36232759)
14. van Dievoet MA, Eeckhoudt S, Stephenne X. Primary Hemostasis in Chronic Liver Disease and Cirrhosis: What Did We Learn over the Past Decade? Int J Mol Sci 2020;21(9):3294. (PMID: 32384725)
15. Xu C, Wu F, Du L, Dong Y, Lin S. Significant association between high neutrophil-lymphocyte ratio and poor prognosis in patients with hepatocellular carcinoma: a systematic review and meta-analysis. Front Immunol 2023;14:1211399. (PMID: 37809083)
16. Alkhouri N, Morris-Stiff G, Campbell C, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2012;32(2):297-302. (PMID: 22097893)

17. Bettinger D, Sturm L, Pfaff L, et al. Refining prediction of survival after TIPS with the novel Freiburg index of post-TIPS survival. J Hepatol 2021;74(6):1362-72. (PMID: 33508376)

18. Semmler G, Meyer EL, Kozbial K, et al. HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease. J Hepatol 2022;76(4):812-21. (PMID: 34871626)

19. Jiang C, Liu J, Li R, et al. Clinicopathologic characteristics of liver inflammation and fibrosis in 310 patients with chronic hepatitis B. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2023;48(5):698-706. (PMID: 37539572)

20. Ndow G, Shimakawa Y, Leith D, et al. Clinical outcomes of untreated adults living with chronic hepatitis B in The Gambia: an analysis of data from the prospective PROLIFICA cohort study. Lancet Gastroenterol Hepatol 2024;9(12):1133-46. (PMID: 39521002)

21. Pennisi G, Di Maria G, Wong VW, et al. Impact of first and further decompensation in patients with compensated ACLD due to MASLD. J Hepatol 2025 Dec;83(6):1266-77. (PMID: 40550340)

22. Morrow GB, Beavis J, Harper S, et al. Coagulation status of critically ill patients with and without liver disease assessed using a novel thrombin generation analyzer. J Thromb Haemost 2020; 18(7):1576-85. (PMID: 32196929)

23. Scarlatescu E, Levy JH, Moore H, et al. Disseminated intravascular coagulation and cirrhotic coagulopathy: overlap and differences. The current state of knowledge. Communication from the SSC of the ISTH. J Thromb Haemost 2025;23(3):1085-106. (PMID: 39662873)

24. Milosevic I, Vujovic A, Barac A, et al. Gut-Liver Axis, Gut Microbiota, and Its Modulation in the Management of Liver Diseases: A Review of the Literature. Int J Mol Sci 2019;20(2):395. (PMID: 30658519)

25. Groeneveld D, Cline-Fedewa H, Baker KS, et al. Von Willebrand factor delays liver repair after acetaminophen-induced acute liver injury in mice. J Hepatol 2020;72(1):146-55. (PMID: 31606553)

26. Moreno C, Mueller S, Szabo G. Non-invasive diagnosis and biomarkers in alcohol-related liver disease. J Hepatol 2019;70(2): 273-83. (PMID: 30658728)

27. Chen B, Liu J, Li Y, et al. Elevated D-Dimer levels correlate with the development of hepatorenal syndrome and a poor outcome in patients with cirrhosis. Scand J Gastroenterol 2022;57(12):1486-93. (PMID: 35833837)

28. Tian LY, Smit DJ, Jücker M. The Role of PI3K/AKT/mTOR Signaling in Hepatocellular Carcinoma Metabolism. Int J Mol Sci 2023;24(3):2652. (PMID: 36768977)

29. Berndt N, Eckstein J, Heucke N, et al. Metabolic heterogeneity of human hepatocellular carcinoma: implications for personalized pharmacological treatment. FEBS J 2021;288(7):2332-46. (PMID: 33030799)

30. Li B, Xiong F, Yi S, Wang S. Prognostic and Clinicopathologic Significance of Neutrophil-to-Lymphocyte Ratio in Esophageal Cancer: An Update Meta-Analysis. Technol Cancer Res Treat 2022;21:15330338211070140. (PMID: 35025614)

31. Gao Q, Quan M, Zhang L, Ran Y, Zhong J, Wang B. Neutrophil-To-Lymphocyte Ratio as a Prognostic Indicator in Thyroid Cancer. Cancer Control 2024;31:10732748241309048. (PMID: 39696882)