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Original Article

Elevated Serum DcR3, Fas, and NLR Ratio are correlated with the progression of Liver Cirrhosis

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Abstract: Objective: To investigate the correlation between serum levels of decoy receptor 3 (DcR3), neutrophil-to-lymphocyte ratio (NLR), and Fas with the prognosis of liver cirrhosis, with the aim of providing clinical reference for the evaluation of cirrhosis. Methods: 123 patients with liver cirrhosis were retrospectively selected as the observation group, and 123 healthy individuals as the control group. Serum DcR3, Fas, and peripheral blood NLR were measured and compared between groups. Differences in these indicators were analyzed among patients with varying cirrhosis types and those with liver cancer. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of each indicator for cirrhosis progression to liver cancer. Results: Serum levels of DcR3, Fas, and peripheral blood NLR were significantly higher in the observation group compared to the control group ($P < 0.05$). Among cirrhosis subtypes, patients with liver cancer exhibited the highest levels of DcR3, Fas, and NLR, followed by those with decompensated cirrhosis, with the lowest levels observed in patients with compensated cirrhosis ($P < 0.05$). Additionally, cirrhosis patients showed significantly higher levels of these markers than compensated cirrhosis patients ($P < 0.05$). Among patients with different grades of cirrhosis, the levels of each indicator were highest in grade C, followed by grade B, and lowest in grade A ($P < 0.05$). ROC curve analysis showed that DcR3, Fas, and NLR were significant predictors of cirrhosis progression to liver cancer ($P < 0.05$). Conclusion: Serum levels of DcR3, Fas, and peripheral blood NLR increase with the progression of liver cirrhosis, demonstrating significant diagnostic value for assessing the prognosis of cirrhosis.

Keywords: Liver cirrhosis, decoy receptor 3, Fas, neutrophil-to-lymphocyte ratio

Introduction

Liver cirrhosis is a chronic, progressive liver disease primarily caused by viral infections, characterized by a prolonged course, low cure rate, and high mortality [1-3]. In China, the incidence of cirrhosis is approximately 17 per 100,000 people, with a higher prevalence among men aged 20-50, and this trend is increasing with social development [4-6]. In the early stages, cirrhosis mainly manifests with symptoms of liver dysfunction and portal hypertension. However, as the disease progresses to advanced stages, complications such as gastrointestinal bleeding, secondary infections, and hepatic encephalopathy may develop, significantly threatening patient health. Currently, there is no specific therapeutic agent for liver cirrhosis, and due to compromised liver function, the overuse of medications is generally avoided to minimize further hepatic damage. As a result, recent research has increasingly focused on early diagnosis and treatment of cirrhosis, particularly in identifying sensitive and specific auxiliary diagnostic markers.

Decoy receptor 3 (DcR3) is a type of tumor necrosis factor receptor, known for its role in regulating cell proliferation and inhibiting apoptosis [7, 8]. Emerging studies have shown that DcR3 may contribute to liver fibrosis and act as an oncogene in the development of liver cancer,

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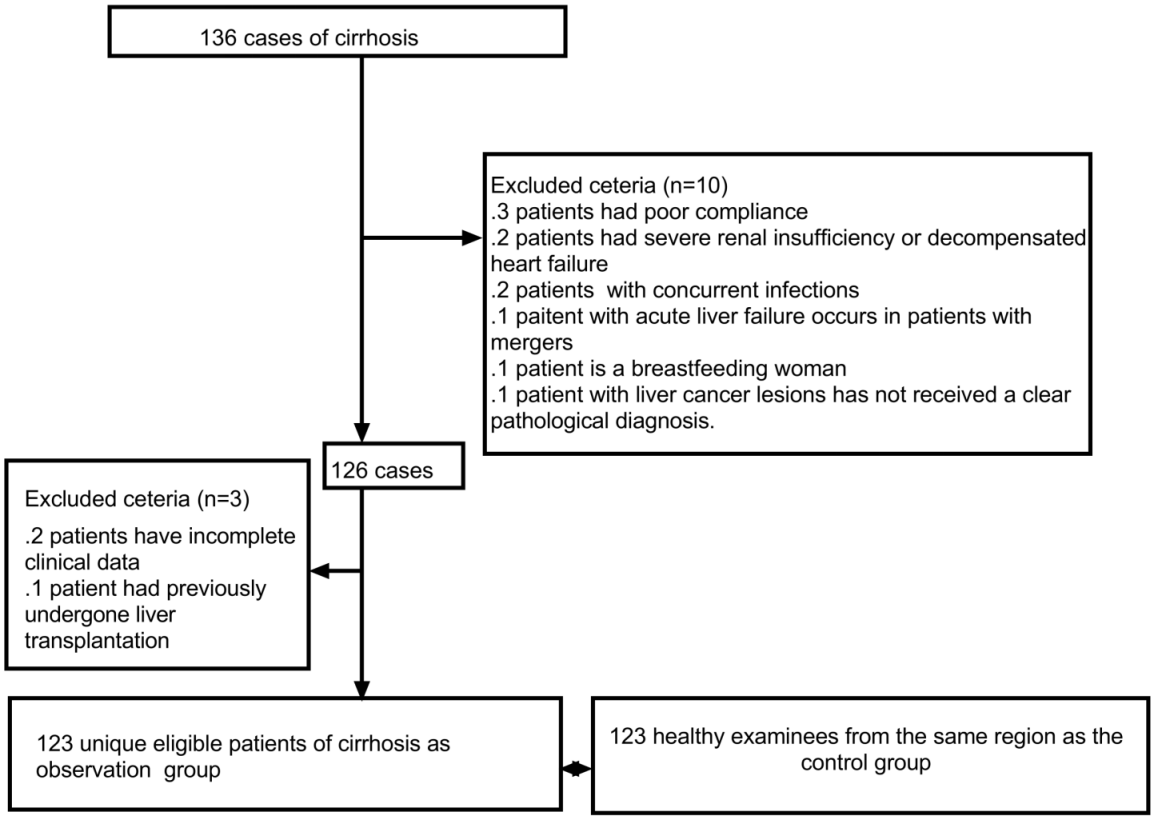

Figure 1. Selection process for the two groups.

although current evidence remains limited [8]. The neutrophil-to-lymphocyte ratio (NLR), a well-established marker of systemic inflammation, has been widely studied and shown to correlate with the prognosis of various critical conditions, including malignancies and acute pancreatitis. Elevated NLR levels are typically associated with poorer outcomes [9, 10]. The Fas/Fas ligand (FasL) signaling pathway is crucial in regulating apoptosis. Studies have demonstrated that Fas is expressed at varying levels in hepatocytes chronically infected with hepatitis B virus (HBV), suggesting its significant role in the development and progression of cirrhosis and liver cancer [11, 12].

Given these findings, the present study investigates the correlation of serum levels of DcR3, NLR, and Fas with the prognosis of liver cirrhosis, aiming to provide clinical evidence for evaluating cirrhosis progression.

Materials and methods

Case selection

This retrospective study employed a case-control design. A total of 123 patients with liver cirrhosis, admitted to The Second Affiliated Hospital, Shantou University Medical College between January 2021 and December 2023, who met the inclusion and exclusion criteria, were selected as the observation group. Concurrently, 123 healthy individuals were recruited as the control group. The patient selection process is shown in **Figure 1**. Within the observation group, patients were categorized based on the severity of cirrhosis into compensated cirrhosis (43 cases), decompensated cirrhosis (51 cases), and primary liver cancer (29 cases) [13]. Additionally, based on the Child-Pugh classification, they were further divided into grade A (44 cases), grade B (50 cases), and grade C (29 cases) [14]. This study was approved by The Second Affiliated Hospital, Shantou University Medical College's Ethics Committee.

Inclusion Criteria: Participants were eligible for inclusion if they met all of the following criteria: (1) a confirmed diagnosis of liver cirrhosis, with liver biopsy demonstrating diffuse hepatic fibrosis with pseudolobule formation [14]; (2) no history of surgical or interventional treat-

ment; (3) age between 18 and 60 years; (4) completion of the entire treatment cycle at our hospital.

Exclusion Criteria: Participants were excluded if any of the following conditions applied: (1) presence of severe comorbidities; (2) poor compliance or inability to adhere to the treatment; (3) absence of a definitive pathological diagnosis for liver cancer lesions; (4) presence of infection; (5) incomplete clinical or laboratory data; (6) acute liver failure; (7) history of liver transplantation; (8) pregnancy or lactation.

Data collection

On the morning following enrollment, 5 mL of venous blood was collected from each participant into two anticoagulant tubes and immediately processed for analysis. One tube was analyzed for NLR levels using the Mindray BC-5390 automated hematology analyzer (Mindray, China). All procedures were performed in strict accordance with the manufacturer's instructions. The second tube was centrifuged at 3000 rpm for 5 minutes to isolate the serum. Serum levels of DcR3 and Fas were measured using enzyme-linked immunosorbent assay (ELISA) on the SpectraMax Paradigm multifunctional microplate reader (Molecular Devices, USA). ELISA kits for DcR3 and Fas were obtained from Abcam, USA (catalog numbers: ab242244 and ab183360, respectively).

Primary indicators: Comparison of DcR3, Fas, and NLR levels between the observation group and the control group; analysis of the diagnostic performance of DcR3, Fas, and NLR in predicting the progression of cirrhosis to liver cancer.

Secondary indicators: Comparison of general data between the observation group and the control group; comparison of DcR3, Fas, and NLR levels among patients with different stages of cirrhosis; comparison of DcR3, Fas, and NLR levels among patients stratified by Child-Pugh classification.

Statistical analysis

Statistical analyses were conducted using SPSS 19.0. Categorical data were expressed as case numbers and percentages, with comparisons between groups conducted using the χ^2 test. Continuous data following normal distribution were presented as mean ± standard deviation (SD), with between-group comparisons performed using the t-test. Non-normally distributed data were represented by medians with interquartile ranges (P25-P75) and were analyzed using the Mann-Whitney U test for comparisons between two groups. For comparisons among multiple groups, one-way analysis of variance (ANOVA) was applied, followed by Tukey test for pairwise comparisons. Intergroup comparisons of continuous data were performed using the t-test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of each indicator for cirrhosis progression to liver cancer. The Spearman correlation coefficient was calculated to evaluate the relationship between DcR3 and Fas expression levels. A *P*-value < 0.05 was considered statistically significant.

Results

Comparison of general data between the two groups

There were no statistically significant differences in age, gender, or other general data between the two groups (all P > 0.05), as shown in **Table 1**.

Comparison of peripheral blood Hb, platelet count, and C-reactive protein between the two groups

No statistically significant differences were observed in peripheral blood hemoglobin (Hb), platelet count, or C-reactive protein (CRP) levels between the two groups (all P > 0.05), as shown in **Table 2**.

Comparison of serum DcR3, Fas, and peripheral blood NLR between the two groups

Serum levels of DcR3, Fas, and peripheral blood NLR were significantly higher in the observation group compared to those in the control group (all P < 0.05), as shown in **Table 3**.

Comparison of serum DcR3, Fas, and peripheral blood NLR among patients with different stages of cirrhosis

Compared to patients with compensated cirrhosis, those with decompensated cirrhosis and primary liver cancer showed significantly elevated levels of serum DcR3, Fas, and periph-

Table 1. Comparison of general data between the two groups

Indicators	Observation group (n=123)	Control group (n=123)	t/χ^2	*P*
Age (years)	42.4±5.9	42.9±6.1	0.653	0.514
Gender			0.148	0.700
Male	70	67		
Female	53	56		
Body Mass Index (kg/m^2)	23.24±2.17	23.12±2.33	0.418	0.676
Smoking history			0.498	0.480
Yes	21	17		
No	102	106		
Drinking history			0.618	0.432
Yes	28	23		
No	95	100		
Hypertension			0.332	0.564
Yes	17	14		
No	106	109		
Diabetes			0.001	0.980
Yes	11	10		
No	112	113		

Table 2. Comparison of peripheral blood indicators between the two groups

Group	Hb (g/dl)	Platelet count (×10^9/L)	C-reactive protein (g/L)
Observation group (n=123)	13.4±2.5	287.5±56.8	5.94±3.9
Control group (n=123)	13.8±2.4	298.4±57.8	5.01±3.5
t	-1.280	-1.493	1.968
P	0.203	0.137	0.050

Note: Hb: blood hemoglobin.

Table 3. Comparison of serum DcR3, Fas and peripheral blood NLR levels between the two groups

Group	Fas (ng/L)	DcR3 (ng/mL)	NLR (%)
Observation group (n=123)	177.80±33.07	199.68±32.19	4.57±1.30
Control group (n=123)	133.17±26.68	148.14±24.49	2.05±0.69
t	11.649	14.132	18.990
P	< 0.001	< 0.001	< 0.001

Note: DcR3: decoy receptor 3; NLR: neutrophil-to-lymphocyte ratio.

eral blood NLR (all P < 0.05). Moreover, primary liver cancer patients had significantly higher levels of these indicators than decompensated cirrhosis patients (all P < 0.05), as shown in **Table 4**.

Comparison of serum DcR3, Fas, and peripheral blood NLR across Child-Pugh classes

Serum levels of DcR3, Fas, and peripheral blood NLR were significantly elevated in Child-Pugh Classes B and C patients compared to Class A patients (all P < 0.05). Additionally, these indicators were significantly higher in Class C patients compared to those in Class B patients (all P < 0.05), as shown in **Table 5**.

Diagnostic efficacy of DcR3, Fas, and NLR for predicting cirrhosis progression to liver cancer

ROC curve analysis indicated that serum levels of DcR3, Fas, and peripheral blood NLR had statistically significant diagnostic value for predicting the progression of cirrhosis to liver cancer (all P < 0.05), as shown in **Table 6** and **Figure 2**.

Table 4. Comparison of serum DcR3, Fas and peripheral blood NLR levels in patients with different stages of cirrhosis

Group	Fas (ng/L)	DcR3 (ng/mL)	NLR (%)
Compensated cirrhosis (n=43)	154.45±37.21	163.77±29.93	4.02±0.96
Decompensated cirrhosis (n=51)	179.08±30.22[a]	213.01±30.06[a]	4.19±1.12[a]
Primary liver cancer (n=29)	211.03±30.57[a,b]	229.97±28.29[a,b]	6.06±1.14[a,b]
F	25.799	52.595	37.057
P	< 0.001	< 0.001	< 0.001

Note: Compared with compensated cirrhosis, [a]P < 0.05; Compared with decompensated cirrhosis, [b]P < 0.05. DcR3: decoy receptor 3; NLR: neutrophil-to-lymphocyte ratio.

Table 5. Comparison of serum DcR3, Fas and peripheral blood NLR levels across different Child-Pugh classes

Group	Fas (ng/L)	DcR3 (ng/mL)	NLR (%)
Child-Pugh Grade A (n=44)	154.37±37.73	163.44±29.58	3.98±0.94
Child-Pugh Grade B (n=50)	179.15±3.13[a]	213.45±30.17[a]	4.22±1.08[a]
Child-Pugh Grade C (n=29)	211.03±30.57[a,b]	229.97±28.29[a,b]	6.06±1.14[a,b]
F	38.426	53.827	39.148
P	< 0.001	< 0.001	< 0.001

Note: Compared with patients with Child-Pugh grade A cirrhosis, [a]P < 0.05; Compared with Child-Pugh grade B, [b]P < 0.05. DcR3: decoy receptor 3; NLR: neutrophil-to-lymphocyte ratio.

Table 6. Analysis of diagnostic efficacy of DcR3, Fas and NLR in predicting the progression of liver cirrhosis to liver cancer

Indicators	AUC	95% *CI*	*P*
Fas (ng/L)	0.841	0.793,0.890	0.001
DcR3 (ng/mL)	0.914	0.954,0.991	< 0.001
NLR (%)	0.973	0.879,0.949	< 0.001

Note: DcR3: decoy receptor 3; NLR: neutrophil-to-lymphocyte ratio.

Correlation analysis between DcR3 and Fas in peripheral blood of cirrhosis patients

Spearman correlation analysis revealed a strong negative correlation between DcR3 and Fas expression levels in the peripheral blood of cirrhosis patients (r=-0.883, P < 0.01), as shown in **Figure 3**.

Discussion

Liver cirrhosis is a progressive disease with a gradual course and can remain compensated for a period. According to the Child-Pugh classification, patients with Class A cirrhosis are generally in the compensated stage, where clinical symptoms are often mild. Consequently, by the time of diagnosis, many patients have already progressed to more advanced stages of the disease. Patients in Class B and C are generally in the decompensated stage, characterized by severe liver dysfunction and the development of serious complications, including jaundice, ascites, hematemesis, and hepatic encephalopathy. As the disease progresses, these complications may lead to life-threatening outcomes [15, 16]. Therefore, in the absence of effective therapeutic drugs, the identification of specific biomarkers for early diagnosis is essential for improving cirrhosis management and treatment.

DcR3 and Fas are members of the tumor necrosis factor receptor family, with Fas mediating apoptosis through its interaction with FasL [17, 18]. In the context of HBV infection, immune-activated cells can engage Fas-expressing target cells via FasL, thereby promoting apoptosis [12]. Our study shows that serum Fas levels increase with the severity of cirrhosis, and disease staging is closely associated with Fas expression. DcR3 acts by competitively binding with FasL, LIGHT, and TLIA ligands, thereby inhibiting apoptosis mediated by these pathways. This mechanism helps tumor cells evade immune surveillance and clearance. Previous studies have indicated that DcR3 is overex-

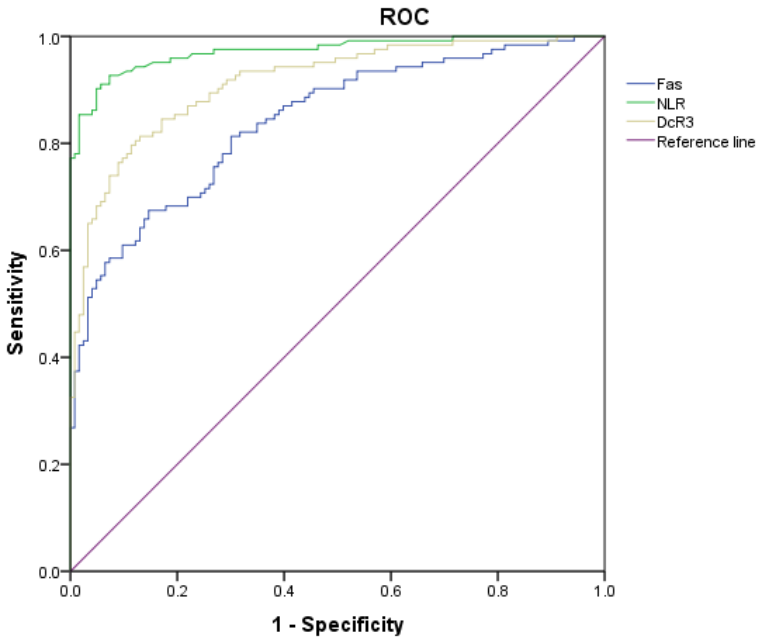

Figure 2. ROC curve. Note: DcR3: decoy receptor 3; NLR: neutrophil-to-lymphocyte ratio.

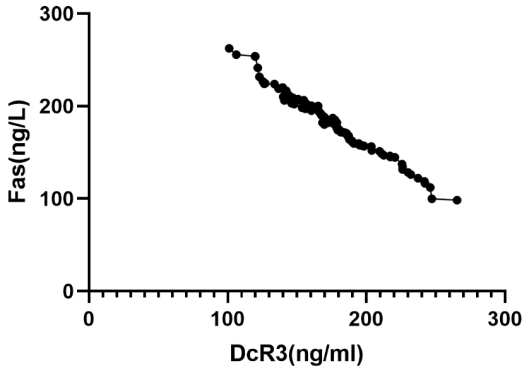

Figure 3. Correlation analysis between DcR3 and Fas in peripheral blood of patients with cirrhosis. Note: DcR3: decoy receptor 3.

pressed in various inflammatory diseases and can serve as a diagnostic marker for these conditions [9, 10]. Research by Yang et al. reported significantly elevated serum DcR3 levels in liver cancer patients, which were strongly associated with cirrhosis, tumor metastasis, and recurrence. This suggests that DcR3 may play a pivotal role in the onset, progression, and metastasis of primary liver cancer [19]. In line with these findings, our study shows significantly higher serum DcR3 levels in cirrhosis patients compared to healthy individuals, with levels increasing alongside disease severity. These findings align with previous studies, indicating that DcR3 is involved in the progression of cirrhosis.

As an indicator of inflammatory status, NLR is a cost-effective and readily available biomarker. Studies have shown that elevated NLR levels may reflect an impaired host immune response to tumors, with higher NLR values often correlating with a poorer prognosis [20]. An increase in neutrophils or a decrease in lymphocytes can both lead to elevated NLR levels. Neutrophil elevation may be associated with IL-17 or tumor-associated macrophages, which promote the secretion of chemokines such as IL-6 and IL-8, thereby increasing neutrophil levels. High neutrophil counts can, in turn, foster tumor angiogenesis by promoting the release of vascular endothelial growth factor [21]. Conversely, lymphocytes, which mediate immune responses, play a key role in antitumor immunity. A reduction in lymphocyte levels signifies a decline in antitumor immunity and cytotoxicity, thereby weakening the body's ability to combat tumors. This decrease in lymphocytes facilitates tumor progression, recurrence, invasion, and metastasis [22]. In this study, NLR levels were significantly higher in cirrhosis patients compared to healthy controls, with levels increasing as the disease severity progressed. These findings suggest that peripheral blood NLR levels are closely associated with cirrhosis severity. Furthermore, ROC curve analysis demonstrated that DcR3, Fas, and NLR each showed good diagnostic efficacy for predicting the progression of cirrhosis to liver cancer, underscoring their clinical value in evaluating the prognosis of cirrhosis.

However, this study has several limitations: (1) the sample was derived from a single center with a relatively small sample size; (2) the dynamic changes in each indicator over time were not assessed; and (3) the study focused on a limited number of biological markers, providing an incomplete analysis of the underlying mechanisms. Therefore, further studies with

larger, multi-center, and multi-indicator cohorts and the inclusion of additional biomarkers are warranted.

In conclusion, as cirrhosis progresses, serum DcR3, Fas, and peripheral blood NLR levels exhibit an upward trend, demonstrating significant diagnostic value in assessing the prognosis of cirrhosis.

Disclosure of conflict of interest

None.

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