Original Article

Diagnostic significance of serum type IV collagen (IVC) combined with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio in liver fibrosis

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Background: Liver fibrosis is a necessary stage for various chronic liver diseases to develop into cirrhosis. The detection of serum markers of liver fibrosis is a commonly used method for early screening of liver fibrosis, mainly including type IV collagen (IVC), hyaluronic acid (HA), laminin (LN), and type III procollagen (PCIII). However, the high cost of the instrument and the slow detection speed are not conducive to mass screening and detection of the population. In this study, the widely used biochemical platform was used to jointly detect the liver fibrosis marker IVC and aspartate aminotransferase (AST) and alanine aminotransferase (ALT), We investigated the feasibility of serum IVC combined with the AST and ALT ratio (AST/ALT ratio) as a marker for liver fibrosis.

Methods: A total of 81 patients with liver disease by clinical liver biopsy comprised the study group, and 50 healthy people who underwent physical examination in the study period were selected as the control group. Serum IVC, AST and ALT levels were detected by biochemical testing, AST/ALT ratio was calculated, and four serum markers of liver fibrosis (IVC, HA, LN, and PCIII) were measured by chemiluminescence. Moreover, imaging by color Doppler ultrasound (B-ultrasound) was performed for statistical analysis.

Results: (I) Serum IVC and the AST/ALT ratio were significantly higher in the study group than in the control group ($P<0.05$). (II) The sensitivity of serum IVC combined with AST/ALT ratio detected biochemically and the four markers of liver fibrosis detected by chemiluminescence in the diagnosis of liver cirrhosis was 95.83%, 97.92%, without significant difference, but the specificity and accuracy of IVC + AST/ALT ratio in the diagnosis of liver cirrhosis were significantly higher (94.00%, 94.90%). (III) The detection rate of serum IVC + AST/ALT ratio for the diagnosis of early liver fibrosis was significantly higher than with imaging examination (45.45% *vs.* 21.21%).

Conclusions: Serum IVC + AST/ALT ratio determined by biochemical analysis has high diagnostic accuracy in the diagnosis of liver fibrosis and liver cirrhosis, and is worthy of clinical application and promotion.

Keywords: Aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT ratio); cirrhosis; liver fibrosis; type IV collagen (IVC)

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Introduction

China is one of the countries with an extremely high incidence of liver disease, with about 400 million patients with chronic liver disease. Patients with chronic liver disease are prone to liver fibrosis, which can further develop into nodules and result in cirrhosis. Without timely treatment, it can eventually evolve into liver cancer, a serious threat to the life and health of patients. Clinical studies have found that early diagnosis and treatment of liver fibrosis can effectively prevent further development of disease or even reverse the process of liver fibrosis (1,2).

Liver biopsy is the "gold standard" for the diagnosis of liver fibrosis in clinical practice. However, liver biopsy needs to collect living tissue, which is highly traumatic and easy to cause complications and pain to patients. B-ultrasound is the main method of imaging detection, but the early sensitivity is poor, and affected by the professional level of operators, the early sensitivity is low. Type IV collagen (IVC) is one of the main serological markers in the early stage of liver fibrosis, and because it reflects the severity of liver disease and the process of liver fibrosis, it is important in the diagnosis and treatment of liver fibrosis (3). Chemiluminescence has been the main detection platform used in previous studies of IVC, combined with other serological markers, hyaluronic acid (HA), laminin (LN), and type III procollagen (PCIII). However, the method is time consuming and costly. Biochemical detection of IVC is an alternative. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the main indicator of liver injury and their ratio reflects the extent of liver parenchymal injury. Several studies have shown that AST/ALT ratio plays an important role in the diagnosis and severity assessment of liver diseases such as acute hepatitis, chronic hepatitis and cirrhosis (4,5). We investigated the diagnostic value of measuring serum IVC biochemically combined with the AST/ALT ratio for detecting liver fibrosis. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5010/rc).

Highlight box

Key findings

- Serum IVC + AST/ALT ratio could effectively improve the diagnostic rate of liver fibrosis and liver cirrhosis.

What is known and what is new?

- Liver fibrosis is a necessary stage for various chronic liver diseases to develop into cirrhosis;
- The sensitivity of serum IVC + AST/ALT ratio in the diagnosis of liver cirrhosis was high, and moreover, the specificity and accuracy were significantly higher than those of the four markers of liver fibrosis by chemiluminescence and imaging.

What is the implication, and what should change now?

- Serum IVC + AST/ALT ratio determined by biochemical analysis has high diagnostic accuracy in the diagnosis of liver fibrosis and liver cirrhosis, and is worthy of clinical application and promotion.

Methods

Baseline data

In this study, 81 patients with liver disease confirmed by clinical liver biopsy admitted to the Department of Gastroenterology of Sanhe Yanjiao Second and Third Hospital between January 2018 and January 2019 were divided into a liver hepatitis group (n=33) and a liver cirrhosis group (n=48). The hepatitis group included 11 patients with chronic hepatitis, 9 with acute hepatitis B and 13 with fatty liver. The liver cirrhosis group included 48 patients with clinically confirmed liver cirrhosis. The control group consisted of 50 healthy normal adults who underwent physical examination during the study period. Inclusion criteria were (6): (I) liver disease diagnosed in accordance with the diagnostic criteria revised by the Sixth National Academic Conference on Infectious Diseases and Parasites in 2001 (5); (II) physical examination results confirmed the control subjects were healthy; (III) age 30–70 years; (IV) voluntary participation and written informed consent given. Exclusion criteria were: (I) coronary heart disease, aortic stenosis and congenital heart disease; (II) severe heart failure; (III) severe mental illness or nervous system diseases preventing cooperation with the study; (IV) hypertension, diabetes, severe liver and kidney dysfunction.

The study group consisted of 43 men and 38 women, aged 32–70 years old, with a mean age of 53.19±4.93 years; disease course was from 1 to 28 months, with a mean of 14.3±3.7 months; the control group consisted of 26 men and 24 women, aged 30–70 years old, with a mean age of 50.93±5.17 years; disease course was 1–27 months, with mean disease course of 13.8±3.3 months; without disease; and the specific physical examination time was between January 2017 and January 2018. There was no statistical significance in sex, age and other baseline data between the two groups (P>0.05), so they were comparable. The

Table 1 Comparison of IVC and AST/ALT in the two groups (mean ± SD)

Group	IVC (ng/mL)	AST (U/L)	ALT (U/L)	AST/ALT
Study group	263.0±118.8*	132.9±105.8*	79.5±46.6*	1.59±0.90*
Control group	101.0±23.9	12.7±7.7	19.5±9.4	0.79±0.47

*, P<0.05, compared with control group. IVC, type IV collagen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SD, standard deviation.

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Sanhe Yanjiao Second and Third Hospital (No. 2018-LL-0012) and informed consent was taken from all the patients.

Study methods

A 6–8 mL sample of peripheral venous blood was drawn from the antecubital vein of fasting patients in the two groups in the morning on the same day. Samples were incubated at 37 ℃ for 30 min, then centrifuged at 1,500 g for 10 min. The supernatant was stored at –40 ℃ until testing. IVC, ALT and AST levels in serum were measured by Beckman AU5811 automatic biochemical analyzer, and the respective kits were purchased from Beijing Bioassay Technologies Corporation. The four markers of liver fibrosis (IVC, HA, LN and PCIII) in serum were detected by chemiluminescence analyzer Antu A2000Plus and reagents were provided by ANTUBIO. Imaging was performed with a color Doppler ultrasound diagnostic instrument (Siemens).

Outcome measures

(I) Differences in the serum IVC and AST/ALT ratio between the study and control groups were compared. (II) The sensitivity, specificity and accuracy of biochemical detection of IVC combined with AST/ALT were compared with that of the four markers by chemiluminescence in the diagnosis of liver fibrosis and cirrhosis. (III) Difference between biochemical detection of IVC combined with AST/ALT and imaging diagnosis for early liver fibrosis was analyzed.

Statistical analysis

All statistical data were analyzed by SPSS 23.0, and all measurement data were expressed as mean ± standard deviation. Groups were compared by *t*-test, and P<0.05 was statistically significant. Sensitivity = true positive number/(true positive number + false negative number) ×100%; specificity = true negative number/(true negative number + false positive number) ×100%; accuracy = (true positive number + true negative number)/total number.

Results

Comparison of serum IVC and AST/ALT between groups

The mean IVC level of the study group and control group was 263.0±118.8 and 101.0±23.9 ng/mL, respectively, with the study group being significantly higher than the control group (P<0.05). The respective AST/ALT ratios were 1.59±0.90 and 0.79±0.47, with the study significantly higher than in the control group (P<0.05; *Table 1*).

Comparison of serum IVC + AST/ALT ratio detected biochemically and four markers of liver fibrosis by chemiluminescence for diagnosis of early liver cirrhosis

The serum IVC and AST/ALT ratio of the biochemical platform were analyzed together. IVC positive and AST/ALT ratio >1 were taken as positive. At least one of IVC, HA, LN and PCIII was positive in four chemiluminescence liver fiber diagnoses. The number of positive cases and negative cases of the two combinations in the liver cirrhosis group and the control group were calculated respectively (*Table 2*).

The sensitivity, specificity and accuracy of serum IVC + AST/ALT ratio in the diagnosis of liver cirrhosis were 95.83% (46/48), 94.00% (47/50) and 94.90% (93/98), respectively, and 97.92% (47/48), 76.00% (38/50) and 86.73% (85/98), respectively, for chemiluminescent detection of the four markers. The sensitivity of both methods for the diagnosis of cirrhosis was good and >95% without significant difference, but the specificity and accuracy of IVC + AST/ALT ratio in the diagnosis of cirrhosis were significantly higher (*Table 2*).

Table 2 Comparison of IVC + AST/ALT ratio and four markers of liver fibrosis in accordance with clinical diagnosis of liver cirrhosis

Group	IVC + AST/ALT ratio		Markers of liver fibrosis	
	Positive	Negative	Positive	Negative
Liver cirrhosis group (n=48)	46	2	47	1
Control group (n=50)	3	47	12	38

IVC, type IV collagen; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3 Comparison of IVC + AST/ALT and ultrasonography in the diagnosis of early liver fibrosis

Variables	Positive IVC + AST/ALT ratio	Positive B-ultrasound diagnosis
Hepatitis group (n=33)	15	7
Detection rate (%)	45.45	21.21

IVC, type IV collagen; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Comparison of serum IVC + AST/ALT and imaging for diagnosis of early liver fibrosis

IVC + AST/ALT ratio detected 15 patients with early liver fibrosis among the 33 patients with hepatitis, with a detection rate of 45.45%; 7 patients with early liver fibrosis in the hepatitis group were revealed by ultrasonography, with a detection rate of 21.21% (*Table 3*).

Discussion

Liver fibrosis is a pathophysiological process in which abnormal proliferation of intrahepatic connective tissue is caused by various pathogenic factors. It occurs in the process of repair and healing regardless of the degree of liver injury. However, if the initiating factors become chronic, cirrhosis can develop as a long-term sequela of fibrosis. There are many causes of liver fibrosis (7-11), but in clinical practice they are mainly fatty liver, viral hepatitis, alcoholic liver disease, and autoimmune diseases. In China, viral hepatitis, especially chronic hepatitis B and C, and long-term heavy alcohol abuse are the main factors causing liver fibrosis. Liver fibrosis is usually asymptomatic and not easily detected clinically until cirrhosis develops (12,13). In China, there are two main categories of cirrhosis: posthepatitic and alcoholic. Histopathologically, cirrhosis presents as extensive hepatocyte necrosis, nodular regeneration of residual hepatocytes, connective tissue hyperplasia, and fibrous septa formation, causing destruction of the hepatic lobular structure and pseudolobular formation. Physically, the liver gradually deforms and hardens. Because of the strong compensatory function of the liver, even early cirrhosis usually demonstrates no obvious clinical symptoms, and it is not until the late stage of cirrhosis that severe liver function damage and portal hypertension are the main clinical manifestations, accompanied by multi-system involvement. Moreover, upper gastrointestinal bleeding, hypersplenism, ascites, secondary infection, hepatic encephalopathy, carcinogenesis and other complications often occur. Hepatic encephalopathy is the leading cause of death in patients with cirrhosis. Liver fibrosis and cirrhosis are mainly diagnosed by imaging examination, pathological biopsy and biochemical testing. Pathological examination is the gold standard (14), and considered to be able to confirm the diagnosis, measure inflammatory activity and the degree of fibrosis, and determine the efficacy of drugs. However, there are sampling limitations, a degree of trauma, postoperative complications, high cost and other disadvantages of pathological examination by biopsy.

IVC, HA, LN and PCIII are collectively referred to as the markers of liver fibrosis (15). HA is an acidic mucopolysaccharide synthesized by interstitial cells and a major component in the connective tissue matrix (16). Synthesis of HA is mainly in hepatic stellate cells, which are overactivated when chronic liver disease develops, synthesizing large amounts of HA, which increases the serum HA level significantly as the disease progresses (17). Therefore, HA is a valuable indicator of endothelial cell function and cirrhosis (18). LN is a non-collagenous sugar and a component of the basement membrane together with collagen in the liver, mainly synthesized by endothelial cells and adipocytes, and its synthesis increases when cells undergo inflammatory responses. Its biological function is regulation of cell growth and differentiation. Collagen is the most abundant protein in mammals, accounting for 25–30% of the total protein (19), and the main component of the extracellular matrix. A total of 28 different types of collagens have been found, of which interstitial types I, III and IV are predominant. In chronic hepatitis, the sinusoidal capillaries are damaged, releasing a large amount of IVC degraded from the basement membrane into the blood. Because the ability to restore IVC is reduced and synthesis is greater than degradation when liver function is

impaired, so that IVC serum level significantly increases. Detection of dynamic changes in the levels of HA, LN, PCIII and IVC in clinical practice has significance for the diagnosis of disease, monitoring progression and treatment prognosis in patients with chronic liver disease (19,20). However, detection of the four markers of liver fibrosis by chemiluminescence has the disadvantages of high sensitivity and poor specificity (21). The four items of liver fiber not only increase in liver fibrosis, but also in renal fibrosis, pulmonary fibrosis and other organ fibrosis. At the same time, they are also affected by bone growth, drugs, etc., which has the disadvantages of high sensitivity and poor specificity. ALT and AST mainly exist in the liver. Among them, ALT mainly exists in the cytoplasm, while part of AST exists in the cytoplasm, but most of it exists in the mitochondria of liver cells. Under normal circumstances, the content of ALT and AST in blood is less, and the AST/ALT ratio dimension is at a stable level. When liver cells are slightly damaged, the permeability of cell membrane increases, and the ALT and AST in cytoplasm are released into the blood, which increases the concentration of serum ALT and AST, and the AST/ALT ratio decreases less than 1. If liver cells are seriously damaged and mitochondria are damaged, mitochondrial AST will be released, making the AST/ALT ratio increase more than 1. With the further development of the disease, AST/ALT will further increase, up to 2 or more. Thus, the AST/ALT ratio can well reflect the degree of hepatocyte damage. With severe damage, such as cirrhosis, active chronic hepatitis and primary liver cancer, the AST/ALT ratio will increase significantly and the greater the ratio, the more severe the degree of hepatocyte damage, with poor prognosis (4).

In our study, the sensitivity of serum IVC + AST/ALT ratio in the diagnosis of liver cirrhosis was high, and moreover, the specificity and accuracy were significantly higher than those of the four markers of liver fibrosis by chemiluminescence ($P<0.05$). The detection rate of IVC + AST/ALT ratio in the diagnosis of early liver fibrosis was significantly higher than that of imaging ($P<0.05$), which could effectively improve the diagnostic rate of liver fibrosis and liver cirrhosis. These results were consistent with the study of Zhang and Wu (22).

Conclusions

In summary, serum IVC and the AST/ALT ratio measured biochemically had high diagnostic accuracy for liver fibrosis and cirrhosis, so can be applied to detect and diagnose early liver fibrosis. Biochemical detection is easy to operate, with low cost, making it more suitable for early screening detection. Therefore, it is worthy of clinical application and promotion.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5010/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5010/dss

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5010/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Sanhe Yanjiao Second and Third Hospital (No. 2018-LL-0012) and informed consent was taken from all the patients.

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