

BRIEF ARTICLES

## A dose-up of ursodeoxycholic acid decreases transaminases in hepatitis C patients

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**CONCLUSION:** Oral administration of 900 mg/d of UDCA was more effective than 600 mg/d for reducing ALT, AST, and GGT levels in patients with HCV-related chronic liver disease.

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**Key words:** Chronic hepatitis; Hepatitis C virus; Liver fibrosis; Transaminase; Ursodeoxycholic acid

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### Abstract

**AIM:** To examine whether a dose-up to 900 mg of ursodeoxycholic acid (UDCA) decreases transaminases in hepatitis C patients.

**METHODS:** From January to December 2007, patients with chronic hepatitis C or compensated liver cirrhosis with hepatitis C virus (HCV) (43-80 years old) showing positive serum HCV-RNA who had already taken 600 mg/d of UDCA were recruited into this study. Blood parameters were examined at 4, 8 and 24 wk after increasing the dose of oral UDCA from 600 to 900 mg/d.

**RESULTS:** Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) levels were significantly decreased following the administration of 900 mg/d as compared to 600 mg/d. The decrease in ALT from immediately before the dose-up of UDCA to 8 wk after the dose-up was 14.3 IU/L, while that for AST was 10.5 IU/L and for GGT was 9.8 IU/L. Platelet count tended to increase after the dose-up of UDCA, although it did not show a statistically significant level ( $P = 0.05$ ). Minor adverse events were observed in 3 cases, although no drop-outs from the study occurred.

### INTRODUCTION

Current treatment for chronic hepatitis C virus (HCV) infection is based on the administration of pegylated interferon (IFN) alone or in combination with other anti-viral agents such as ribavirin or protease inhibitors. However, these treatments are not completely effective in all patients with HCV genotype 1 and high viral load or in patients with liver cirrhosis<sup>[1-4]</sup>. Ursodeoxycholic acid (UDCA) was identified in 1902 from polar bear bile by Hammarsten and was isolated and crystallized by Shoda<sup>[5]</sup>. UDCA is used worldwide for the treatment of primary biliary cirrhosis (PBC) and chronic liver diseases<sup>[6-14]</sup>. Up to 2006, a dose of 150 mg/d of UDCA was approved as the standard treatment for hepatic protection in patients with chronic viral hepatitis by the public health insurance agency of Japan. However, this dosage is not effective for the treatment of chronic hepatitis<sup>[15]</sup>. A randomized, controlled-dose study of UDCA for chronic hepatitis C (CH-C) patients reported that UDCA administered at a dose of 600 or 900 mg/d resulted in greater decreases in the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl

transpeptidase (GGT) compared to 150 mg/d, which was the dose recommended by the Japanese national health insurance policy at that time; however, the results with doses of 600 mg/d or 900 mg/d were similar. In contrast, 600 mg of UDCA, which is the maximum administration dose in PBC or other biliary system diseases such as gallstones, was used ambiguously in CH-C patients<sup>[16]</sup>.

To determine the effect of 900 mg/d of UDCA for CH-C, the present study was conducted primarily as a dose-up trial from 600 mg/d to 900 mg/d in hepatitis C patients, with changes in ALT levels as the primary endpoint.

## MATERIALS AND METHODS

### Patients

From January to December in 2007, patients with CH-C or compensated liver cirrhosis with HCV (mean age 65.8, range 43 to 80 years) who tested positive for serum HCV-RNA were recruited into this study. All the enrolled patients had already received 600 mg/d of UDCA, and showed over 40 IU/L of ALT at the two points in the 4 wk prior to dose-up of UDCA. Patients were excluded from the study if they had received antiviral treatment with interferon with or without ribavirin or anticancer treatment for hepatocellular carcinoma (HCC). Patients with other malignancies diagnosed within 24 wk before the observation period or patients treated with corticosteroids and/or immunosuppressive drugs were also excluded. Patients with decompensated cirrhosis, hepatitis B, autoimmune liver disease, alcoholic or drug-induced liver injury, malignant tumors and biliary disorders were excluded. Patients receiving intravenous glycyrrhizin were enrolled in this study. However, when the dose or frequency of administration of glycyrrhizin was changed, this was defined as the study endpoint. Written informed consent was obtained from each patient before enrollment into the study.

### Methods

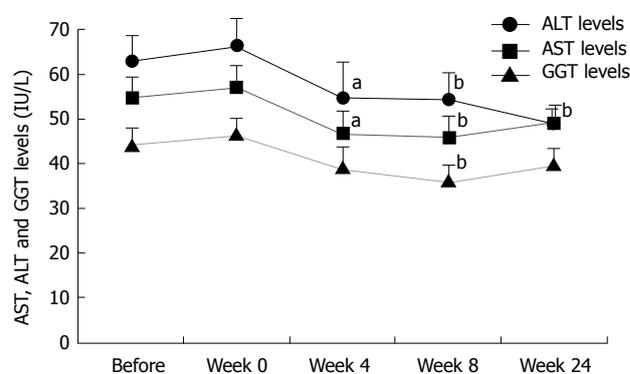
After the 4-wk observation period, the dose of UDCA (Urso<sup>®</sup>, Mitsubishi Tanabe Pharma Corp., Osaka, Japan) was increased from 600 mg/d to 900 mg/d. Serum ALT was measured as a primary endpoint of liver function, and AST and GGT as secondary endpoints, using conventional methods. Blood samples were taken at the start of the observation period, at 0, 4, 8 and 24 wk after initiation of treatment, and at the final observation period. Serum concentrations of ALT, AST, GGT, albumin, total bilirubin and platelet counts were measured. CT and ultrasonography for HCC screening was carried out every 12 wk or 24 wk. Compliance with UDCA administration and adverse effects were determined by patient interview or confirmation of drug diaries.

### Statistical analysis

Changes in AST, ALT, GGT, total bilirubin, albumin,

**Table 1** Patient characteristics before beginning the study (mean  $\pm$  SE)

	Total (n = 32)
Mean age (range)	65.8 $\pm$ 2.6 (43-80)
Gender (male)	18 (56)
Liver cirrhosis (%)	7 (22)
Controlled hepatocellular carcinoma (%)	4 (12)
Glycyrrhizin administration (%)	6 (19)
AST (IU/L)	66.5 $\pm$ 4.1
ALT (IU/L)	57.1 $\pm$ 3.4
GGT (IU/L)	44.2 $\pm$ 2.1
Total bilirubin (mg/dL)	0.76 $\pm$ 0.5
Serum albumin (g/dL)	4.0 $\pm$ 0.1
Platelet count ( $\times$ 1000/ $\mu$ L)	14.5 $\pm$ 1.0
HCV RNA (KIU/mL)	1309 $\pm$ 469
HCV genotype (1b/non 1b/not decided)	24/6/2



**Figure 1** Changes in serum alanine aminotransferase (ALT) levels, serum aspartate aminotransferase (AST) levels and serum gamma-glutamyl transpeptidase (GGT) levels in patients before and during dose-up to 900 mg/d. Data are expressed as mean  $\pm$  SD. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$ ; paired *t*-test compared to week 0 in each parameter.

and platelet count were analyzed by paired Student's *t*-test.  $P < 0.05$  was considered significant.

## RESULTS

We enrolled 32 patients to this study. Patient characteristics are described in Table 1. In seven patients with liver cirrhosis, five patients were estimated as Child A and the others as Child B. Three patients with a history of HCC had been clinically diagnosed by dynamic computed tomography as having a complete response to trans-catheter arterial embolization and/or percutaneous radiofrequency ablation 24 wk or more before the start of the observation period. Compliance rate with UDCA administration was over 95%.

### Changes in AST, ALT and GGT by dose-up of UDCA

Serum ALT, AST and GGT levels before and after the start of 900 mg of UDCA are shown in Figure 1. Serum ALT, AST and GGT levels were significantly decreased at 4, 8 and 24 wk after dose-up to 900 mg/d. The decrease (decreasing rate, %) in ALT levels before and 8 wk after dose-up to 900 mg of UDCA was 14.3 IU/L (22.1%) as shown in Figure 1. The decrease in AST and GGT were 10.5 IU/L (19.1%), and 9.8 IU/L (22.1%), respectively (Figure 1).

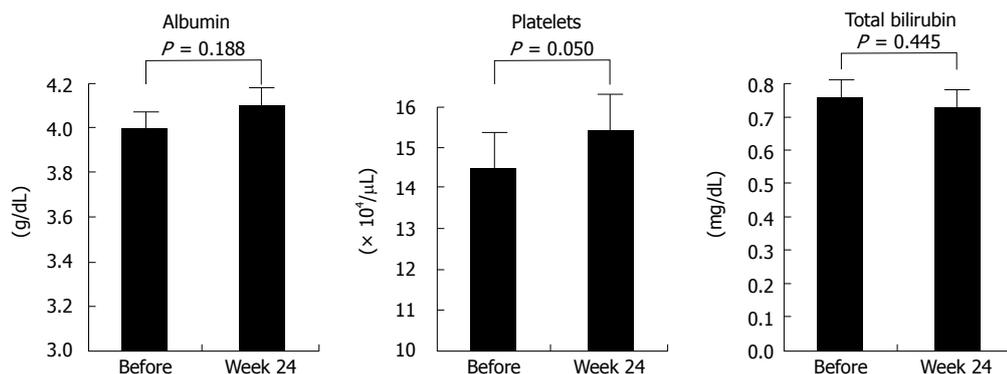


Figure 2 Changes in serum albumin, platelet count, and total bilirubin levels in chronic hepatitis C patients before and 24 wk after beginning the dose-up to 900 mg/d.

### Changes in serum concentrations of albumin, total bilirubin and platelet count

Serum albumin level changed from 4.0 g/dL to 4.1 g/dL at 24 wk after the dose-up of UDCA. Platelet count changed from 145 000 to 154 000/ $\mu\text{L}$ , and total bilirubin changed from 0.76 to 0.73 mg/dL, although the difference did not reach a statistically significant level ( $P = 0.05$ , Figure 2). Serum HCV-RNA level did not change during the study period.

### Safety

The number of adverse events during the administration of 900 mg UDCA, totaled three (9.4%), mild diarrhea in two patients and mouth discomfort in one patient. None of these adverse events influenced compliance with UDCA. Although HCC recurrence was detected in one patient at just 24 wk after dose-up of UDCA, this lesion was completely treated with percutaneous radiofrequency ablation.

## DISCUSSION

The results of this study revealed that the dose-up trial of UDCA from 600 mg/d to 900 mg/d improved biochemical markers such as serum AST, ALT and GGT as early as the first or second dose-up week and continued to improve biochemical markers up to 24 wk after dose-up of UDCA was initiated. In addition, platelet count tended to increase following this dose-up therapy. These results suggested that 900 mg of UDCA can improve liver function tests in patients with chronic hepatitis C who have already received 600 mg of UDCA. In this study, the frequency of adverse events was lower than those in previous reports<sup>[15-18]</sup>. A possible reason for this is that patients enrolled in this study were not naïve to UDCA and may have quickly gotten used to the administration of UDCA.

In the natural course of CH-C, patients with normal serum aminotransferase levels show a slow fibrosis progression and a low incidence of HCC. Rino *et al*<sup>[19]</sup> demonstrated that the mode of reduction therapy and ALT levels were the most important factors, by multivariate analysis, to affect HCC development in patients with HCV-related cirrhosis of Child A

classification followed for over 10 years. In addition, a previous study of postoperative patients with HCC found that recurrence was more frequent among patients with high serum ALT levels over 80 IU/L<sup>[20]</sup>. Moreover, using multivariate analysis in the Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) study, the risk of HCC after interferon treatment without virological response was strongly influenced by ALT levels, and the odds ratio of HCC in sustained virological responders was the same as that in sustained biochemical responders<sup>[21]</sup>. Therefore, high dose UDCA possibly reduced the occurrence and recurrence of HCC through the reduction of serum ALT level.

The anti-inflammatory mechanism of UDCA was considered to cause a reduction in the cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion, suppression of NF- $\kappa$ B-dependent transcription by binding to the glucocorticoid receptor, and a decrease in proinflammatory cytokine-induced transcription of phospholipase A2<sup>[22-28]</sup>.

The long-term effects of UDCA therapy in CH-C patients have not been fully elucidated<sup>[29]</sup>. Changes in liver histology following UDCA administration may not be clear from short-term observation periods. In this study, the dose-up treatment with 900 mg/d UDCA for 24 wk tended to increase serum platelet counts. In patients with hepatitis C virus-related chronic liver diseases, platelet counts reflect histological findings. When the platelet count is low in the patient, progression of liver fibrosis is suggested<sup>[30-33]</sup>. It is necessary to show histologically the morphological hepatic tissue changes in future studies.

In conclusion, oral administration of high dose 900 mg UDCA, despite the absence of an anti-viral effect, shows beneficial effects in reducing the activity of chronic hepatitis or cirrhosis.

## COMMENTS

### Background

Administration of pegylated interferon alone or in combination with anti-viral agents has improved the treatment for chronic hepatitis C, but is not very effective in some patients-especially those with hepatitis C virus (HCV) genotype 1 and high viral load or liver cirrhosis. Such patients may benefit from therapies which reduce liver inflammation and fibrosis.

### Research frontiers

Researchers assessed the effect of ursodeoxycholic acid (UDCA) on serum liver enzyme levels in patients with chronic hepatitis C or compensated liver cirrhosis with HCV. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) levels were significantly decreased with 900 mg/d compared with 600 mg/d.

### Innovations and breakthroughs

Increasing the oral UDCA dose to 900 mg/d was effective in reducing ALT, AST, and GGT levels. Adverse effects were reported in 3 cases (9.4%), but none of these adverse effects influenced UDCA compliance.

### Applications

The study results suggest that patients with HCV genotype 1 and high viral load or liver cirrhosis may benefit from oral UDCA therapy.

### Peer review

This manuscript demonstrates that raising the UDCA dose from 600 mg/d to 900 mg/d improves liver chemistries including AST, ALT, and GGT over a 6 mo period. The authors then suggest that this may lead to suppression of fibrosis in a HCV population. Also, this research suggests that UDCA is safe at this dose. This is novel in a Japanese HCV cohort and the methods are quite straightforward. While not particularly novel, it does suggest that higher dose UDCA can improve liver chemistries.

## REFERENCES

- Sarrazin C, Rouzier R, Wagner F, Forestier N, Larrey D, Gupta SK, Hussain M, Shah A, Cutler D, Zhang J, Zeuzem S. SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. *Gastroenterology* 2007; **132**: 1270-1278
- Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355
- Kieffer TL, Sarrazin C, Miller JS, Welker MW, Forestier N, Reesink HW, Kwong AD, Zeuzem S. Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology* 2007; **46**: 631-639
- Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, Ling MH, Albrecht J. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; **122**: 1303-1313
- Poupon R, Serfaty L. Ursodeoxycholic acid in chronic hepatitis C. *Gut* 2007; **56**: 1652-1653
- Bateson MC, Ross PE, Diffey BL. Ursodeoxycholic acid in primary biliary cirrhosis. *Lancet* 1989; **1**: 898-899
- Oka H, Toda G, Ikeda Y, Hashimoto N, Hasumura Y, Kamimura T, Ohta Y, Tsuji T, Hattori N, Namihisa T. A multi-center double-blind controlled trial of ursodeoxycholic acid for primary biliary cirrhosis. *Gastroenterol Jpn* 1990; **25**: 774-780
- Crosignani A, Podda M, Battezzati PM, Bertolini E, Zuin M, Watson D, Setchell KD. Changes in bile acid composition in patients with primary biliary cirrhosis induced by ursodeoxycholic acid administration. *Hepatology* 1991; **14**: 1000-1007
- Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. *N Engl J Med* 1994; **330**: 1342-1347
- Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, Michieletti P, Minuk GY, Pappas SC, Scully LJ. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1994; **19**: 1149-1156
- Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Dickson ER. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. *Gastroenterology* 1996; **110**: 1515-1518
- Jackson H, Solaymani-Dodaran M, Card TR, Aithal GP, Logan R, West J. Influence of ursodeoxycholic acid on the mortality and malignancy associated with primary biliary cirrhosis: a population-based cohort study. *Hepatology* 2007; **46**: 1131-1137
- Chazouillères O, Poupon R, Capron JP, Metman EH, Dhumeaux D, Amouretti M, Couzigou P, Labayle D, Trinchet JC. Ursodeoxycholic acid for primary sclerosing cholangitis. *J Hepatol* 1990; **11**: 120-123
- Nakagawa S, Makino I, Ishizaki T, Dohi I. Dissolution of cholesterol gallstones by ursodeoxycholic acid. *Lancet* 1977; **2**: 367-369
- Takano S, Ito Y, Yokosuka O, Ohto M, Uchiumi K, Hirota K, Omata M. A multicenter randomized controlled dose study of ursodeoxycholic acid for chronic hepatitis C. *Hepatology* 1994; **20**: 558-564
- Omata M, Yoshida H, Toyota J, Tomita E, Nishiguchi S, Hayashi N, Iino S, Makino I, Okita K, Toda G, Tanikawa K, Kumada H. A large-scale, multicentre, double-blind trial of ursodeoxycholic acid in patients with chronic hepatitis C. *Gut* 2007; **56**: 1747-1753
- Olsson R, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, Bell H, Gangsøy-Kristiansen M, Matre J, Rydning A, Wikman O, Danielsson A, Sandberg-Gertzén H, Ung KA, Eriksson A, Lööf L, Prytz H, Marshall HU, Broomé U. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology* 2005; **129**: 1464-1472
- Lirussi F, Beccarello A, Bortolato L, Morselli-Labate AM, Crovatto M, Ceselli S, Santini G, Crepaldi G. Long-term treatment of chronic hepatitis C with ursodeoxycholic acid: influence of HCV genotypes and severity of liver disease. *Liver* 1999; **19**: 381-388
- Rino Y, Tarao K, Morinaga S, Ohkawa S, Miyakawa K, Hirokawa S, Masaki T, Tarao N, Yukawa N, Saeki H, Takanashi Y, Imada T. Reduction therapy of alanine aminotransferase levels prevent HCC development in patients with HCV-associated cirrhosis. *Anticancer Res* 2006; **26**: 2221-2226
- Tarao K, Takemiya S, Tamai S, Sugimasa Y, Ohkawa S, Akaike M, Tanabe H, Shimizu A, Yoshida M, Kakita A. Relationship between the recurrence of hepatocellular carcinoma (HCC) and serum alanine aminotransferase levels in hepatectomized patients with hepatitis C virus-associated cirrhosis and HCC. *Cancer* 1997; **79**: 688-694
- Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999; **131**: 174-181
- Miura T, Ouchida R, Yoshikawa N, Okamoto K, Makino Y, Nakamura T, Morimoto C, Makino I, Tanaka H. Functional modulation of the glucocorticoid receptor and suppression of NF-kappaB-dependent transcription by ursodeoxycholic acid. *J Biol Chem* 2001; **276**: 47371-47378
- Park IH, Kim MK, Kim SU. Ursodeoxycholic acid prevents apoptosis of mouse sensory neurons induced by cisplatin by reducing P53 accumulation. *Biochem Biophys Res Commun* 2008; **377**: 1025-1030
- Rodrigues CM, Fan G, Ma X, Kren BT, Steer CJ. A novel role for ursodeoxycholic acid in inhibiting apoptosis by modulating mitochondrial membrane perturbation. *J Clin Invest* 1998; **101**: 2790-2799
- Tanaka H, Makino I. Ursodeoxycholic acid-dependent activation of the glucocorticoid receptor. *Biochem Biophys Res Commun* 1992; **188**: 942-948

- 26 **Ikegami T**, Matsuzaki Y, Fukushima S, Shoda J, Olivier JL, Bouscarel B, Tanaka N. Suppressive effect of ursodeoxycholic acid on type IIA phospholipase A2 expression in HepG2 cells. *Hepatology* 2005; **41**: 896-905
- 27 **Kano M**, Shoda J, Irimura T, Ueda T, Iwasaki R, Urasaki T, Kawauchi Y, Asano T, Matsuzaki Y, Tanaka N. Effects of long-term ursodeoxycholate administration on expression levels of secretory low-molecular-weight phospholipases A2 and mucin genes in gallbladders and biliary composition in patients with multiple cholesterol stones. *Hepatology* 1998; **28**: 302-313
- 28 **Yoshikawa M**, Tsujii T, Matsumura K, Yamao J, Matsumura Y, Kubo R, Fukui H, Ishizaka S. Immunomodulatory effects of ursodeoxycholic acid on immune responses. *Hepatology* 1992; **16**: 358-364
- 29 **Attili AF**, Rusticali A, Varriale M, Carli L, Repice AM, Callea F. The effect of ursodeoxycholic acid on serum enzymes and liver histology in patients with chronic active hepatitis. A 12-month double-blind, placebo-controlled trial. *J Hepatol* 1994; **20**: 315-320
- 30 **Shiratori Y**, Omata M. Predictors of the efficacy of interferon therapy for patients with chronic hepatitis C before and during therapy: how does this modify the treatment course? *J Gastroenterol Hepatol* 2000; **15** Suppl: E141-E151
- 31 **Giannini E**, Borro P, Botta F, Fumagalli A, Malfatti F, Podestà E, Romagnoli P, Testa E, Chiarbonello B, Polegato S, Mamone M, Testa R. Serum thrombopoietin levels are linked to liver function in untreated patients with hepatitis C virus-related chronic hepatitis. *J Hepatol* 2002; **37**: 572-577
- 32 **Macías J**, Girón-González JA, González-Serrano M, Merino D, Cano P, Mira JA, Arizcorreta-Yarza A, Ruíz-Morales J, Lomas-Cabeza JM, García-García JA, Corzo JE, Pineda JA. Prediction of liver fibrosis in human immunodeficiency virus/hepatitis C virus coinfecting patients by simple non-invasive indexes. *Gut* 2006; **55**: 409-414
- 33 **Shaheen AA**, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: a systematic review. *Hepatology* 2007; **46**: 912-921

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